Nervus Intermedius Symptoms following Surgical or Radiation Therapy for Vestibular Schwannoma

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Abstract

Objectives. This study compares the functional outcomes of nervus intermedius impairment following surgery, radiation, or observation for the treatment of vestibular schwannoma.

Study Design. Retrospective cohort study.

Settings. Tertiary care medical center.

Subjects and Methods. We retrospectively examined 141 charts of patients with a vestibular schwannoma seen in the Dartmouth-Hitchcock Acoustic Neuroma Clinic between 2012 and 2014. Seventy-one patients underwent intervention (including radiation) as their primary treatment, and 70 were treated with observation. As part of routine care, patients were interviewed at clinic visits and with a questionnaire assessing nervus intermedius impairment.

Results. At presentation, 25 patients (19%) reported nervus intermedius impairment. Most common disturbances were xerophthalmia (dry eyes, 13%) and dysgeusia (taste alteration, 7.6%). Postintervention, 35 patients (53%) had symptoms of nervus intermedius dysfunction, which is increased in comparison with patients in the observation group (17 patients, 26.5%, \(P < .05\)). Twelve intervention patients had symptoms resolve postoperatively, making no long-term difference between the observation and intervention groups \(P = .20\). Motor function of the facial nerve postoperatively is correlated with nervus intermedius symptoms. Surgical approaches were compared with radiation therapy, and no significant difference in nervus intermedius outcomes was found.

Conclusion. This study demonstrates the clinical importance of monitoring nervus intermedius symptoms, since a high percentage of all patients undergoing intervention will be symptomatic during management. Patients with motor dysfunction are at a higher risk of developing nervus intermedius sequelae and need close follow-up. Although impairment is common, many symptoms will improve over time with no long-term difference between intervention patients and those under observation.

Keywords

nervus intermedius, vestibular schwannoma, radiosurgery, acoustic, neuroma surgery, intermediate nerve, facial nerve, Wrisberg nerve

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The nervus intermedius (NI), also known as the nerve of Wrisberg, carries parasympathetic secretomotor fibers, special sensory, and somatic sensory fibers that are critical for lacrimation, salivation, and taste. It is typically a component of the facial nerve proximal to the geniculate ganglion, but its distal course may be more variable. In 1 study, the NI joined CNVIII 92% of the time and was adherent to CNVIII for the entire course throughout the posterior fossa in 20% of patients.1 Due to the variable anatomic location of the NI, it is at risk of being compromised during otologic and neurotologic procedures.

Compared with hearing loss and facial motor function, NI symptoms receive relatively little attention and are often neglected when patients are counseled about management. Pre- and posttreatment NI dysfunction has been demonstrated in several studies focusing on either surgical or radiation therapy. Park et al reviewed patients following Gamma Knife radiation treatment and found 18% with preoperative dysfunction and 22% with new dysfunction posttreatment.2 Irving et al performed a retrospective review of patients treated surgically and found 18% with preoperative dysfunction and 22% with new dysfunction posttreatment.2 Their study showed 44% of patients with postoperative paroxysmal

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lacrimation, 72% of patients with reduction of tears, and 48% of patients with dysgeusia when treated surgically. However, there has been no direct comparison between surgical approaches and radiation treatment modalities.

In this study, we evaluated pre- and posttreatment lacrimation (including xerophthalmia and paroxysmal lacrimation), salivation, and taste changes in patients treated with observation, surgery (middle fossa, retrosigmoid, and translabyrinthine approaches), and radiation to compare the effect of treatment approaches on NI outcomes.

**Methods**

The institutional review board at Dartmouth-Hitchcock Medical Center approved this study. A retrospective review was performed of 141 consecutive patients with a vestibular schwannoma (new diagnoses and follow-up care) at a tertiary care center between 2012 and 2014. Seventy-one patients received intervention, and 70 were observed for tumor progression. Five patients were excluded from the intervention group: 1 for incorrect diagnosis, 1 for history of intervention, and 3 for lost follow-up. Six patients were excluded from the observation group: 2 for deciding to pursue intervention elsewhere during the follow-up period and 4 for incomplete follow-up. Patients undergoing an intervention during the study period were included in the appropriate intervention group. A small proportion of patients were previously being observed, and their observation data were not included. Data were collected retrospectively by reviewing patient charts as well as questionnaire results. The questionnaire was supplemental to routine questioning of NI symptoms at visits. It was administered at presentation and at most follow-up appointments.

