Original research article

Clinical course and management of intracranial meningiomas in neurofibromatosis type 2 patients

Arkadiusz Nowak *, Tomasz Dziedzic, Tomasz Czernicki, Przemyslaw Kunert, Andrzej Marchel

Department of Neurosurgery, Medical University of Warsaw, Warsaw, Poland

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ABSTRACT
Objective: The aim of this study is to evaluate our surgical experience with intracranial meningiomas in NF2 patients and provide knowledge of the natural history of these lesions. Methods: We included in the natural growth study patients with the diagnosis of NF2 who harbored intracranial meningiomas and were observed for at least 1 year. Tumors that were resected before achieving long-term follow-up were excluded from this analysis. Results: We found 118 intracranial meningiomas in 34 patients in our series. 8 meningiomas in 7 patients were symptomatic. It was found that with an increase in tumor volume, brain edema and with the tumor location at the skull base, meningiomas are more likely to be symptomatic. Univariate analysis revealed that tumor growth was associated with a younger age at the onset of NF2-related symptoms, greater initial tumor volume, brain edema and with the presence of intracranial non-vestibular schwannoma. Multivariate analysis showed that the probability of tumor growth is associated with prolonged follow-up time. De novo meningiomas exhibited a significantly higher growth rate than other meningiomas. These tumors were more frequent in patients with intracranial non-vestibular schwannoma and with increasing length of meningioma observation. Conclusion: Meningiomas occur in about half NF2 patients. Many of them exhibit slow growth and long remain asymptomatic, however, those associated with early onset of NF2 symptoms and other features of the disease severity should be monitored in case of clinical and radiological progression that may require surgical treatment.

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1. Introduction

Neurofibromatosis type 2 is an autosomal dominant syndrome predisposing to multiple benign tumors of the central and peripheral nervous system. The hallmark of this disease is the development of bilateral vestibular schwannomas, which occurs in 90–95% of patients [1–3]. Meningiomas are the second most frequent tumor type in NF2. They are often multiple [1–3] and occur in about half of these patients [4]. They develop at a younger age than their counterparts with sporadic cases of meningiomas [2,3,5]. In the pediatric age...

* Corresponding author at: Klinika Neurochirurgii, Warszawski Uniwersytet Medyczny, ul. Banacha 1a, 02-097 Warszawa, Poland.
Tel.: +48 606 787 433; fax: +48 225991574.
E-mail address: arkady.n@wp.pl (A. Nowak).
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group meningoïdias are often the first sign of NF2 [6]. Furthermore NF2 is diagnosed in 10–29% of children presenting with meningoïdias [7–10]. Meningiomas associated with NF2 frequently show aggressive features on pathological examination [11,12]. A higher proliferative potential of NF2 meningiomas, however, is observed in tumors requiring surgery while remaining slow-growing lesions are probably less aggressive nature [13]. Meningiomas in NF2 patients are associated with disease severity as risk of mortality is 2.5-fold greater in people with meningiomas compared to those without such lesions [14].

Yet little is known about long-term natural history of meningiomas in NF2 patients. Data about meningioma surgery in NF2 are sparse in the literature. Knowledge of meningioma behavior in NF2 patients should be determined for their optimal management, including timing of surgical treatment. The aim of this study is to evaluate our surgical experience with intracranial meningiomas in NF2 patients and provide knowledge of natural history of these lesions. We sought to define whether meningiomas are a major problem in the treatment of patients with NF2, and whether we can safely observe meningiomas in these patients. We assessed clinical characteristics, new tumor development, surgical outcome and growth patterns of meningiomas in NF2 patients with long-term clinical and radiographic follow-up. Furthermore we compare NF2 patients with intracranial meningiomas to those without to identify differences between the two patient subgroups.

2. Materials and methods

2.1. Patient population

Thirty four patients with neurofibromatosis type 2, as defined on the basis of the modified National Institute of Health (NIH) Consensus Panel Criteria [15], were surgically treated at our institution between 1996 and 2014. We have retrospectively reviewed the clinical records, neuroimaging studies, and follow-up data of the treated patients. Among 34 patients, 13 had no intracranial meningiomas and 21 had one or multiple intracranial meningiomas. We included in the natural growth study patients with the diagnosis of NF2 who harbored intracranial meningiomas and were observed for at least 1 year. Tumors that were resected before achieving long-term follow-up were excluded from this analysis. Two meningiomas were resected at another institution and were not included in the study. Another 3 tumors were excluded from growth rate analysis given their short follow-up before resection. A total of 118 meningiomas in 21 patients met the inclusion criteria and were suitable for growth rate analysis. Resected tumors were graded according to the WHO 2000 and the WHO 2007 [16] grading scheme. All patients had a clinical examination and brain MRI study performed at least once a year.

