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# Profound hearing loss following surgery in pediatric patients with posterior fossa low-grade glioma

**Yahya Ghazwani, Ibrahim Qaddoumi, Johnnie K. Bass, Shengjie Wu, Jason Chiang, Frederick Boop, Amar Gajjar, and Zsila Sadighi**

*Department of Oncology, St. Jude Children's Research Hospital, 262 Danny Thomas Place MS 260, Memphis, TN 38105, USA (Y.G., I.Q., A.G.); Rehabilitation Services, St. Jude Children's Research Hospital, 262 Danny Thomas Place MS 113, Memphis, TN 38105, USA (J.K.B.); Department of Biostatistics, St. Jude Children's Research Hospital, 262 Danny Thomas Place MS 723, Memphis, TN 38105, USA (S.W.); Department of Pathology, St Jude Children's Research Hospital, Memphis, TN 38105, USA (J.C.); Department of Neurosurgery, University of Tennessee Health Science Center, Memphis, TN 38163, USA; Le Bonheur Neuroscience Institute, Le Bonheur Children's Hospital, Memphis, TN 38105, USA; Semmes Murphey Neurologic and Spine Institute, Memphis, TN 38120, USA; and Division of Neurosurgery, St Jude Children's Research Hospital, Memphis, TN 38105, USA (F.B.); Department of Pediatric Medicine, Division of Neurology, St. Jude Children's Research Hospital, 262 Danny Thomas Place MS 135, Memphis, TN 38105, USA (Z.S.)*

**Corresponding Author:** Zsila S. Sadighi, MD, Department of Pediatric Medicine, Division of Neurology, St. Jude Children's Research Hospital, 262 Danny Thomas Place MS 135, Memphis, TN 38105, USA (zsila.sadighi@stjude.org).

**Abstract**

**Background:** Hearing loss may occur in patients with posterior fossa low-grade glioma who undergo surgery.

**Methods:** We retrospectively reviewed 217 patients with posterior fossa low-grade glioma, including 115 for whom results of hearing tests performed after surgery and before chemotherapy or radiation therapy were available. We explored the association of UHL with age at diagnosis, sex, race, tumor location, extent of resection, posterior fossa syndrome, ventriculoperitoneal shunt placement, and histology.

**Results:** Of the 115 patients, 15 (13.0%: 11 male, 6 black, 8 white, 1 multiracial; median age 7 years [range, 1.3–17.2 years]) had profound UHL after surgery alone or before receiving ototoxic therapy. Median age at tumor diagnosis was 6.8 years (range, 0.7–14.1 years), and median age at surgery was 6.8 years (range, 0.7–14.1 years). Patients with UHL had pathology characteristic of pilocytic astrocytoma (n = 10), ganglioglioma (n = 4), or low-grade astrocytoma (n = 1). Of these 15 patients, 4 underwent biopsy, 1 underwent gross total resection, 1 underwent near-total resection, and 9 underwent subtotal resection. UHL was more frequent in black patients than in white patients (OR 7.3, $P = .007$) and less frequent in patients who underwent gross total resection or near-total resection than in those who underwent subtotal resection (OR 0.11, $P = .02$).

**Conclusions:** Children undergoing surgery for posterior fossa low-grade glioma are at risk for UHL, which may be related to race or extent of resection. These patients should receive postoperative audiologic testing, as earlier intervention may improve outcomes.