**Treatment**

Patients managed with an observation approach were compared with those who received treatment with radiation therapy or surgical management. Patient characteristics are provided in Table 1. The surgical patients were further subdivided into middle fossa, retrosigmoid, and translabyrinthine approaches. Surgical patients were combined for comparison with the radiation and observation groups due to small sample sizes.

**Outcome Measures**

Pre- and postoperative NI dysfunction was compared with a questionnaire administered at the time of the initial visit and at subsequent follow-up visits as part of routine care. The questionnaire monitored changes in eye symptoms (xerophthalmia or paroxysmal lacrimation), taste changes or dry mouth, and total number of symptoms. Additional chart review provided supplemental information about NI symptoms. Secondary outcomes in this study included facial nerve function and tumor size as measured with the House-Brackmann (HB) scoring system and magnetic resonance imaging, respectively.

**Statistical Analysis**

Descriptive statistics were used to characterize NI dysfunction in patients receiving different therapeutic interventions. The percentage of patients with positive findings was calculated in each group (ie, observation, surgery, and radiation). Statistical significance of symptoms in each subgroup was determined by Fisher’s exact test, 2-sample t test, and 1-way analysis of variance when appropriate. Multivariable logistical regression was performed with Stata 14.0 (SAS Institute Inc, Cary, North Carolina). Each intervention was compared with the observation subgroup, and risk was determined with odds ratio. An a error of \( P < .05 \) was considered statistically significant.

**Results**

This study involved 130 unique patients who met inclusion criteria, including 61 men (47%) and 69 women (53%). Sixty-seven patients (51%) had tumors on the left and 63 (49%) on the right. Sixty-six patients received intervention, and 64 were observed. The mean age of presentation is 57.2 (range, 22-88 years), and the mean follow-up for radiation and surgery was 3.75 and 2.6 years, respectively (ranges, 0.21-7 and 0.25-7 years; \( P = .15 \)). The surgical patients were further subdivided into a middle fossa approach (21%,
n = 12), a retrosigmoid approach (63%, n = 36), and a translabyrinthine approach (16%, n = 9). There was no difference among groups for age, sex, laterality, symptoms at presentation, or length of follow-up (Table 1). The patients treated with a surgical approach had on average a larger tumor size at presentation than the observation group. The study was underpowered when surgical approaches were analyzed individually, so analysis was done by comparing the entire surgical group with the radiation or observation group. Fifty-three percent of the intervention group reported NI symptoms during management, whereas only 27% of the observation group noted abnormalities. Of all the patients with postintervention symptoms, 7 had preoperative symptoms that persisted or worsened. The odds ratio for experiencing NI symptoms among patients undergoing treatment was 3.12 as compared with the observation group, which reaches statistical significance with a 95% confidence interval of 1.49 to 6.5 (P < .05). Xerophthalmia (dry eyes) was the most common disturbance, accounting for 36% of the combined intervention groups and 20% of the observation group (P < .05). Dysgeusia was the next most common abnormality, involving 28% of the intervention patients and 11% of the observation patients (P < .05). Paroxysmal lacrimation (including crocodile tears) and xerostomia were observed in 7% and 4% of the intervention group, respectively, whereas these impairments were not seen in the observation group (P < .05 and P = .20). Subgroup analysis was also performed by treatment approach to compare outcomes in the surgical and radiation therapy groups (see Table 2).

A comparison of outcomes of NI function between the radiation and surgical groups found no overall difference in the proportion of patients with individual symptoms or any symptoms of NI impairment in general. Interestingly, the paroxysmal lacrimation group showed the greatest difference, with higher rates in the radiation group (P = .07).

**Pre- and Postintervention Comparison**

In those patients undergoing intervention, a pre- and postintervention comparison was performed to assess development of nerve dysfunction with therapy. Eight patients (12%) presented with pretreatment symptoms. Of these patients, 1 had symptoms resolve postintervention; 3 had stable symptoms; and 4 developed different or additional NI abnormalities. Overall, the percentage of impairment increased from 12% to 53% in the treatment group (odds ratio, 7.7; P < .05). Subgroup analysis was performed on each symptom (xerophthalmia, dysgeusia, paroxysmal lacrimation, and xerostomia). All demonstrated significant changes, with the exception of xerostomia.

