Clinical course of vestibular schwannoma in pediatric neurofibromatosis Type 2

Clinical article

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Object. Neurofibromatosis Type 2 (NF2) is an autosomal-dominant inherited disease, characterized by multiple neoplasia syndromes, including meningioma, schwannoma, glioma, and ependymoma. In this report, the authors present their clinical experience with pediatric NF2 patients. In particular, they focused on the clinical course of vestibular schwannoma (VS), including the natural growth rate, tumor control, and functional hearing outcomes.

Methods. From May 1988 to June 2012, the authors recruited patients who were younger than 18 years and fulfilled the Manchester criteria. In total, 25 patients were enrolled in this study. The authors analyzed the clinical course of these patients. In addition, they measured the natural growth rate of VS before any treatment in these children with NF2. Then, they evaluated the tumor control rate and functional hearing outcomes after the treatment of VS.

Results. The mean age at the onset of NF2-related symptoms was 9.9 ± 4.5 years (mean ± SD, range 1–17 years). The mean age at the diagnosis of NF2 was 12.9 ± 2.9 years (range 5–17 years). The mean follow-up period was 89.3 months (range 12–311 months). As initial manifestations, nonvestibular symptoms were frequently observed in pediatric patients with NF2. The mean natural growth rate of VS was 0.33 ± 0.41 cm³/year (range 0–1.35 cm³/year). The tumor control rate of VS was 35.3% at 3 years after Gamma Knife surgery (GKS). The actuarial rate of useful hearing preservation was 67% in the 1st year and 53% in the 5th year after GKS.

Conclusions. Clinical manifestations in children with NF2 were highly variable, compared with their adult counterparts. The natural growth rate of VS in children is slow, and this oncological feature may explain the diverse clinical manifestations besides vestibular symptoms in children with NF2. The treatment outcome of GKS for VS in children with NF2 was not favorable compared with previous reports of affected adults.

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KEY WORDS • neurofibromatosis • schwannoma • growth rate • Gamma Knife surgery • pediatric • oncology

Neurofibromatosis Type 2 (NF2) is an autosomal-dominant inherited disease, characterized by multiple neoplasia syndromes of the central nervous system (CNS) or the peripheral nervous system (PNS). Meningioma, schwannoma, glioma, and ependymoma are representative of NF2-associated tumors. This disorder results from a mutation in the NF2 tumor sup-pressor gene on 22q12, which encodes a 595–amino acid protein called Merlin or Schwannomin.

The diagnostic prevalence of NF2 has recently been reported as 1 case in 25,000–100,000 persons. This prevalence is now increasing because of advanced detection with modern imaging techniques and improved survival due to improvements in treatment. Nevertheless, NF2 is a devastating disorder that requires a lifetime of ongoing treatments, including surgery, Gamma Knife surgery (GKS), radiotherapy, and chemotherapy, due to tumor occurrence throughout the body.

There are several reports regarding the natural
history or treatment outcomes of adult patients with NF2. However, only a few series have been reported for pediatric patients with NF2. Moreover, the standard managing protocol for NF2 in children is as a controversial issue as ever.

In this report, we present our clinical experiences with pediatric NF2 patients with vestibular schwannomas (VSs). Outcomes of interest are 1) natural growth rate of the lesions during preintervention period, 2) tumor control rate with GKS, and 3) hearing preservation rate with GKS.

Methods

Patient Population

From May 1988 to June 2012, we searched for pediatric patients younger than 18 years who presented to our institution and fulfilled the Manchester criteria for the diagnosis of NF2. The Manchester criteria are some of the most sensitive diagnostic criteria, and these criteria are the most widely used for diagnosis of NF2. Patients who had a follow-up period of less than 1 year were excluded.