2.2. Tumor measurements.

The T1-weighted multiplanar images with gadolinium enhancement were used for volume measuring. Tumor volumes were determined manually using the 3-diameters technique 

\[ V = (D_1 \times D_2 \times D_3)/2 \]

Multilobulated tumors were divided into individual compartments and tumor volumes of these components were then summed. 3D MRI sequences for the calculation of exact changes in tumor’s volumes were not available. Tumors with no increase in its tumor volume were defined as stable. Tumor growth was defined as an increase in tumor size over a measurement interval. Tumor growth rate was calculated as: (final volume – initial volume)/follow-up interval. Tumor quiescence was defined as no tumor growth over 1-year interval. De novo meningiomas were defined as tumors that were undetectable on the previous imaging.

2.3. Factors affecting tumor growth rate

Clinical and radiological features that might be related to meningioma growth were recorded: age at first symptoms of NF2, sex, length of observation, tumor volume at diagnosis, peritumoral edema, skull-base tumor location, number of intracranial meningiomas and presence of non-vestibular schwannomas and spinal tumors.

2.4. Statistical analysis

Statistical analyses were performed in STATISTICA version 10.0 (StatSoft Inc., 2011). Quantitative variables were characterized by the arithmetic mean, standard deviation, median, minimum and maximum values and 95% CI (confidence interval). Statistical significance of differences between the two groups was analyzed with t-Student-test or Mann–Whitney U-test. Statistical significance of differences between more than two groups was tested by an F test (ANOVA) or Kruskal–Wallis test. In the case of two variables associated model t-Student-test or Wilcoxon-test were used. Chi-square tests were used for categorical variables. Statistical significance was presumed \( p = 0.05 \).

3. Results

3.1. Patient and tumor characteristics

There were 19 women and 15 men in the entire cohort of NF2 patients. Characteristics of the patients and the comparison between NF2 patients with intracranial meningiomas and those without the lesions are given in Table 1. Among the 21 patients with meningiomas spinal epedynomas and non-vestibular schwannomas were more frequently observed. We found 118 intracranial meningiomas in 21 patients in our series (mean 5.2 ± 3.9 tumors/patient, range 1–16 tumors). 16 (76.2%) patients had multiple meningiomas. The most common locations of meningioma were convexity (37.3%), parasagittal and falx region (29.7%), and the skull base (27.1%). In 5 patients extensive tumor growth was observed along the parasagittal and falx region and convexity. MRI revealed adjacent parenchymal edema in 8 tumors (7%). 8 meningiomas in 7 patients were symptomatic. In 3 cases these tumors produced the first symptoms of the disease. In the other 5 cases meningiomas became symptomatic during the follow-up interval. In a univariate analysis, it was found that with an
increase in tumor volume \((p = 0.001)\), brain edema \((p = 0.001)\) and with the tumor location at the skull base \((p = 0.032)\). Meningiomas are more likely to be symptomatic. These factors, however, did not reach statistical significance in multivariate analysis (Table 2).

### Table 1 - NF2 patients’ characteristics.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of patients (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intracranial meningioma present</td>
<td>Intracranial meningioma absent</td>
</tr>
<tr>
<td>Female</td>
<td>21 (61.8)</td>
<td>13 (38.2)</td>
</tr>
<tr>
<td>Mean age at first symptoms (SD)(years)</td>
<td>12 (57.1)</td>
<td>7 (53.8)</td>
</tr>
<tr>
<td>Bilateral vestibular schwannoma</td>
<td>18 (85.7)</td>
<td>13 (100)</td>
</tr>
<tr>
<td>Non-vestibular schwannoma</td>
<td>8 (38.1)</td>
<td>1 (7.7)</td>
</tr>
<tr>
<td>Spinal meningioma/schwannoma</td>
<td>17 (81)</td>
<td>7 (53.8)</td>
</tr>
<tr>
<td>Spinal ependymoma</td>
<td>10 (47.6)</td>
<td>1 (7.7)</td>
</tr>
</tbody>
</table>

SD – standard deviation. Values in bold indicate statistical significance.