Many patients reported resolution of NI impairment during the follow-up period. Twelve patients (45%) with xerophthalmia reported improvement, and 8 patients (47%) with dysgeusia noted resolution by the end of the follow-up period. Paroxysmal lacrimation was the least likely symptom to improve, showing resolution in only 1 patient (20%). Twelve patients reported complete resolution of all NI impairment. A comparison of the long-term NI outcomes between the intervention group and the observation group showed no significant difference in patients with dysfunction (P = .20).

**Relationship of Symptoms with Treatment Approach**

The rate of NI impairment in the surgical intervention group was 12% upon presentation and 54% after intervention, with an odds ratio of 8.5 (95% confidence interval, 4.04-22.1, P < .001). Xerophthalmia and dysgeusia were the 2 most frequent complaints in the surgical intervention group, as portrayed in Figure 1.

Eleven percent of the radiation group displayed NI dysfunction upon presentation, and 44% had impairment postradiation therapy. Specifically, dysgeusia and paroxysmal lacrimation (crocodile tears) were the most common symptoms affected by the radiation therapy with an odds ratio for total symptoms of 4.8. In the postradiation patients, no significant change (P = .22) was observed as compared with pretreatment symptoms.

At the most recent follow-up appointment, 50% of symptomatic patients in the radiation group had resolution of all symptoms, whereas 38% of the surgery group reported complete resolution (P = .47). These changes are illustrated in Figure 2.

**Relationship with Motor Dysfunction**

The mean HB grade was higher in the NI dysfunction group (2.66) when compared with patients without evidence of dysfunction (1.42). There was a strong correlation between

### Table 2. Patients with Nervus Intermedius Symptoms by Treatment Group.

<table>
<thead>
<tr>
<th>Therapy, n (%)</th>
<th>Radiation</th>
<th>Surgical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xerophthalmia</td>
<td>1 (11)</td>
<td>22 (38)</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>3 (33)</td>
<td>16 (28)</td>
</tr>
<tr>
<td>Paroxysmal lacrimation</td>
<td>2 (22)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Xerostomia</td>
<td>0 (0)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Any nervus intermedius symptoms</td>
<td>4 (44)</td>
<td>31 (54)</td>
</tr>
</tbody>
</table>
HB grade and the proportion of patients with NI symptoms ($P < .001$). In a multivariate analysis of tumor size, treatment approach (radiation, observation, and surgery), and HB grade (1-2 or $>2$), only HB scores independently predicted NI symptoms. Figure 3 displays the correlation of motor and NI symptoms.

**Relationship of Symptoms with Tumor Size**

The surgery group had overall larger tumors (15.1 mm) than the observation group (10.2 mm; $P < .05$). There was significant variability in tumor size within groups (see Figure 4); therefore, no difference was seen with the tumor size of the radiation therapy patients (14.2). Patients were assigned to 4 groups based on tumor size (<10 mm, 10 to <20 mm, 20-30 mm, $>30$ mm). There was no correlation between tumor size and presence of NI symptoms in the postintervention group (see Table 3). However, there was a noticeable trend in terms of nervus impairment and tumor size regardless of treatment strategy. With multivariate analysis to control for HB grade and treatment approach, there was no significant correlation between tumor size and NI symptoms ($P = .12$).

**Discussion**

Hearing and facial motor outcomes are frequently reported and discussed in conjunction with vestibular schwannoma management, while NI outcomes are often overlooked. A substantial proportion of both the intervention group (53%) and the observation group (27%) experienced NI impairment at some point in their care. NI symptoms have been described and are common in vestibular schwannoma patients, but there are no current comparisons by treatment approach or longitudinal analysis.