Based on Manchester criteria, we found 25 patients (48 VSs) who fulfilled the NF2 diagnosis with more than 1 year of follow-up. Twenty-three patients were treated with neurosurgical interventions, such as surgery, GKS, or radiotherapy. The other 2 patients underwent clinical follow-up but did not received any neurosurgical interventions. We retrospectively reviewed the medical records and radiological findings of these 25 patients in detail. This clinical study was approved by the institutional review board of the Seoul National University Hospital.

Image Analysis for Measuring the Natural Growth Rate of VS

We measured the natural growth rate of VS in pediatric patients with NF2 during the observation period before any treatment (microsurgery or GKS) for VS. All but 1 patient had bilateral VSs during the diagnostic or follow-up periods. Among 48 VSs, we excluded VSs that had less than 2 years of an observation period before the treatment, those fused with other cranial nerve schwannomas, and those that had poor image quality. Thus, a total of 26 VSs in 17 patients were used for the natural growth rate measurements (Fig. 1A). In detail, 11 VSs were subsequently treated (1 VS was treated with microsurgery followed by GKS and 10 VSs were treated with only GKS) with more than a 2-year observation period and 15 VSs have been observed without any treatment until now. The mean observation period of these 26 VSs was 45.2 ± 22.5 months (mean ± SD, range 24–96 months).

We reviewed all of the MR images obtained during the pretreatment period. The T1-weighted axial images with gadolinium enhancement were used for volume measuring. Because the MR images were differently obtained using a 1.0-, 1.5-, or 3.0-T magnet and the thickness of the slices varied case by case, the volume of each VS was calculated as follows for accurate measuring (trace method): we measured the surface area of every T1-weighted axial image with gadolinium enhancement of the VS by drawing a region of interest (ROI). The area of the ROI was automatically calculated through our hospital’s picture archiving and communication system (PACS; Marosis, Infinitt Healthcare Co., Ltd.). This surface area was multiplied by the interval space thickness between each cut, and finally the volume of the VS was calculated by summing all of these values as follows:

\[
\text{Tumor volume} = t \times \sum S_n
\]

where \(t\) = the slice thickness, \(f\) = the first tumor slice, \(l\) = the last tumor volume, and \(S_n\) = the ROI area on each slice. The mean growth rate of VS was estimated using simple linear regression of the VS volume over the full follow-up period before any treatment as previously described.

Evaluation of Tumor Control Rate After GKS for VS in Children With NF2

We evaluated the tumor control rate of the VS treated by GKS over more than 3 years of follow-up after GKS. Of the 24 VSs that were treated, 17 VSs had more than 3 years of follow-up (Fig. 1B). The mean follow-up period of these 17 VSs was 72 ± 26.8 months (range 36–127 months).

We defined tumor regression as decrease in tumor volume. Stable tumor was defined as tumor volume 100%–110% of the pre-GKS volume. Tumor progression was defined as growth of more than 10% in volume after GKS or consequent microsurgery due to tumor growth. The tumor control state was defined as tumor regression or stable tumor state after GKS.

Measurement of Hearing Function of Patients After Neurosurgical Management

To evaluate the functional hearing outcome after the treatment, the patients were selected as follows. A total of 24 VSs in 17 patients were treated; 18 VSs were treated with GKS only, and 6 VSs were treated with microsurgery and GKS (Fig. 1B). For these patients, otological examinations, including pure tone audiometry (PTA) and speech discrimination, were performed before and after the treatment. The Gardner-Robertson class was used as a functional hearing scale. Gardner-Robertson Classes I and II are considered useful hearing. Classes III and IV are nonserviceable and poor, respectively. Class V represents deafness. The evaluation of hearing preservation for the microsurgery group was not appropriate because all patients except one had nonuseful hearing function prior to their operations (Gardner-Robertson Class V in 3 VSs, Class III in 2 VSs, and Class I in 1 VS). One patient who had preoperative ipsilateral (treated side) Gardner-Robertson Class I hearing function was not evaluated for postoperative PTA after microsurgery. Thus, the evaluation of the hearing preservation rate was limited to the GKS group.