**Key words**

hearing loss | low-grade glioma | pediatric | posterior fossa | surgery

Low-grade gliomas are the most common brain tumors in children and are most often located in the posterior fossa.[1–4] Cerebellar low-grade gliomas are the most amenable to resection, and children with these tumors have 10-year survival rates of 90% or higher; the rare tumor recurrences can be cured by gross total resection alone.[5–9] Resection is the initial treatment of choice when surgery is feasible. However, when gross total resection of a tumor would produce unacceptable sequelae, as in the case of a tumor located in the brainstem, surgery may be limited to biopsy

or subtotal resection. The optimal treatment after incomplete resection of a tumor or for patients who experience tumor progression after surgery remains uncertain; both radiation therapy and chemotherapy may be effective. Some studies have shown an improvement in progression-free survival with adjuvant postoperative radiation therapy, whereas other studies have shown no such improvement.[6,10–13] Adjuvant chemotherapy is preferable for children with incompletely resected or progressive low-grade glioma because such treatment can delay the initiation of radiation therapy and its associated toxicity.[14–22]

Hearing loss may be a neurotoxic sequela of the conventional chemotherapy and radiation therapy used to treat low-grade gliomas.[23–26] Surveillance with audiologic assessments for patients receiving ototoxic chemotherapy or radiation has become the standard of care for these patients, but such surveillance is not routinely performed for patients treated with surgery alone. Unfortunately, surgery for pediatric low-grade glioma is also not without long-term cognitive, medical, and neurologic consequences.[27,28] Hearing loss secondary to tumor invasion or surgical damage to the vestibulocochlear nerve (cranial nerve [CN] VIII) has been reported, albeit rarely, in children with posterior fossa tumors.[29–35]

Despite the excellent prognosis of pediatric posterior fossa low-grade glioma, it is important to recognize that neurologic consequences such as hearing loss after surgery alone may affect the patient's overall quality of life. We present the first large study of pediatric patients with posterior fossa low-grade glioma who developed hearing loss after undergoing surgery but before receiving ototoxic chemotherapy and radiation therapy, and we identify potential risk factors for this development.

## Materials and Methods

### Data and Study Population

After obtaining Institutional Review Board approval, we retrospectively reviewed 217 patients with posterior fossa low-grade glioma for unilateral hearing loss (UHL) that was diagnosed at our institution between 1985 and 2015. The tumors were categorized by their location as cerebellar, brainstem, cerebellar and brainstem, midbrain extending to the lower brainstem and/or cerebellum, or cervicomedullary. The age at tumor diagnosis was defined as the age on the day of upfront surgery or on the day of imaging diagnosis if no initial surgery was performed. The age at initial surgery was obtained from medical records. The date of the audiologic assessment by which hearing loss was first identified was used to calculate the age at onset of hearing loss. UHL was defined as any hearing loss in one ear that was sensorineural or neural in nature. Patients with a history of hearing insults that could account for their hearing loss before tumor treatment were excluded. Otoscopy and tympanometry were performed on every patient to determine the status of the outer ear canal, tympanic membrane, and middle ear cavity. Audiologic assessments were obtained via evoked auditory brainstem responses or behavioral pure-tone audiometry (at 0.25, 0.5, 1, 2, 3, 4, 6, and 8 kHz), depending on the patient's age and development. The severity of UHL was measured in accordance with Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Hearing loss was present if there was UHL of CTCAE grade ≥1, based on audiograms at 1, 2, 3, 4, 6, and 8 kHz. The hearing loss was graded from 1 to 4 as follows: grade 1: threshold shift exceeding 20 dB at 8 kHz in at least one ear; grade 2: threshold shift exceeding 20 dB at 4 kHz or higher in at least one ear; grade 3: hearing loss sufficient to indicate therapeutic intervention (including provision of hearing aids), with a threshold shift exceeding 20 dB at 3 kHz or higher in at least one ear, and additional speech-language–related services indicated; grade 4: audiologic indication for a cochlear implant and additional speech-language–related services indicated.

