Optic Nerve Sheath Meningiomas in Patients With Neurofibromatosis Type 2

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Objective: To determine the prevalence of optic nerve sheath meningiomas (ONSMs) in patients with neurofibromatosis type 2 (NF2).

Methods: An observational retrospective case series of 30 consecutive patients with NF2 referred to an academic ophthalmology unit from November 1, 1991, through August 31, 2003. Twenty-six patients were followed up for a mean of 93 months (range, 3-150 months). One individual was lost to follow-up, and 3 had been referred recently. Diagnosis of ONSM was made based on typical neuroradiologic and clinical features in 7 patients and on histologic criteria in 1.

Results: Eight of 30 patients harbored unilateral (n = 6) or bilateral (n = 2) ONSMs. Six ONSMs were diagnosed at initial examination, and 4 during follow-up.

Conclusions: There is a strong association between ONSMs and NF2 that parallels the well-known association of optic nerve gliomas with NF1. Physicians should be aware of the possibility that patients with ONSMs may also have NF2.


Neurofibromatosis type 2 (NF2) is a rare autosomal dominant disease that can be distinguished from the more common NF1 on genetic and clinical grounds. The birth incidence of NF2 is estimated to be approximately 1 in 33,000 to 40,000. It is caused by inactivating mutations of a tumor suppressor gene on chromosome 22q12. The gene’s inactivation plays a crucial role in the development of sporadic and NF2-associated tumors of the central nervous system, with the occurrence of intracranial and spinal schwannomas and meningiomas being the main trait of this illness. Families with the NF2 gene show a penetrance for bilateral vestibular schwannomas of more than 95%. This is why they have been included in the clinical diagnostic criteria for NF2. Ophthalmologic stigmata of NF2 include juvenile cataracts, epiretinal membranes, combined pigment epithelial and retinal hamartomas, and optic disc gliomas.

Optic nerve sheath meningiomas (ONSMs) represent 1% to 2% of all meningiomas diagnosed in the general population. Sporadic ONSMs occur mostly in middle-aged women. They are rarely seen in children, in whom these tumors tend to be particularly aggressive. Most cases are unilateral, and only 5% are bilateral. Optic nerve sheath meningiomas cause early compression or vascular compromise of the nerve’s axons, with consecutive reduction in visual acuity (VA) and color vision and visual field defects. The triad of visual loss, optic atrophy, and optociliary shunt vessels is considered pathognomonic for ONSM. Effects due to intraorbital expansion, that is, proptosis and strabismus, emerge at a later stage.

Neurofibromatosis types 1 and 2 were closely linked and often confused. In 1987, their causative gene defects were localized to 2 separate chromosomes. The similarity of the 2 names is deceiving, as the central nervous system tumors typical of NF2 do not occur more frequently in NF1 than in the general population, and the skin tumors in NF2 are most often schwannomas, not neurofibromas.

Methods

Patients

Thirty consecutive patients with NF2 who had been referred to the Department of Ophthalmology, University Hospital of Zurich, from November 1, 1991, through August 31, 2003, were included in this retrospective study. Twenty-six study patients were followed up for a mean of 93 months (range, 3-150 months). One patient was lost to follow-up (he moved to another country 5 months after first being seen by us). One patient died shortly after the first examination, and 3 had been referred lately. No patients were excluded. All the patients fulfilled the Manchester group criteria (Table 1), which...
have been found to be the most sensitive currently.26 Thirteen patients’ diagnoses were genetically confirmed; another 9 patients’ mutations could not be determined by mutation analysis. Informed consent was obtained from all the study patients. All the patients underwent a thorough neuro-ophthalmologic examination. Neuroimaging was performed at the referral clinic if it was lacking when the patient was first seen. The images were run again at regular intervals as required based on the clinical situation. Imaging was repeated in patients with radiographic evidence or clinical signs of visual pathway tumors detected within the scope of the study. The patients were allotted to 1 of 3 groups—severe, mild, or intermediate phenotype—according to their clinical manifestations. The mild phenotype, also known as the “Gardner” subtype, is characterized by the late onset of symptoms (>20 years old), fewer than 2 associated intracranial neoplasms, and a generally more benign clinical course. Patients with the severe phenotype or “Wishart” subtype show an earlier onset of symptoms (<20 years old) and the presence of 2 or more additional central nervous system and spinal tumors. Patients who did not fit into these 2 groups were classified as intermediate phenotypes.