Of the 24 treated VSs, only the 11 VSs with a preraspidual ipsilateral useful hearing capacity were used to analyze the hearing preservation rate through the Kap-
Statistical Analysis

Statistical analysis was performed using a commercial software program (SPSS, version 18.0, IBM Co.). The simple linear regression was used for estimating growth rate of VS. The Mann-Whitney U-test was used for comparing the growth rate by variables. The useful hearing preservation rate after GKS was analyzed using the Kaplan-Meier survival method. Probability values < 0.05 were regarded as statistically significant.

Results

Clinical Characteristics of Pediatric Patients With NF2 and Treatment for NF2-Related Tumors

The number of patients who fit each of the Manchester criteria at the time of diagnosis with NF2 is described in Table 1. Of the 25 patients, 13 were male and 12 were female. The mean age at the onset of NF2-related symptoms was 9.9 ± 4.5 years (range 1–17 years). The mean age at the diagnosis of NF2 was 12.9 ± 2.9 years (range 5–17 years). The mean follow-up period was 89.3 months (range 12–311 months). Three patients (12%) had a family history of NF2, and these 3 patients already had bilateral
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TABLE 1: Manchester criteria for the diagnosis of NF2 and the number of patients fulfilling each diagnostic criterion in this study

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Additional Lesions Needed for NF2 Diagnosis</th>
<th>No. of Patients*</th>
</tr>
</thead>
<tbody>
<tr>
<td>bilat VSs</td>
<td>none</td>
<td>21</td>
</tr>
<tr>
<td>family history of NF2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>unilat VS</td>
<td>2 NF2-associated lesions‡</td>
<td>0†</td>
</tr>
<tr>
<td>unilat VS</td>
<td>2 NF2-associated lesions</td>
<td>0</td>
</tr>
<tr>
<td>multiple meningiomas (≥2)</td>
<td></td>
<td>3§</td>
</tr>
<tr>
<td>unilat VS</td>
<td></td>
<td>1§</td>
</tr>
</tbody>
</table>

* The number of patients according to the diagnostic criteria when the patients were initially diagnosed with NF2 in this study.
† Three patients who had a family history in this study already harbored bilateral VSs at the time of initial diagnosis. Thus, these patients were categorized as having bilateral VSs.
‡ Neurofibromatosis-associated lesions are meningioma, glioma, neurofibroma, schwannoma, or cataract.
§ Multiple meningiomas, multiple non-VSs, and neurofibroma were detected in this patient.

The initial presenting symptoms were highly variable according to the tumor location (Table 2). The presenting symptoms (we did not consider a surgical history for cataracts as an initial symptom because cataracts are not a tumorous condition) were as follows: hearing loss, skin mass, and neurological symptoms such as gait disturbance, leg pain, neck pain, and foot drop due to PNS tumor or spinal intradural extramedullary mass were the most common presenting symptoms in the present study (20% for each). Ocular symptoms were present in 3 cases (12%). Hoarseness occurred in 2 patients (8%).

The tumor locations at the time of the first visit were also variable. Ten patients (40%) presented with both intracranial and spinal lesions at the initial workup. Nine patients (36%) presented with tumors only in the intracranial area, including the orbit. Two patients (8%) had lesions only in the spinal area. Four patients (16%) had tumors in extraneuraxial areas (adrenal gland or the skin).

The VSs were discovered in 17 (68%) of 25 patients with NF2 upon their initial visit. However, among them, only 5 patients complained of hearing discomfort. Three patients had spinal cord tumors (ependymomas). Two of the ependymomas were detected during the initial diagnostic period, and one ependymoma occurred during the follow-up period.

All but 4 patients underwent surgery to remove various types of tumors. Two of these patients were treated using only GKS for VS, and 2 patients only underwent clinically follow-up without any treatment. No patient received chemotherapy during the follow-up period of this study.