### Statistical Analysis

Descriptive statistics were obtained for continuous variables, including age at tumor diagnosis, age at surgery, and age at hearing loss. Distributions of sex, race, tumor location at diagnosis, extent of initial resection, tumor histology, tumor grade, BRAF duplication status, $BRAF^{v600E}$ mutation status, placement of a ventriculoperitoneal shunt (VPS), and posterior fossa syndrome were also reported. For the continuous variables, the *t* test was used to compare the differences between patients with normal hearing and those with hearing loss. The chi-squared test or Fisher's exact test was used to test the association of categorical variables with hearing loss. Logistic regression was used to explore the association of hearing loss with age at diagnosis, sex, race, tumor location, posterior fossa syndrome, placement of a VPS, extent of initial resection, histology, BRAF duplication, and $BRAF^{v600E}$ mutation with backward selection. SAS 9.3 version was used for the analyses.

## Results

### Patient and Clinical Characteristics

A total of 115 patients with posterior fossa low-grade glioma for whom hearing test results were available and who had undergone surgery as the initial treatment for their tumor were included in the analysis. Fifteen (13.0%) of the 115 patients had confirmed UHL after undergoing surgery and before receiving any chemotherapy or radiation therapy. Among the 15 patients with UHL at their baseline hearing evaluation, 14 had profound hearing loss (no response observed or CTCAE grade 4) in one ear but normal hearing in the other ear; one patient had severe hearing loss (CTCAE grade 3) in one ear and normal hearing in the other ear. Of the 115 patients with posterior fossa low-grade glioma, 100 (87.0%) had normal hearing or transient conductive hearing loss. Statistical analysis was performed for those patients for whom the results of hearing tests were available, and the descriptive statistics of age at diagnosis, age at surgery, and age at onset of hearing loss are reported, along with the corresponding *P* values, in Table 1. The median time from tumor diagnosis to the hearing exam was 0.3 years (range, 0.01–7.2 years). Surgery

**Table 1** Descriptive statistics of patients with posterior fossa low-grade glioma who underwent surgery and had hearing-test results available (n = 115)

| Variables | Normal hearing | Hearing loss present | *P* value |
|---|---|---|---|
| Patients | 100 (86.9%) | 15 (13.0%) | |
| Median age at surgery, years (range) | 6.4 (0.6–16.8) | 6.8 (0.7–14.1) | |
| Median age at tumor diagnosis, years (range) | 6.1 (0.5–16.8) | 6.8 (0.7–14.1) | |
| Median age at hearing loss, years (range) | | 7.0 (1.3–17.2) | |
| Median time from tumor diagnosis to baseline testing of hearing loss, years (range) | | 0.3 (0.01–7.2) | |
| Median time from baseline hearing test to last follow-up hearing test, years* (range) | | 8.6 (0.7–13.2) | |
| Median severity of baseline hearing loss, CTCAE grade (range) | | 4 (3–4) | |
| Median severity of hearing loss at last follow-up, CTCAE grade (range) | | 4 (1–4) | |
| Sex | | | .1394 |
| Female | 47 (92.2%) | 4 (7.8%) | |
| Male | 53 (82.8%) | 11 (17.2%) | |
| Race | | | .0499 |
| Black | 17 (73.9%) | 6 (26.1%) | |
| White | 80 (90.9%) | 8 (9.1%) | |
| Multiple race | 3 (75.0%) | 1 (25.0%) | |
| Location of tumor | | | .9651 |
| Brainstem | 29 (87.9%) | 4 (12.1%) | |
| Cerebellum | 17 (89.5%) | 2 (10.5%) | |
| Cervicomedullary | 8 (88.9%) | 1 (11.1%) | |
| Midbrain extending to brainstem/cerebellum | 3 (100.0%) | | |
| Brainstem and cerebellum | 43 (84.3%) | 8 (15.7%) | |
| Extent of resection | | | .2920 |
| Biopsy | 22 (84.6%) | 4 (15.4%) | |
| GTR | 31 (96.9%) | 1 (3.1%) | |
| NTR | 8 (88.9%) | 1 (11.1%) | |
| STR | 38 (80.9%) | 9 (19.1%) | |
| Cyst aspiration | 1 (100.0%) | | |
| Posterior fossa syndrome | | | .3731 |
| No | 90 (88.2%) | 12 (11.8%) | |
| Yes | 10 (76.9%) | 3 (23.1%) | |
| Ventriculoperitoneal shunt | | | .8517 |
| No | 82 (87.2%) | 12 (12.8%) | |
| Yes | 18 (85.7%) | 3 (14.3%) | |
| Histology | | | .0836 |
| Diffuse astrocytoma | 7 (100.0%) | | |
| Pilocytic astrocytoma | 83 (89.3%) | 10 (10.8%) | |
| Low-grade astrocytoma | 2 (66.7%) | 1 (33.3%) | |
| Low-grade glioma (not otherwise specified) | 1 (100.0%) | | |
| Low-grade neuroepithelial | 1 (100.0%) | | |
| Ganglioglioma | 6 (60.0%) | 4 (40.0%) | |
| Grade | | | .5921 |
| Unknown | 4 (80.0%) | 1 (20.0%) | |
| 1 | 89 (86.4%) | 14 (13.6%) | |
| 2 | 7 (100.0%) | | |