Table 1. Clinical Diagnostic Criteria for NF2*: Manchester Group 1992

<table>
<thead>
<tr>
<th>Category</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilateral vestibular schwannomas</td>
<td>First-degree relative with NF2 and unilateral vestibular schwannoma or 2 of the following: meningioma, schwannoma, glioma, neurofibroma, posterior subcapsular lenticular opacities</td>
</tr>
<tr>
<td>Unilateral vestibular schwannoma and any 2 of the following: meningioma, schwannoma, glioma, neurofibroma, posterior subcapsular lenticular opacities</td>
<td>Multiple meningiomas (&gt;2) and unilateral vestibular schwannoma or any 2 of the following: glioma, schwannoma, neurofibroma, cataract</td>
</tr>
</tbody>
</table>

Abbreviation: NF2, neurofibromatosis type 2. *NF2 may be diagnosed when 1 of the table criteria is present. †Any 2 means 2 individual tumors or cataract.

**Figure 1.** Illustration of primary (1) and secondary (2) optic nerve sheath meningiomas.

NEUROIMAGING

The ONSMs reported in this study were detected on magnetic resonance images (MRIs) primarily of the brain and orbit based on typical diagnostic criteria, including nerve sheath enlargement, which can be diffuse or segmental and appears in 3 patterns—tubular, fusiform, and excrecent or globular. A typical feature of the tubular or slightly fusiform ONSM is the so-called tram-track sign of the optic nerve on slices parallel to its course portraying a nonenhancing optic nerve sandwiched between the enhancing meningioma on either side. Calcifications of the ONSM are found occasionally and, when existent, are very characteristic. Distal cystic nerve changes have also been described. Further findings are superficial hyperostosis or diffuse sclerosis (in cases of intraosseous growth) of adjacent bone and, in later stages, enlargement of the optic canal. Optic glioma as a differential diagnosis can be excluded reliably based on the imaging pattern because it develops in the center of the optic nerve itself and does not arise from its periphery, as does the ONSM. The neuroradiologic criteria of ONSM are characteristic but not pathognomonic. Differential diagnoses such as orbital pseudotumor, periopic neuritis, sarcoidosis, leukemia, and lymphoma were widely excluded by clinical presentation.

CATEGORIZATION

Primary ONSMs develop from the meningothelial cap cells of arachnoid villi along the intracanalicular or the intraorbital nerve sheath (Figure 1 and Figure 2). Secondary ONSMs, which account for most orbital meningiomas, initially evolve from a neighboring intracranial site and extend between the dura and the arachnoid of the optic nerve sheath via periforaminal sulcus chiasmaticus through the optic canal or via a superior orbital fissure. Sphenoid ridge meningiomas can invade the orbital apex through the superior orbital fissure. Although not clearly stated in the literature, these meningiomas may invade...
the posterior optic nerve sheath because the superomedial aspect of the superior orbital fissure is separated from the optic canal by only a thin bony optic strut36 (Figures 1, 3, and 4). A definite distinction between primary and secondary ONSMs can be challenging. It is often not possible to determine the exact site of origin in tumors with intraorbital and extraorbital extension and when serial imaging is lacking. We thus created 2 additional categories, probable primary ONSM and probable secondary ONSM, according to findings in early and current imaging. The former features early evidence of major tumor bulk located intraorbitally, and the latter is characterized by major tumor bulk in extraorbital areas seen in early images. They all showed consecutive intraorbital or extraorbital extension of the tumor mass.