In our study, no patient died during the follow-up period. However, major morbidity (needing assistance for normal activity) occurred in 2 patients after additional surgery for NF2-related tumors. One patient had Grade 4 muscle weakness in all 4 extremities after surgery for a spinal cord ependymoma. Another patient had morbidity of lower-extremity weakness (muscle strength Grade III) after surgery for a spinal meningioma.

Natural Growth Rate of VS in Pediatric Patients With NF2

The natural growth rate of VS in pediatric patients with NF2 was very low. The mean natural growth rate was 0.33 ± 0.41 cm³/year (range 0–1.35 cm³/year). The natural growth rate was evaluated according to age, sex, vestibular symptoms (that is, hearing difficulty, tinnitus, or dizziness), side of VS, and family history (Table 3). Univariate analysis revealed that VSs in the NF2 patients with vestibular symptoms showed a significantly fast growth rate (0.77 cm³/year vs 0.28 cm³/year, p = 0.041).

Microsurgical Outcomes of VS in Pediatric Patients With NF2

Microsurgical treatments were performed for 6 VSs in 4 patients. Near-total removals were achieved in 2 VSs, and subtotal removals were achieved in the remaining 4 VSs. All 6 VSs were later treated with GKS for recurrent or residual masses. The hearing function was nearly unchanged after microsurgery because all but one VSs (one patient had preoperative useful hearing; however, postoperative hearing function was not checked) had already caused nonuseful hearing function. There were no deaths. However, permanent facial nerve palsy after the microsurgery occurred in 2 patients, who had House-Brackmann facial nerve grades of II and IV.

Tumor Control Rate of GKS for VS in Pediatric NF2

The mean patient age at the time of GKS for 17 VSs was 15.2 ± 2.1 years (range 11–18 years). The mean volume treated using GKS was 4.8 ± 3.2 cm³ (range 0.2–13.6 cm³). The mean marginal dose was 12.4 ± 0.6 Gy delivered to the 50% isodose line. As a result, 6 VSs showed tumor regression after GKS. However, the remaining 11 VSs showed tumor progression. No VS was classified as...
TABLE 3: Univariate analysis on the natural growth rate of VS in children with NF2

<table>
<thead>
<tr>
<th>Variable*</th>
<th>Growth Rate (cm³/yr)†</th>
<th>p Value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>age</td>
<td></td>
<td>0.217</td>
</tr>
<tr>
<td>&lt;10 (n = 11)</td>
<td>0.21 ± 0.35</td>
<td></td>
</tr>
<tr>
<td>≥10 (n = 15)</td>
<td>0.42 ± 0.44</td>
<td></td>
</tr>
<tr>
<td>sex</td>
<td></td>
<td>0.920</td>
</tr>
<tr>
<td>M (n = 13)</td>
<td>0.34 ± 0.42</td>
<td></td>
</tr>
<tr>
<td>F (n = 13)</td>
<td>0.32 ± 0.41</td>
<td></td>
</tr>
<tr>
<td>vestibular symptoms§</td>
<td>0.041</td>
<td></td>
</tr>
<tr>
<td>yes (n = 3)</td>
<td>0.77 ± 0.28</td>
<td></td>
</tr>
<tr>
<td>no (n = 23)</td>
<td>0.28 ± 0.39</td>
<td></td>
</tr>
<tr>
<td>side of VS</td>
<td></td>
<td>0.286</td>
</tr>
<tr>
<td>rt (n = 10)</td>
<td>0.23 ± 0.37</td>
<td></td>
</tr>
<tr>
<td>lt (n = 16)</td>
<td>0.40 ± 0.43</td>
<td></td>
</tr>
<tr>
<td>family history</td>
<td>0.486</td>
<td></td>
</tr>
<tr>
<td>yes (n = 5)</td>
<td>0.15 ± 0.17</td>
<td></td>
</tr>
<tr>
<td>no (n = 21)</td>
<td>0.38 ± 0.41</td>
<td></td>
</tr>
</tbody>
</table>

* n = the number of VSs.
† Reported as the mean ± SD.
‡ Mann-Whitney U-test.
§ Hearing difficulty, tinnitus, or dizziness.

stable tumor after GKS. Therefore, the tumor control rate at 3 years after GKS was 35.3%. There was no aggravated permanent facial nerve palsy after GKS.

