Development of new or worsening headache after cochlear implant activation: A hypothesis-generating pilot study of incidence, timing, and clinical factors

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Abstract
The objectives of the study are to investigate the incidence of new or worsening headache after cochlear implant (CI) surgery and activation and to determine whether there are predictors of associated headache. We performed a cross-sectional survey of patients who had CI surgery. The frequency and severity of headache, onset of headache relative to surgery and device activation, medication use, family history, headache triggers, and accompanying cranial autonomic symptoms were recorded and analyzed. Thirty-seven subjects were enrolled. In the time period after CI surgery but before CI activation, none reported a new headache and four (11%) reported a worsening headache. After CI activation, six (16%) developed new headache and five (14%) developed worsening headache. These 11 subjects also experienced a significantly higher mean of 6.3 headache days/month following CI activation (\(p < 0.009\)). Providers should be aware that new or worsening headache can be reported following CI activation, although not immediately following CI surgery.

Keywords
cochlear implant, headache, migraine, neurotology

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Introduction
Cochlear implants (CIs) have gained widespread use since their FDA approval to treat sensorineural hearing loss in 1984.\(^1\) A CI consist of two parts: (1) an internal device that is surgically placed and (2) an external device that is worn externally like a hearing aid. The internal device consists of a receiver stimulator that is typically housed under the temporalis muscle and an electrode array placed into the cochlea through a mastoidectomy approach with a postauricular incision. In adult CI recipients at our center, there is a 2- to 3-week waiting period after surgery before the implant is activated. At the time of activation, the auditory nerve is stimulated by electrical impulses generated by CI, which causes auditory percepts that become increasingly recognizable with device usage.

Two adult CI recipients who developed a new onset of severe headache after surgery were referred to our headache clinic. Both patients were postlingually deafened and prior to CI were headache-free. Although surgical
implantation of the devices in both patients was performed without complications, both patients suffered an immediate onset of severe persistent headache approximately 2–3 weeks after surgery when the implants were activated. Both had a family history of migraine. As part of their workup, labs, imaging, audiology, and otolaryngologic testing were performed to rule out infection, device instability, and secondary headache. One patient improved after intravenous dihydroergotamine infusions, and the other preferred to avoid medications and spontaneously improved about a year after surgery.

Based on these cases, we sought to further investigate the association between CI surgery, CI activation, and headache. In addition, we sought to establish whether patients with specific characteristics—including female sex, a family history of headache, menstrual headache, prior history of headache, head trauma, migrainous features of headache, and cranial autonomic symptoms during headache—were more likely to develop new or worsening headache after CI surgery and/or activation.

**Methods**

This study was approved by the institutional review board of the University of California, San Francisco (UCSF) with approval number 15-15893. The inclusion criteria were adult subjects who underwent CI surgery and were able to complete a questionnaire that was specifically designed for this study. Exclusion criteria were subjects unable to provide consent and those deemed unsuitable for enrollment by the investigator. Potential subjects were recruited from the UCSF Headache Center or the UCSF Cochlear Implant Center. After providing written informed consent, subjects were asked to fill out a two-page standard questionnaire during one of the audiological clinical appointments after CI activation (Supplementary Appendix 1). The time between CI activation and questionnaire was variable. Retrospective chart review and telephone follow-up were used in addition to the questionnaires to fill in any missing data. Frequency and severity of headache were recorded, along with pain medication use, family history, history of head trauma, and triggers for headache, including menstrual cycle, hunger, and lack of sleep. Data were extracted from a secure database and analyzed.

New headache was defined as any self-reported increase in the number of headache days for subjects who did not have headache before. Worsening of headache was defined as a self-reported increase in headache severity (yes/no answer) or headache frequency (50% or more increase in the number of headache days after surgery and after activation for subjects with a preexisting headache). The “average” headache days/month was reported to account for cases where the questionnaire was obtained between 2 weeks and 4 weeks after surgery or after activation. This allowed us to avoid overlap in data on headache days/month between the time period after surgery and activation. Migrainous features were defined as nausea and/or vomiting, hunger or lack of sleep triggering headache, and sensitivity to light, sounds, and smells. Cranial autonomic symptoms were defined as eye tearing, nasal congestion or runny nose, eye swelling/puffy, eye redness, and eyelid drooping.

**Statistical analysis**

Data were first assessed using standard descriptive statistics. Repeated-measures Wilcoxon signed-rank test was used to assess differences in the number of headache days/month that subjects experienced during the time period before CI surgery, after surgery, and after activation.

A logistic regression model was constructed to identify subject characteristics that could be associated with developing new or worsening headache following activation. Odds ratios were calculated to determine the odds of subjects developing new or worsening headache following activation given each characteristic. A p value <0.05 was considered statistically significant. All statistical analyses were performed using Excel (Microsoft Corporation, Redmond, Washington, USA) and Stata statistical software (Stata Corporation, College Station, Texas, USA).

**Results**

Thirty-seven research subjects were enrolled, with a mean age of 62 years (median 66 years, range 22–86 years). Females represented 51% of the cohort (n = 19). Before CI surgery, 14 subjects (38%) reported a mean of 2.73 headache days/month (Figure 1). After CI surgery but before activation, no subjects reported a new headache and four subjects (11%) reported worsening of a preexisting headache. The mean headache days/month was 2.97. However, after CI activation, six subjects reported a new headache and five subjects had a worsening headache, which combined was significantly greater compared to the number of subjects with these symptoms after CI surgery (χ² = 5.1, p = 0.043). After CI activation, these 11 subjects also experienced 6.29 headache days/month on average, which was significantly higher compared to before CI surgery (2.73 days, p = 0.009) and after surgery (2.97 days, p = 0.006). Individual headache trajectories during the perioperative period are shown in Figure 2.