LITERATURE REVIEW

Literature concerning patients with ONSM and neurofibromatosis predating the segregation of the 2 entities NF1 and NF2 was reviewed. The described patients with both neurofibromatosis and ONSM were retrospectively matched to either NF1 or NF2 using modern diagnostic criteria.5,7,37

RESULTS

Of 30 patients (13 females and 17 males), 16 (8 females and 8 males) were classified as having severe phenotypes, and 10 (4 females and 6 males) met the criteria for the mild phenotype at final examination. Four patients (1 female and 3 males) were allotted to the intermediate phenotype.

Brain MRI, performed at 7 different neuroradiologic institutions in Switzerland, was available in all the patients at or shortly after initial examination. Every image was initially evaluated by a radiologist of the according institution and also in a retrospective review within the scope of this study by one of us (W.W.W.), a neuroradiologist with an interest in orbital imaging. Twelve patients with radiographic evidence or clinical signs of visual pathway tumors during the study had additional detailed orbital investigations using high spatial resolution (3-mm through-plane) precontrast and fatsuppressed postcontrast multiplanar T1- and T2-weighted images. Computed tomography of the head was performed in 22 patients during their illness.

Eight (27%) (3 females and 5 males) of 30 patients were diagnosed as having ONSMs, unilaterally in 6 cases and bi-
laterally in 2 (Table 2). Three ONSMs were primary, 3 were secondary, 3 were designated as probable primary, and 1 was designated as probable secondary. Six ONSMs had already been diagnosed at initial examination; 4 were detected within the scope of the study. Five individuals were diagnosed as having ONSMs before and 3 after reaching age 20 years but still younger than 45 years. All the patients with ONSMs had the severe phenotype.

In addition, 4 individuals had meningiomas localized in areas directly adjacent to the optic nerve that extended toward and were tangent to the nerve but did not (yet) invade its sheaths. Two of these patients had subsequent compressive optic neuropathy. The first symptom leading to the diagnosis of NF2 in 4 patients (patients 2, 4, 5, and 6) was visual loss, caused by ONSMs in 2 patients. In patients 4 and 7, ONSM was diagnosed shortly after the onset of visual symptoms; in patients 1, 2, 3, 6, and 8, delay of diagnosis ranged from 1 to 20 years (mean, 6 years).

### Table 2. Characteristics of the 8 Patients With ONSMs at the Final Examination

<table>
<thead>
<tr>
<th>Patient No./Sex/Age, y</th>
<th>Side/Type/Location</th>
<th>Visual Acuity</th>
<th>Optic Disc</th>
<th>Visual Field</th>
<th>Ocular Motility</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M/33</td>
<td>LE/probable primary/predominantly intraorbital with extraorbital extension</td>
<td>NLP</td>
<td>Pallor</td>
<td>NA</td>
<td>Reduced abduction, adduction, and infraduction</td>
</tr>
<tr>
<td>2/M/55</td>
<td>RE/probable primary/early images with tumor at orbital apex, later extraorbital extension</td>
<td>RE: 20/50 LE: NLP</td>
<td>RE: pallor LE: opaque media (pallor and optociliary shunt vessels previously documented)</td>
<td>RE: minimal concentric contraction, enlarged blind spot LE: NA</td>
<td>BE: all versions severely reduced</td>
</tr>
<tr>
<td>4/F/21</td>
<td>RE/primary/intraorbital</td>
<td>CF in 10 cm</td>
<td>Optociliary shunt vessels, pallor Minimal pallor Normal</td>
<td>Complete loss of upper half of visual field Central scotoma Concentric contraction of all isopters, central scotoma</td>
<td>All versions severely reduced Palsy of abduction Reduced adduction and infraduction</td>
</tr>
<tr>
<td>5/M/28</td>
<td>LE/primary/intraorbital</td>
<td>CF in 30 cm 20/400</td>
<td>LE: normal Optociliary shunt vessels, pallor Minimal pallor Normal</td>
<td>Disc edema</td>
<td>Enlarged blind spot Reduced supraduction, infraduction, adduction Normal</td>
</tr>
<tr>
<td>6/M/10</td>
<td>RE/secondary/predominantly extraorbital</td>
<td>20/20</td>
<td>LE: normal Disc edema</td>
<td>Enlarged blind spot, paracentral scotoma</td>
<td>Reduced supraduction, infraduction, adduction Normal</td>
</tr>
<tr>
<td>7/F/37</td>
<td>RE/secondary/predominantly extraorbital</td>
<td>20/20</td>
<td>LE: normal Disc edema</td>
<td>Enlarged blind spot, paracentral scotoma</td>
<td>Reduced supraduction, infraduction, adduction Normal</td>
</tr>
<tr>
<td>8/F/14</td>
<td>RE/primary/intraorbital</td>
<td>20/70</td>
<td>LE: normal Disc edema</td>
<td>Enlarged blind spot, paracentral scotoma</td>
<td>Reduced supraduction, infraduction, adduction Normal</td>
</tr>
</tbody>
</table>