Hearing Preservation of GKS for VS in Pediatric NF2

We analyzed the hearing preservation rate after GKS in the patients with 11 VSs who had preradiosurgical ipsilateral useful hearing capacity (Fig. 1B). The mean age at the time of GKS was 14.5 ± 2.4 years (range 10–18 years). The mean volume treated using GKS was 3.75 ± 2.55 cm³ (range 0.2–7.0 cm³). The mean marginal dose was 12.0 ± 0.5 Gy delivered to the 50% isodose line. The endpoint in the Kaplan-Meier plot was indicated as the moment when useful hearing deteriorated to nonuseful hearing function. The actuarial rate of useful hearing preservation was 67% in the 1st year and 53% in the 5th year after GKS (Fig. 2). The facial nerve function was unconverted after GKS.

Discussion

Clinical Features of Pediatric NF2

Neurofibromatosis Type 2 usually occurs in young adulthood, and patients present with vestibular symptoms such as hearing difficulty, tinnitus, and dizziness, which are caused by VSs. Previous studies on pediatric NF2 reported the diverse presenting symptoms of this patient population.12,25,33,35 In contrast to adults with NF2, children with NF2 more frequently present with nonvestibular symptoms, such as ocular manifestations (for example, cataract, retinal hamartoma, ophthalmoplegia, amblyopia, strabismus, diplopia, and exophthalmos), mononeuropathy, skin masses, café au lait spots, symptoms of spinal cord tumors, and signs associated with non-VS brain tumors.12,26,33 The present study confirmed these findings; only 5 patients (20%) had vestibular symptoms at the time of diagnosis, whereas a large proportion of our patients suffered from nonvestibular symptoms. However, 16 patients already harbored VSs that were revealed by the pretreatment imaging examination, although vestibular symptoms were not a common symptom in this series. Young children complain of auditory symptoms less frequently because they cannot voice their complaints, and this factor may lead to the underestimation of the incidence of hearing problems.

Ophthalmological and dermatological manifestations are often observed as the earliest sign in childhood NF2.33 Thus, many children with NF2 visit various clinical departments initially because of their diverse symptoms. Given the diverse clinical manifestations of NF2 in children, clinicians must consider CNS evaluations including the brain and spine in children who have unusual tumors at these ages, even though the patients do not complain of CNS symptoms. Therefore, the clinical suspicion is the most important for diagnosis of NF2 in the pediatric age group.

Treatment for Children With NF2

Surgery has played a central role in the treatment of NF2 patients, both children and adults. Resection is the treatment of choice for benign tumors in NF2, but the mere presence of NF2-associated tumors is not a surgical indication. Moreover, tumor growth on follow-up examination in the absence of symptoms or signs is not by itself an indication for surgery because the majority of NF2-associated tumors will enlarge for a certain period of time and then have prolonged silent periods of inactivity while the patient remains asymptomatic.10 In general, neurological deterioration or cosmetic reasons are the indications for surgery in patients with NF2.

Gamma Knife surgery also plays an important role in the treatment of intracranial tumors of NF2 including VS, and the role of GKS has been increasing. Gamma Knife surgery has great merits in its comparative safety and effectiveness, especially in adult patients. Because the current trend in the management of NF2 is the preservation of function and maintenance of the quality of life, the application of GKS will likely increase. However, reports on outcomes after GKS in pediatric patients is limited.

Conventional radiotherapy has a limited role in the treatment of NF2. It is generally used only for NF2 patients with spinal ependymomas or intracranial high-grade gliomas.6 In the case of benign tumors, radiotherapy can be an alternative treatment choice in patients who are not eligible for surgery because of largely extended masses or in those who refuse to undergo surgery.