In our study, the intervention group was analyzed according to approach (surgical vs radiation therapy) and compared with a control group of patients undergoing observation. We found that intervention in general is a risk factor for NI impairment, with an odds ratio of 3.12 ($P = .002$). Surgical patients had the highest rates of dysfunction and showed the largest change when compared with symptoms at...
presentation, with an odds ratio of 8.5 ($P < .001$). These high rates of dysfunction underscore the importance of discussing NI impairment with surgical patients preoperatively. This surgical data compared well to the literature. Stripf et al reviewed the influence of surgical approach on NI outcomes and found an overall rate of impairment near 50%. Similarly, 44% of patients treated with radiation therapy in our study experienced some NI impairment, which is consistent with the 36% observed by Park et al. There was an odds ratio of 4.8 ($P = .22$) when the pre- and postradiation patients were compared. The radiation group is underpowered, and we were unable to show radiation therapy as an independent risk factor.

Not surprising, facial paresis was more common in the NI impairment group as compared with the asymptomatic group. Stripf et al also showed a strong correlation between patients with motor involvement and NI symptoms. There was a trend between NI symptoms and tumor size but no correlation between different treatment approaches. When multivariate analysis is performed to account for tumor size, treatment approach, and HB grade, the most important factor affecting NI outcome is HB grade.

Individual symptoms assessed included xerophthalmia, dysgeusia, abnormal lacrimation, and xerostomia. In our study, we found xerophthalmia and dysgeusia to be the most common symptoms, but this may be influenced by the data collection format. A review of the literature demonstrates a wide range of postintervention NI symptoms. Xerophthalmia has been reported as 10% to 72%, with the higher numbers reported by surgical intervention groups. Similarly, dysgeusia is reported in the literature as ranging from 10.6% to 48%, with the higher values once again attributed to surgical treatment options. Additional symptoms studied include paroxysmal lacrimation (10%-45%), xerostomia (6.2%), and rhinorrea (2%-44%), which all are consistent with our findings.

Our study is the first to follow NI symptoms after an intervention and report the changes of these symptoms over time. The symptoms of xerophthalmia and dysgeusia often resolved during follow-up. Gold weight placement and other lid correction surgeries may have contributed to improvement in ocular symptoms. Overall, 34% of patients who experienced NI dysfunction after an intervention reported total resolution of symptoms. Although the percentage of patients with NI symptoms at the last follow-up was still higher in the intervention group than the observation group, long-term rates of impairment were not statistically significant between these groups. This is an important finding, as it demonstrated that NI impairment after an intervention is most likely temporary and these patients do equally well as the observation group over time.

Limitations and Future Directions

There are some limitations to this study. This is a retrospective study based on chart review and a subjective nonvalidated questionnaire. This eliminates the presence of recall bias; however, limited data were included from the survey about paroxysmal lacrimation, rhinorrhea, and xerostomia. There was also no control group of otologic patients without vestibular schwannomas to compare symptoms that may not actually be related to the NI pathology (eg, dysgeusia).

The relatively small sample size of the radiation group significantly limits meaningful comparisons of outcomes. We were not able to demonstrate radiation therapy as an independent risk factor for NI impairment. In the future, we plan to further elucidate if radiation therapy is an independent risk factor for the development of NI impairment by expanding the current study to a larger patient group. Likewise, longer-term follow-up would allow for better delineation of symptoms over time.

Conclusions

This study demonstrates the clinical importance of monitoring NI impairment associated with management of vestibular schwannoma, since more than half of all patients undergoing treatment will experience NI symptoms. Posttreatment NI impairment correlates with motor function of the facial nerve. Surgical intervention and radiation therapy both have potential risk for NI dysfunction, and it is therefore important
to have an informative preoperative discussion. Patients are more likely to develop dysfunction in the surgery group, although overall outcomes were similar between patients undergoing radiation therapy and surgical intervention. Many patients with NI impairment resolve with time. In fact, there was no statistical difference of long-term outcomes between the intervention and observation groups.

**Author Contributions**

Kathryn Y. Noonan, design of work; acquisition, analysis, and interpretation of data, drafting/editing manuscript; Cong Rang, acquisition, analysis, and interpretation of data, drafting/editing manuscript; Katherine Callahan, acquisition of data, editing manuscript; Nathan E. Simmons, conception of idea, editing of manuscript; Kadir Erkmen, conception of idea, editing of manuscript; James E. Saunders, conception of idea, design of study, interpretation of data, editing/revising of manuscript.

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