Abbreviations: BE, both eyes; CF, counting fingers; LE, left eye; LP, light perception; NA, not applicable; NLP, no light perception; ONSMs, optic nerve sheath meningiomas; RE, right eye.

INDIVIDUAL PATIENT CHARACTERISTICS

Patient 1 had a unilateral ONSM and showed restricted ocular motility, pale optic disc, and exophthalmos at initial examination (Table 2). He underwent orbital decompression elsewhere, with excision of meningiomatous tissue at the optic foramen in an attempt to preserve visual function. The diagnosis was histologically confirmed. His profoundly reduced VA of 20/200 declined to no light perception after surgery. The latest neuroimaging showed tumor progression, with infiltration of the extraocular muscles at the orbital apex. His course of NF2 is particularly severe, and no additional intervention concerning his ONSM is planned.

Patient 2 had bilateral ONSMs and had already lost all vision in his left eye within 5 months of becoming 18 years old. At initial examination the right eye had a best-corrected VA of 20/50, with a constricted visual field, a slight proptosis, and disc edema. Also, optic disc atrophy with optociliary shunt vessels on the left was noted. Ocular motility was reduced bilaterally. Ophthalmologic examination 9 years later showed regression of disc edema in the right eye with commencing atrophy of the optic nerve head. Optic nerve function was stable. Tumor progression in both orbits on MRIs was declared minimal. Therefore, observation has been chosen as current management.

Patient 3 had an enophthalmos and an atypical morning glory disc malformation in the right eye (published elsewhere), with severely reduced ocular motility. Neuroimaging revealed an ONSM on the right (Figure 3). During the illness, slow tumor growth in the left cavernous sinus with extension toward the optic canal on the left was observed. Owing to visual field deficits noted at the current examination, without ocular motility deficits, MRI was performed and disclosed bilateral ONSMs (Figure 4). Surgical removal of the secondary ONSM on the left was performed without any postoperative functional deficits.

Patient 4 had a unilateral ONSM (Figure 2) and was first seen with best-corrected VA of 20/25, with a constricted visual field, and ocular motility deficits on the right. She was lost to follow-up from March 2001 to October 2003 and returned with a VA of counting fingers and marked visual field loss on the right. Progressive exophthalmos and op-
tectociliary shunt vessels had also developed in the meantime. Stereotactic fractionated conformal radiotherapy was discussed with the patient even at this late stage of compressive optic neuropathy to salvage residual function. She declined further therapy at the moment.

Patient 5 was amblyopic due to dense juvenile cataract, and he had a history of progressive sixth nerve palsy for 4 years. High spatial resolution computed tomography of the orbit during the study rendered a small ONSM without intracranial expansion. Management in this case is observation alone.

Patient 6 had restricted ocular motility and visual field constriction of the left eye. He had a history of juvenile cataract in both eyes, recurrent idiopathic vitreoretinal proliferations with retinal detachments in the right eye, and a macular scar in the left eye. Targeted neuroimaging of the visual pathways disclosed an ONSM on the left. Because of stable optic nerve function, current management is observation.