**Table 1** *Continued*

| Variables | Normal hearing | Hearing loss present | *P* value |
|---|---|---|---|
| BRAF duplication | | | .8953 |
| No | 8 (88.9%) | 1 (11.1%) | |
| Yes | 21 (84.0%) | 4 (16.0%) | |
| NA | 71 (87.7%) | 10 (12.4%) | |
| $BRAF^{v600E}$ mutation | | | .1949 |
| No | 19 (79.2%) | 5 (20.8%) | |
| Yes | 3 (75.0%) | 1 (25.0%) | |
| NA | 78 (89.7%) | 9 (10.3%) | |

*Hearing test at last follow-up available for 14 of the 15 patients with unilateral hearing loss; PF, posterior fossa; LGG, low-grade glioma; CTCAE, Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. (grade 1: threshold shift > 20 dB at 8 kHz in at least one ear; grade 2: threshold shift > 20 dB at 4 kHz and above in at least one ear; grade 3: hearing loss sufficient to indicate therapeutic intervention, including hearing aids, threshold shift > 20 dB at 3 kHz and above in at least one ear, and additional speech-language–related services indicated; grade 4: audiologic indication for cochlear implant and additional speech-language–related services indicated); GTR, gross total resection; NTR, near-total resection (at least 90% of the tumor resected); STR, subtotal resection; NA, not available.

was the initial treatment for 115 patients, being performed at a median age of 6.5 years (range, 0.6–16.8 years). The 15 surgical patients with UHL had undergone their initial surgery at a median age of 6.8 years (range, 0.7–14.1 years), and their hearing loss was diagnosed at a median age of 7 years (range, 1.3–17.2 years).

The patient population included 115 patients (57 female and 74 male) for whom the results of hearing tests were available. UHL was reported in 4 (7.8%) of the 51 female patients and in 11 (17.2%) of the 64 male patients. Three racial groups were identified in the 15 patients with posterior fossa low-grade glioma and UHL: 6 patients (40%) were black, 8 (53.3%) were white, and 1 (6.6%) was multiracial. UHL was found in 8 (15.7%) of 51 patients with tumors in the brainstem and cerebellum, in 2 (10.5%) of 19 patients with cerebellar tumors, in 4 (12.1%) of 33 patients with brainstem tumors, in 1 (11.1%) of 9 patients with cervicomedullary tumors, and in no patients with midline tumors extending to the brainstem and/or cerebellum. Four patients with UHL had tumor involvement of the cerebellopontine angle, and 1 patient had internal auditory canal involvement. The extent of resection in the 15 patients with UHL was as follows: 4 (26.7%) had undergone biopsy, 1 (6.7%) had undergone gross total resection, 1 (6.7%) had undergone near-total resection, and 9 (60.0%) had undergone subtotal resection. A record of the surgical approach was available for all 10 of the patients with UHL who had undergone surgery at our institution; the reported approaches were midline suboccipital (6 cases), retromastoid (2 cases), retrosigmoid (1 case), and an s-shaped incision parallel to C1-C2 (1 case). Twenty-one of the 115 patients had undergone VPS placement, and 3 (14.3%) of these 21 patients had UHL. Posterior fossa syndrome was seen in 13 of the 115 patients; 3 (23.1%) of these 13 had UHL. UHL was seen in patients with the following tumor types: pilocytic astrocytoma (10 patients), ganglioglioma (4 patients), and low-grade astrocytoma (1 patient). Of the 115 patients, the results of BRAF duplication testing were available for 34 (29.6%) patients. BRAF duplication was present in 25 (73.5%) of these 34 patients (4 with UHL and 21 with no hearing loss). The results of $BRAF^{v600E}$ mutation testing were available for 28 (24.3%) of the 115 patients and were positive for the mutation in 1 patient with UHL and in 3 patients with no hearing loss (Table 1).