### Table 2 - Prognostic factors for symptomatic intracranial meningiomas in NF2 patients.

<table>
<thead>
<tr>
<th>Prognostic factor</th>
<th>p (univariate analysis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at first symptoms</td>
<td>0.949</td>
</tr>
<tr>
<td>Tumor volume</td>
<td>0.001</td>
</tr>
<tr>
<td>Length of observation</td>
<td>0.924</td>
</tr>
<tr>
<td>Number of tumors</td>
<td>0.898</td>
</tr>
<tr>
<td>Sex</td>
<td>0.773</td>
</tr>
<tr>
<td>Skull-base tumor location</td>
<td>0.032</td>
</tr>
<tr>
<td>Brain edema</td>
<td>0.001</td>
</tr>
<tr>
<td>Non-vestibular schwannoma present</td>
<td>0.463</td>
</tr>
<tr>
<td>Spinal ependymoma present</td>
<td>0.562</td>
</tr>
<tr>
<td>Spinal meningioma/schwannoma present</td>
<td>0.534</td>
</tr>
</tbody>
</table>

Values in bold indicate statistical significance.

3.2. **Natural growth rate of meningioma in NF2 patients**

The mean length of radiological follow-up was 6.5 ± 3.7 years (range 2–16 years) (Fig. 1). 58 (49%) tumors demonstrated growth during the follow-up period. The mean volume of meningiomas at diagnosis was 3.4 ± 5.8 cm³ (95%CI [2.4; 4.5], range 0.1–39.2 cm³). The mean growth rate for all intracranial meningiomas was 0.5 ± 1.1 cm³/year (95%CI [0.3; 0.7], range 0–8.4 cm³/year). The mean growth rate for growing meningiomas was 1.1 ± 1.4 cm³/year (95%CI [0.7; 1.4], range 0.2–8.4 cm³/year). Comparing symptomatic and asymptomatic tumors, it was found that the mean growth rate for symptomatic meningiomas was significantly higher than in asymptomatic tumors (Mann–Whitney U-test \(Z = -4.58, p = 0.0001\)) (Table 3).

Univariate analysis revealed that tumor growth was associated with a younger age at the onset of NF2-related symptoms \((p = 0.001)\), greater initial tumor volume \((p = 0.013)\), brain edema \((p = 0.005)\) and with the presence of intracranial non-vestibular schwannoma \((p = 0.042)\). Multivariate analysis confirmed that with increasing age of the first symptoms of the disease decreases the likelihood of tumor growth. Moreover, multivariate analysis showed that the probability of tumor

![Fig. 1 – Graph of the length of observation of intracranial meningiomas in NF2 patients.](image-url)
growth is associated with prolonged follow-up time and brain edema (Table 4).

Of 58 tumors that demonstrated growth, quiescent periods were observed in 12 cases with the mean duration of quiescent periods of 2.8 ± 2.1 years (range 1–7 years). These tumors displayed a saltatory pattern of growth characterized by intervening periods of no tumor growth. Analysis revealed that growing meningiomas with quiescent periods were significantly associated with the length of time of observation \(p = 0.0001\) (Table 5).

### 3.3. Development of new tumors

At the end of follow-up 12 de novo meningiomas appeared in 6 patients. De novo meningiomas exhibited a significantly higher growth rate than other meningiomas \(0.8 \pm 0.6 \text{ cm}^3/\text{year}\) vs. \(0.5 \pm 1.2 \text{ cm}^3/\text{year}\), Mann–Whitney U-test \(Z = -3.61, p = 0.0003\) but did not require surgery more often than other meningiomas \(25\% \text{ vs } 17\%, p = 0.83\). These tumors were more frequent in patients with intracranial non-vestibular schwannoma \(p = 0.003\) and with increasing length of meningioma observation \(p = 0.001\). Interestingly, univariate analysis revealed that the increase in the total number of intracranial meningiomas decreases the likelihood of developing a new tumor \(p = 0.033\) (Table 6). These factors, however, did not reach statistical significance in multivariate analysis.

### 3.4. Surgical treatment

21 \(18\%)\) tumors in 11 \(52\%)\) patients were resected during the course of the study. In 8 of 21 cases \(38\%)\) the reason for tumor resection was occurrence of clinical symptoms (neurological deficit in 4, epilepsy in 2, intracranial hypertension in 2). 11 asymptomatic tumors in the posterior fossa \(5\) of them were growing meningiomas) have been removed by the way of vestibular schwannoma resection. In one patient surgery was performed due significant de novo tumor growth in subsequent imaging studies. In another asymptomatic case surgery was performed due to large tumor burden in the posterior fossa. The main histological subtypes were fibroblastic \(10\) cases), transitional \(6\) cases), and meningothelial \(4\) cases). There was one atypical (WHO Grade II) meningioma. There were no grade III meningioma cases. No operative death we noted. Five patients experienced permanent postoperative neurological deficits (cranial nerves IX and X deficits in 3,
hemiparesis in 1, and blindness in one eye in 1). Simpson grade I or grade II resection was achieved in all but one case. In this case a tumor remnant was left in the cavernous sinus. Tumor remnant was not eligible for adjuvant treatment. Among the 11 patients with meningiomas who underwent surgery the mean postoperative clinical and radiological follow-up period was 3.1 years (range 1.2–8.5 years). Three tumors in 3 patients recurred during the follow-up period. One patient underwent repeated surgery and the other two asymptomatic recurrent tumors are being monitored.