At present, NF2 is an incurable disorder. The goal of surgery or radiotherapy for NF2 patients is the relief of symptoms rather than a cure. Recently, understanding of the molecular biology and genetic mutations of NF2 has been increasing.5,25,30,34,40 Drugs targeting the pathways involved in the molecular pathogenesis of NF2 are now under investigation. Potential treatments for NF2 are expected to emerge in the near future.
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The infrequent vestibular symptoms in children with NF2 compared with those in adults do not reduce the importance of VS. Vestibular schwannoma is the most important and characteristic finding of NF2 in both adults and children. Therefore, understanding the natural course and treatment outcomes of VSs in pediatric NF2 is critical.

The natural growth rate of NF2-related VSs of all ages has been reported to range from 0.3 to 0.7 cm³/year.1,5,10,18,21 Our study showed 0.33 cm³/year of actuarial growth rate, suggesting a slow natural course of VS in children. Our study suggests that the natural growth rate may be slow only in children. The slow growth rate of VS in children with NF2 may explain another reason why pediatric NF2 patients more frequently present with non-vestibular symptoms and consequently show diverse clinical manifestations. The natural growth rate was not different according to age, sex, side, and the presence of a family history. However, presence of vestibular symptoms at the initial presentation was a significant factor for rapid growth. This result may imply that a symptomatic VS could be growing more rapidly. However, multicenter studies are needed to confirm this finding because of the limited sample size of the present study.

Gamma Knife surgery has recently become more important in the management of VSs in patients with NF2, and the efficacy of GKS is indisputable. However, the usefulness of GKS for VSs in NF2 patients is well known to be much less effective than in patients with sporadic VS.10,11,32 Nevertheless, some reports have presented relatively good outcomes of GKS if the VSs in NF2 patients are detected and treated early.20,28,31 In many previous studies, the tumor control rate and hearing preservation rate of NF2-related VSs after GKS has been reported to range from 66% to 85% and from 33% to 48%, respectively.20,28,32 However, there has been no report about GKS outcomes of VSs in children with NF2. Our series showed a hearing preservation rate after GKS that was similar to previous reports of all age groups (67% in the 1st year and 53% in the 5th year after GKS); however, the tumor control rate after was somewhat unsatisfactory GKS (35.3% at 3 years after GKS). Our study may indicate that VSs in pediatric patients with NF2 may be refractory with GKS compared with adults with NF2.

At present, questions remain with respect to how or when to treat VSs in children with NF2. Based on a slow growth rate of VS in these patients, a rather unsatisfactory tumor control rate, and considerable hearing loss over time after GKS in our study, we suggest that patients with asymptomatic VSs who have ipsilateral normal hearing
function could be observed regardless of the mass size even though the tumor may be in a growing state, as long as it is not growing exceptionally rapidly. Only when hearing function has deteriorated or any symptoms occur is prompt treatment recommended for a better outcome. Careful monitoring of hearing function such as PTA, speech discrimination, and brainstem auditory evoked potentials is essential during follow-up in addition to meticulous neuroimaging study.

Conclusions
The slow growth rate of VSs (0.33 ± 0.41 cm/3/year) in children with NF2 may explain why children with NF2 have more nonvestibular symptoms than their adult counterparts and show diverse clinical manifestations. Considering the slow natural growth rate, poor tumor control rate, and possible hearing loss after GKS, the policy of close observation of the VS in pediatric patients with NF2 could be a good management strategy when the VS does not cause any clinical signs or symptoms.

Disclosure
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Author contributions to the study and manuscript preparation include the following. Conception and design: SK Kim, Choi. Acquisition of data: Choi. Analysis and interpretation of data: SK Kim, Choi, Chung. Drafting the article: Choi. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: SK Kim. Statistical analysis: Choi, Phi. Study supervision: SK Kim, Lee, Phi, Wang, Chung, Paek, DG Kim, Park.

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