The results of long-term follow-up hearing tests were available for 14 patients at a median time from their first hearing exam of 8.6 years (range, 0.7–13.2 years). In the original ear with UHL, the hearing loss at long-term follow-up was unchanged in 9 patients, improved in 3 patients, and worse in 1 patient; hearing loss in 1 patient was unchanged in the same ear, but worse in the other ear. Of these 14 patients with long-term follow-up, 11 had experienced recurrences of their tumor requiring additional intervention, including chemotherapy, radiation treatment, or surgery. Hearing assistance devices (ie, frequency modulation systems or contralateral routing of signals [CROS] hearing aids) were recommended for all 15 patients with UHL but were used by only 4 patients (26.6%).

## Hearing Loss and Risk Factor Analysis

We identified risk factors for initial UHL in the patients undergoing initial surgical treatment. We did not assess risk factors for long-term hearing loss, as the patients might have received therapies known to be ototoxic. Of all the variables examined, including age at diagnosis, sex, race, tumor location, posterior fossa syndrome, VPS placement, initial extent of resection, tumor histology, BRAF duplication status, and $BRAF^{v600E}$ mutation status, we found only race and extent of resection to be statistically significantly associated with UHL ($P = .007$ and $P = .02$, respectively). UHL was associated more with black patients than with white patients (OR 7.3, $P = .007$) and less with patients who underwent gross total or near-total resection than with those who underwent subtotal resection (OR 0.11, $P = .02$) (Table 2).

**Table 2** Estimates with odds ratios for risk factors associated with hearing loss

| Analysis of maximum likelihood estimates | | | | | | |
|---|---|---|---|---|---|---|
| Parameter | Estimate | Standard error | *P* value | Odds ratio | 95% CI lower limit | 95% CI upper limit |
| Intercept | −1.3015 | 0.4851 | .0073 | 0.272 | | |
| Sex (female vs male) | −1.1738 | 0.7132 | .0998 | 0.3092 | 0.07641 | 1.2511 |
| Race (black vs white) | 1.9892 | 0.7380 | .0070 | 7.3100 | 1.7209 | 31.0500 |
| Extent of surgical resection | | | | | | |
| Biopsy/cyst vs STR | −0.7443 | 0.7748 | .3367 | 0.4751 | 0.1041 | 2.1690 |
| GTR/NTR vs STR | −2.2413 | 0.9387 | .0170 | 0.1063 | 0.01689 | 0.6693 |
| Biopsy/cyst vs GTR/NTR | 1.4971 | 0.9693 | .1225 | 4.4685 | 0.6685 | 29.8704 |

CI, confidence interval; STR, subtotal resection; GTR, gross total resection; NTR, near-total resection (at least 90% resected); cyst, cyst aspiration.