Patient 7 was first seen with an isolated trochlear palsy on the right. At the recent examination (3 years later) she had new onset of disequilibrium. Bilateral papilledema required neuroimaging and prompted diagnosis of an ONSM on the right with extension through the optic canal. She had surgical removal of the tumor and made an uneventful recovery.

Patient 8 had reduced VA and progressive visual field defects in the right eye. Neuroimaging revealed an ONSM without intracranial extension. Stereotactic fractionated conformal radiotherapy will be considered in this young patient.

LITERATURE REVIEW

A comprehensive review of studies on patients with ONSMs and NF published between 1922 and 1989, thus predating modern neuroimaging and the recognition of NF2 as a distinct entity, yielded 16 patients with neurofibromatosis of 146 patients with ONSMs. Ten patients clearly met the criteria for NF2 in the detailed evaluation of the original studies. The remaining 6 cases could not be allotted to either neurofibromatosis type because of incomplete data. Neurofibromatosis type 1 was never diagnosed retrospectively. The 10 patients with NF2 were aged 3.5 to 25 years (mean, 12.2 years) at the time of ONSM diagnosis. We searched various studies on the clinical spectrum of NF2 for patients with ONSMs (Table 3). Only a few were detected. The incidence was 2% to 8%. Eighteen (5%) of 356 patients with NF2 harbored ONSMs. With 8 patients added, the incidence augments to 26 (6.8%) of 383. These studies were not population based; therefore, there is a selection bias.

The 2 most common tumors of the orbital optic nerve are gliomas (65%) and meningiomas (35%). Several studies showed the high occurrence of optic pathway gliomas in NF1 (15%–21%), thus being the most predominant intracranial neoplasm in these patients. They have been included in the National Institutes of Health diagnostic criteria for NF1, accordingly. Isolated cases of ONSM in patients with neurofibromatosis can be found in the literature. Most studies mention the occurrence of these tumors in children with neurofibromatosis without committing to the type. Walsh and Davis introduced the possible correlation of ONSM with neurofibromatosis. Mautner et al concluded from their study that children with intracranial masses should be examined closely for signs of NF2. Evans et al also noticed that as many as 10% of children with an isolated meningioma go on to develop clinical stigmata of NF2. To our knowledge, this is the first investigation to search for ONSMs in patients with NF2.

This study assessed a higher percentage of ONSMs than most publications. A possible reason could be the intensified search for orbital tumors within the scope of the study. These usually slow-growing neoplasms could have existed previously and not been detected at initial examination because of suboptimal neuroimaging. On the other hand, growth of the tumor is possible during the imaging interval, such as in patient 3, in whom meningiomatic tissue progressed into the left orbit, leading to a secondary ONSM. The detection of an incipient ONSM requires carefully targeted MRI, preferentially with coronal, high spatial resolution fat-saturated gadolinium-enhanced sections of the orbit. Important diagnoses can easily be overlooked on routine brain scans, especially when the lesions are very small or are not specifically sought. This is the most likely reason for the delay in diagnosis in 4 of our patients.

We did not note a higher female prevalence of ONSMs in our small study group, but we did find more children affected than adults. All the patients with ONSMs had the severe phenotype, an obvious finding considering that patients with the severe phenotype harbor more than 2 additional central nervous system tumors, these often being meningiomas.