Data for subjects who developed new or worsening headache after CI activation were stratified to identify potential predictors of headache. While the proportion of these subjects with each of the risk factors was higher, none was found to be statistically significant (Table 1).

**Discussion**

Cochlear implantation for patients with severe-to-profound hearing loss is a well-accepted and established surgical procedure. Complications of the procedure, including meningitis, taste disturbance, dizziness, loss of residual
hearing, tinnitus, imbalance, device failure, and facial nerve palsy, have been previously described, but there are only few reports of headache associated with cochlear implantation. In two separate case reports, one patient developed headache immediately after CI surgery, while another patient developed headache after CI activation. 

More recently, a European study examined the prevalence of headache in patients with CI and concluded that CI was not associated with an increased risk for developing headache. However, a major limitation of the study was that same subjects were not asked about their change in headache frequency and severity from before and after CI. In other words, distinct groups of subjects were compared in the aforementioned study, which is in contrast to our study that employs a within-subjects comparison.

Our results indicate that, compared to the baseline (before CI surgery), subjects experienced a significantly higher incidence of headache days/month on average after CI activation. In addition, there was a significantly greater number of patients who developed new or worsening headache after CI activation compared to after CI surgery. Together, these results suggest CI activation is possibly associated with headache in our cohort. One plausible explanation for this is that the new onset of sound perception from CI activation may trigger disturbances in sensory processing in patients, especially those who had a predisposition for headache such as a family history. The mechanisms underlying this phenomenon could be similar to those of post-traumatic headache, where a large efflux of different neurotransmitters may cause a discrepancy between increased demands on cerebral metabolism and cerebral blood flow. This imbalance could be followed by an elevation in neuroendocrine and inflammatory responses as well as chronic changes in cerebral blood flow and metabolism.

We identified female sex, family history of headache, menstrual headache, prior history of headache, head trauma, migrainous features of headache, and cranial autonomic symptoms during headache as potential predictors of developing new or worsening headache after CI activation. However, none of these associations were found to be statistically significant, despite the fact that all associations had a higher proportion among the subjects who developed new or worsening headache. For subjects with worsening of headache that gradually returns to baseline, the episodic nature of headache disorders could explain our findings. Future studies with more follow-up time points are needed to determine whether a sudden auditory barrage from CI or the effort of relearning to hear triggers headache. It is possible that CI activation places strain on the brain to process sounds without the normal mechanisms to dampen the senses, leading to headache. This may involve serotonergic, autonomic nervous system, and hypothalamic–pituitary–adrenal axis changes similar to stress and migraine.

Limitations of our study include a small sample size, cross-sectional design, and lack of long-term follow-up data. While we found the association between CI activation and headache to be statistically significant in our study cohort, the small sample size limits the generalizability of our findings. In addition, the methodology for data collection may have led to some significant recall bias. We did not have data concerning the occurrence of tinnitus, which might be an important covariate for hearing restoration and headache. Postoperative analgesics may have masked headache symptoms and led to an underestimate of headache occurrence.
after surgery and before activation. Of note, this pilot study did not classify headache phenotypes according to ICHD-3 (International Classification of Headache Disorders 3rd edition) criteria. This was done purposely to avoid inappropriately forcing cases into categories. Instead, we reported the morphology of symptoms which seemed more likely to help in the design of future research.

**Conclusion**

New or worsening headache may occur after CI activation but do not appear to occur with increased frequency in the period between CI surgery and CI activation. Future studies are needed to address confounding factors in this association, such as analgesic use, postoperative complications, and delayed worsening of headache. Providers should be aware that headache symptoms can possibly be triggered following CI activation.

**Clinical implications**

- Our results suggest a higher incidence of new or worsening headache and a higher number of headache days/month on average following CI activation.
- Providers should be aware of these potential outcomes following CI activation.

**Declaration of conflicting interests**

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Dr Riggins reports, unrelated to this work, participation in an RCT for ElectroCore Medical LLC. Mr Chae reports no disclosures. Dr Levin reports, unrelated to this work, consulting fees from Alder, Allergan, Biohaven, Revance, Supernus, Theranica, and Upsher-Smith, and royalties from Oxford University Press. Ms Ehrlich reports, unrelated to this work, consulting fees from Eli-Lilly and Company; and participation in a RCT for ElectroCore Medical LLC. Dr Sawhney reports no disclosures. Dr Polite reports no disclosures. Dr Goadsby reports, unrelated to this work, personal fees from Alder, Allergan, and grants and personal fees from Amgen and Eli-Lilly and Company; and a grant from Celneg; personal fees from Aeon Biopharma, Alder Biopharmaceuticals, ElectroCore LLC, eNeura, Epalex, Impel Neuropharma, Mundipharma, Novartis, Pfizer, Sanofi, Santara Therapeutics, Teva Pharmaceuticals, Trigemina Inc., and WL Gore; and personal fees from MedicoLegal work, Massachusetts Medical Society, Up-to-Date, Oxford University Press, and Wolters Kluver; and a patent Magnetic stimulation for headache assigned to eNeura without fee.

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**Supplemental material**

Supplemental material for this article is available online.

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