## Discussion

Although patients with posterior fossa low-grade glioma have excellent survival rates, they may develop UHL after undergoing surgery but before receiving ototoxic therapy, and this deficit may be missed if the hearing of the patient is not tested for many years. Audiologic evaluations are routinely performed on patients receiving radiation therapy or ototoxic chemotherapy, but they are not routinely performed before or after surgery alone. Hearing loss has been reported after surgery in patients with cerebellopontine angle tumors involving CN VIII,[35] but reports of hearing loss in patients with other posterior fossa tumors after surgery are rarely cited.[27,29–32] To our knowledge, this is the first report of a large cohort of pediatric patients with posterior fossa low-grade glioma, and we have shown that some of these patients are at risk for profound UHL based on their race and the extent of surgical resection of their tumor if surgery is the primary treatment, even before they receive ototoxic chemotherapy or radiation therapy.

The 13.0% prevalence of UHL in our study is similar to that found in other, broader cancer studies. Turner et al. described hearing loss as a late effect in survivors of cortical and cerebellar low-grade glioma who were treated with surgery alone, although it was found in less than 5% of their patients at last follow-up.[27] Swiss researchers reported that long-term auditory complications in 10% of childhood cancer survivors were associated with platinum compounds, radiation therapy, and brain surgery (OR 2.2, $P = .001$),[36] as compared to 5% in a United States study of childhood cancer survivors.[37] One of our patients in whom profound UHL was diagnosed postoperatively experienced progressive improvement in this hearing, as measured at follow-up assessments, until almost normal function was restored, but this phenomenon is rare, and the only previous cases of such improvement after surgery might have been related to a decrease in mass effect over time.[38]

UHL was found in 4 of our patients with tumors involving the cerebellopontine angle and in 1 patient with a tumor involving the internal auditory canal. Knowing that the location of surgically treated posterior fossa tumors is related to hearing loss, eg, whether the tumor is in the cerebellopontine angle or cerebellum with or without involvement of the internal acoustic canal,[29,33,34,38–43] we omitted these patients from our analysis regarding tumor location and still did not find tumor location to be a statistically significant risk factor for UHL in patients with posterior fossa low-grade glioma. In contrast, one study of long-term survivors of low-grade glioma showed the surgically treated cerebellar tumors to be associated with more severe hearing loss when compared to tumors located in the central midline or brainstem.[39] We did not find tumor histology or BRAF fusion or $BRAF^{v600E}$ mutation status to be significant risk factors for UHL. In one study, however, hearing loss did vary according to tumor histology and was significantly worse in patients who had undergone resection of vestibular schwannomas than in those who had undergone resection of meningiomas in the cerebellopontine angle.[43]

Surgical damage to CN VIII may occur during surgery as a result of the vascular compromise of structures surrounding the nerve or of the nerve itself, or as a result of mechanical injury caused by stretching, compression, dissection, or heat injury. Depending on the approach used during temporal bone drilling, the cochlea can also be significantly damaged, as can the internal auditory nerve and/or internal auditory artery. Given the limited number of operative reports available for review and the small number of patients with UHL in our study, we were unable to assess fully the surgical approach as a risk factor. However, researchers have recommended the middle cranial fossa and retrosigmoid approaches as the best options for avoiding hearing loss.[43,44]

We found that patients with posterior fossa low-grade glioma had a lower risk of UHL after undergoing gross total or near-total resection than after undergoing subtotal resection. There may be some referral bias at our institution regarding the extent of resection, given that we used retrospective data from patients of whom only a limited number actually had surgery at our institution. The extent of resection may be predicted by neurosurgeons with the aid of diffusion tensor imaging (DTI) tractography. Exophytic tumors with intact fascicles on DTI are more amenable to gross total resection, whereas tumors infiltrating or displacing the fascicles on DTI have a lower probability of

total resection and are more likely to be biopsied.[45] Further reductions in CN VIII damage may be achieved with newer methods of intraoperative monitoring by using the brainstem auditory evoked potentials, electrocochleography, and compound nerve action potentials of the cochlear nerve.[46] Intraoperative monitoring of CN VIII had not been used with any of our patients.