4. Discussion

Neurofibromatosis type 2 (NF2) is a heritable tumor predisposition syndrome that leads to the development of multiple intracranial tumors. Meningiomas are the second most frequent tumor type in NF2 patients occurring in about half of these patients. It is believed that meningiomas in NF2 patients are associated with disease severity [13] but little is known about their natural history in these patients. In this study we sought to evaluate tumor growth rate of NF2-associated meningiomas and to define their influence on neurological status of NF2 patients. Moreover we aim to assess the risk and effectiveness of surgical treatment for this tumor type. It should be noted, however, that there was no true volumetric assessment of the tumors. Linear measurements used in the study underestimate tumor growth rate compared with volumetric measures. Moreover, limiting accuracy of calculating tumor growth was lack of the evaluation of the reliability of measurement method (interrater reliability).

The results of the present study tend to agree in several respects with those of previously published works on natural history of meningiomas in NF2 [18–20]. Meningioma growth rates were found to be highly variable but only a small proportion of tumors showed a significant increase. Our study confirms that significant proportion of meningiomas in NF2 patients demonstrated no tumor growth [13]. It is consistent with the previous findings suggested that likewise in other sporadic meningiomas tumors in NF2 patients exhibit variations in growth rates including periods of no tumor growth [18,21–23]. In the study of Dirks et al. [18] 99% of intracranial meningiomas exhibited growth and about 60% displayed extended quiescent periods. They suggest that quiescence described in some studies represents intervals between growth periods and reported lack of tumor growth is solely the result of too short follow-ups. Indeed, in our study the likelihood of observing saltatory pattern of growth increased with a longer duration of follow-up. Nevertheless these observations require refraining from proactive treatment in meningiomas of NF2 patients. Taken into account the possibility of complications after surgery, tumor growth should be confirmed on serial imaging before considering surgical treatment [20]. In contrast to vestibular schwannomas where size matters in terms of hearing preservation, meningiomas do not require such a cautious approach and differences in tumor size are not important. Hence, one can afford to observe the tumor and make a decision about surgery only after proving significant tumor growth. Besides, based on the obtained results, the risk of surgical treatment of NF2-associated meningiomas seems to be comparable to the risk in the event of sporadic meningiomas. Consensus recommendations for current treatments in NF2 stated that most meningiomas occur in surgically accessible locations and surgery is considered the treatment of choice in cases that require treatment [24]. Interestingly, in the opinion of Dirks et al. [18] even demonstrated tumor growth is not an indication for surgery. They thought that past tumor behavior does not predict future growth and do not recommend surgery if the tumor growth is not accompanied by clinical symptoms. As meningiomas in NF2 exhibit differences in growth rates, even among tumors within the same patient, it seems important to determine the risk factors for their growth. Current study data indicate that an increased growth rate is associated with younger age at the onset of NF2-related symptoms, greater initial tumor volume, brain edema and with the presence of intracranial non-vestibular schwannoma. Goutagny et al. [20] found that growing meningiomas were more frequent in males and people up to 30 years old and were associated with tumor edema and tumor size exceeding 25 mm. Similarly, Dirks et al. [18] revealed more rapid tumor growth in young patients but in contrast to the previous work they demonstrated more rapid tumor growth related to female gender.

Histopathological findings in NF2-associated meningiomas are ambiguous. Goutagny et al. [20] in contrast to other published series [11,12,18] found that meningiomas in NF2 patients are not histologically more aggressive than their sporadic counterparts. Our data corroborates these findings. Contrary to previous studies, we found that de novo meningiomas did not required surgery more frequently and did not exhibited more aggressive histological behavior [20].

5. Conclusions

Meningiomas occur in about half NF2 patients. Many of them exhibit slow growth and long remain asymptomatic, however, those associated with early onset of NF2 symptoms and other features of the disease severity should be monitored and in case of clinical and radiological progression may require surgical treatment. Despite the high prevalence of intracranial meningiomas in NF2 patients these tumors do not constitute a significant clinical and surgical problem and observation of asymptomatic tumors seems to be quite safe.

Conflict of interest

None declared.

Acknowledgement and financial support

None declared.

Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical
Association (Declaration of Helsinki) for experiments involving humans; Uniform Requirements for manuscripts submitted to Biomedical journals.

REFERENCES