The necessity to distinguish primary from secondary ONSMs is debatable. It is possible that the so-called sec-

Table 3. Review of the Current Literature on Patients With NF2 and ONSMs

<table>
<thead>
<tr>
<th>Source</th>
<th>Patients, No.</th>
<th>With NF2</th>
<th>With ONSMs and NF2</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evans et al, 1992</td>
<td>120</td>
<td>5</td>
<td>2 of 5 are bilateral</td>
<td></td>
</tr>
<tr>
<td>Cuncliffe et al, 1992</td>
<td>1</td>
<td>1</td>
<td>Bilateral ONSMs</td>
<td></td>
</tr>
<tr>
<td>Bouzas et al, 1993</td>
<td>54</td>
<td>1</td>
<td>Insufficient data on further 3 optic nerve tumors</td>
<td></td>
</tr>
<tr>
<td>Landau and Yasargil, 1993</td>
<td>6</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parry et al, 1994</td>
<td>63</td>
<td>3</td>
<td>1 Child bilateral</td>
<td></td>
</tr>
<tr>
<td>Meyers et al, 1995</td>
<td>15</td>
<td>2</td>
<td>Additional 1 with “optic nerve glioma”</td>
<td></td>
</tr>
<tr>
<td>Ragge et al, 1995</td>
<td>49</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mautner et al, 1996</td>
<td>48</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>356</td>
<td>18</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: NF2, neurofibromatosis type 2; ONSMs, optic nerve sheath meningiomas.
ondary ONSMs either originate from 1 intracranial site other than the orbit and expand toward and invade the optic nerve sheath owing to typical en plaque growth or simultaneously evolve from extraorbital and intraorbital arachnoid cell clusters and fuse to form an ONSM. Neither theory has been proved yet. Of all the secondary ONSMs in our study, only 1 was radiographically documented to have emerged from an extraorbital site with subsequent expansion into the optic nerve sheath.

The ONSMs were diagnosed using neuroimaging. Histologic confirmation was possible in only 1 patient. The biopsy of a suspected ONSM is usually not justifiable in light of precise modern neuroimaging and considering the high risk of optic nerve damage during the intervention.

Our group of patients was not population based. Bias occurred through referral by various specialists to an academic ophthalmology unit. Therefore, our results cannot be generalized or provide precise data concerning the prevalence of ONSMs in patients with NF2. Further studies with more patients are necessary for a definite statement.

Most of our patients with ONSMs had marked reduction of ocular motility. The causative mechanisms were diverse and included restriction through the orbital tumor mass and paresis of the oculomotor nerves, be it by tumor compression or through intrinsic schwannomas. The distinction between these mechanisms could rarely be made owing to the preponderance of tumors in these patients with the severe NF2 phenotype.

Visual acuity in patients with ONSMs being cared for without an intervention naturally declines during the course of their illness, in some very slowly and in others rapidly. Most of our patients with ONSM experienced very poor VA in the affected eye at an early age. This visual loss was rapid, severe, and permanent, usually resulting in optic nerve atrophy.

Management of ONSMs has recently evolved from observation and surgery to the more promising fractionated conformal radiotherapy. Patients with good vision and no signs of optic neuropathy, proptosis, or strabismus are still managed by observation. In primary ONSMs, the outcome of surgery is blindness in most cases because stripping of the tumor tissue that is usually located close to the orbital apex, enveloping the nerve, results in deprivation of the blood supply. If detected at a stage when the tumor tissue has not yet advanced far into the optic canal, surgical removal of secondary ONSMs may be successful without postoperative functional deficits. This was the case in 2 of our patients. Promising results have been reported in recent studies on radiotherapy of ONSMs (mostly primary) using conformal treatment techniques, for example, 3-dimensional conformal radiotherapy, or the more precise stereotactic fractionated conformal radiotherapy. Their advantage is improved sparing of surrounding normal tissue with a high accuracy of dosage delivery to a specific target. Not many long-term adverse effects, such as late-onset radiation-induced retinopathy, have been reported because these therapy modalities are just beginning to be used in routine care. To date, there have been no studies published involving radiotherapy in patients with ONSMs and NF2. These patients carry an additional potential risk of irradiation-induced secondary tumors owing to their tumor suppressor gene defect. In conclusion, the results of this study document a strong association between ONSM and NF2 that parallels the well-known association of optic pathway gliomas with NF1. Retrospective detection of similar cases in the literature assists this implication. Thus, physicians should be aware of the possibility that patients with ONSM may also harbor NF2.

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REFERENCES