We found no statistical correlation between VPS placement and UHL. This is consistent with the findings of the Swiss Childhood Cancer Survivor Study,[36] despite multiple studies showing an associated risk of rapid changes in intracranial pressure as a result of hydrocephalus or shunting affecting cochlear physiology, which may cause hearing loss.[26,47–54] However, as we lack detailed information on changes in intracranial pressure, we may be underestimating their impact.

In addition to the extent of surgical resection, we found race to be a significant risk factor for UHL in patients who had undergone surgery for posterior fossa low-grade glioma. Black patients with such tumors had a higher risk of UHL than did patients of other ethnicities, which is consistent with reports of black children having a prevalence of UHL that is higher than that in the general population.[55] Although not statistically significant, there was a trend in our study for female patients to be less likely than male patients to have UHL. It has even been reported specifically that black boys have a higher prevalence compared with other groups in the general population of individuals with hearing loss.[56] In adults, men, non-Hispanic whites, and non-Hispanic Asians have a higher prevalence of hearing loss when compared to other groups.[57] However, a study of adolescents found no difference between ethnic groups, whereas female patients were less likely than male patients to have hearing loss.[58]

Although we found race and extent of resection to be potential risk factors for UHL, this was a retrospective study, and the sample size for patients with UHL was limited. Furthermore, as baseline preoperative hearing-test results were not available for all patients, pre-existing hearing loss could not be ruled out completely, and host institutional referral patterns might have affected the outcomes. Neurocognitive data became available for many of our patients at long-term follow-up; however, we could not adequately assess in a retrospective manner the impact of UHL alone on long-term neurocognitive, educational, or quality-of-life outcomes because many of the patients had subsequently received ototoxic therapies in response to recurrences. Nevertheless, UHL in children and adolescents is associated with negative effects on speech, language development, and school performance, along with a trend toward worse cognitive scores, and individuals may have poorer self-perceived quality of life.[59–61] These deficits may be related to impaired sound localization and binaural summation making receptive listening difficult in the presence of background noise.[61–63] Studies suggest that earlier intervention in children with UHL is beneficial because younger children derive better bilateral benefit from sound localization with hearing aids than do adolescents, who actually experience bilateral interference from sound localization with hearing aids in place.[64] Early detection and intervention with speech therapy or individualized education plans may improve oral language and verbal IQ scores over time. Aural rehabilitation of patients with UHL can be achieved with CROS hearing aids, bone conduction implants, or cochlear implants, which several of our patients required; these devices may improve speech recognition in both quiet and noisy conditions.[65–68] Our results suggest the need for heightened awareness in the pediatric and neurosurgical communities of the importance of postoperative audiologic testing in posterior fossa low-grade glioma patients treated with surgery alone. We have also provided the basis for a prospective trial with preoperative, postoperative, and routine follow-up hearing assessments, along with early aural intervention for those with UHL, to assess the long-term neurocognitive, educational, and quality-of-life outcomes.

## Conclusion

Because pediatric patients with posterior fossa low-grade glioma are at risk for UHL after undergoing surgery alone and before receiving ototoxic therapy and because race and the extent of surgery might be risk factors for UHL, the astute clinician should order early routine hearing testing for these patients before and after surgery and implement early intervention with aural rehabilitation where necessary. The early detection of postoperative UHL may prompt the modification of adjuvant therapies to reduce the risk of further hearing loss in the good ear, for example, by avoiding platinum-based agents or reducing radiation doses to the contralateral cochlea. Earlier detection and intervention may decrease the risk of adverse outcomes. Future prospective clinical trials in patients with posterior fossa low-grade glioma that include hearing tests conducted before and after surgery and routine follow-up hearing tests with auditory interventions may help to assess the long-term neurocognitive outcomes, speech development, educational attainment, and quality of life in these patients.

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