OST schwannomas are single sporadic benign neoplasms. Bilateral vestibular schwannomas are the classic hallmark of neurofibromatosis type 2 (NF2), which predisposes patients to multiple schwannomas on cranial, spinal, and peripheral nerves and to intracranial and intraspinal meningiomas and intramedullary ependymomas. The term schwannomatosis or neurilemmomatosis has been used to describe patients with multiple nonvestibular schwannomas with no other signs of NF2. Segmental forms of the entity may occur. An exact delineation between schwannomatosis and NF2 has not been made, and an identical genetic background has been suggested.

Clinical Material and Methods

After a review of the files of all 243 patients who underwent operation for spinal schwannomas between 1953 and 1993 at the Department of Neurosurgery, Helsinki University Hospital, we identified 10 patients who had at least one spinal schwannoma and additional spinal or peripheral schwannoma(s), seven of whom were alive. Three patients with a spinal schwannoma and bilateral vestibular schwannomas consistent with NF2 were excluded. Another patient who had been examined at the department because she had four peripheral schwannomas was also included in the study. Informed consent was obtained from all eight living patients or their guardian. The patients were examined clinically by one of the authors (M.T.S.) to detect neurological abnormalities, skin mani-
Multiple schwannomas

Gadolinium-enhanced and noncontrast-enhanced MR images (Picker Outlook; Picker International, Helsinki, Finland) of the head and spine were obtained in all patients by using a 0.23-tesla open MR machine to identify central nervous system neoplasms. A neuroophthalmological examination (K.H.S.) was performed to detect any juvenile posterior subcapsular lenticular opacities or other ocular lesions. The tumor specimens were reexamined by a neuropathologist (M.J.J.H.) to verify the diagnosis and to find histopathological features suggestive of NF2, such as a lobulated architecture or frequent Verocay bodies.

Twenty sporadic spinal schwannomas randomly selected as control specimens were also examined for comparison.

Copies of the death certificates for the deceased patients were obtained from Statistics Finland.

A peripheral venous blood sample was taken from the eight living patients to obtain lymphoblasts for the molecular genetic analysis. All 17 exons of the \( \text{NF2} \) gene–coding region (excluding the first 35 bp from exon 1) were sequenced (M.A.S.), including exon splice sites (at least 3 bp flanking the intronic sequence). The exons were amplified from lymphoblast-derived DNA as described elsewhere,\(^1\) and the sequencing was performed using a sequencing kit (ABI PRISM Dye Terminator; Perkin-Elmer Applied Biosystems Division, Foster City, CA) according to the manufacturer’s instructions. The reactions were run on a sequencer (ABI 377 A; Perkin-Elmer).

**Results**

**Prevalence of NF2**

Among 243 patients with spinal schwannoma treated during a 41-year period, we identified five probable cases of NF2 (2%) and eight of schwannomatosis (3.3%).

Of the three patients who had died (Table 1), two middle-aged individuals (Cases 8 and 9) who presented with multiple spinal schwannomas showed no clinical signs of NF2 and died at a rather old age of unrelated diseases: coronary heart disease and colon cancer. One 11-year-old girl (Case 11) presented with multiple spinal schwannomas and died of progressive tetraplegia. No neuroradiological studies had been obtained in this patient, but the presence of left facial palsy indicated a cerebellopontine mass and we suspect NF2.

The follow-up examination in the eight living patients showed that seven, five men and two women, had schwannomatosis. At presentation these patients had a median age of 43.5 years (range 36.3–55.5 years). In three patients (Cases 2, 4, and 6) only one symptomatic schwannoma was removed primarily, although the myelographic study revealed multiple tumors. All the primary removals were complete. The median follow-up time was 9.9 years (range 3.1–22.6 years). During the follow-up period one patient (Case 2) underwent three lumbar re-laminectomies for six spinal schwannomas in all at 3, 7, and 14 years after the primary surgery. A second cervical schwannoma was partially removed 5 years after the initial surgery in another patient (Case 6). All patients were in good or fair clinical condition at the end of the follow-up period. One patient (Case 3) had moderate muscle atrophy of his right lower extremity, and one (Case 7) had permanent bladder paresis, a surgical complication after the removal of four lumbar schwannomas (Fig. 1). One young girl (Case 10) was found to have presumptive NF2 at follow-up examination.

**Family History of NF2**

The family history in all patients was negative for NF1,\(^1\) NF2,\(^2\) and schwannomatosis. The son of one patient (Case 2) had been treated for a retroperitoneal ganglioneuroma that proved to be benign on histological studies.

**Cutaneous Signs of NF1 or NF2**

At clinical examination none of the patients with schwannomatosis showed any new subcutaneous tumors, NF1-type skin tumors, café-au-lait spots, or axillary or inguinal freckling, but the patient with NF2 (Case 10) had developed new subcutaneous tumors on both arms.
Neuroophthalmological Examination

No patient showed posterior subcapsular lenticular opacities, Lisch nodules, or other ocular signs of NF2 or NF1. One patient (Case 4) had early senile cataracts.

Head and Spine MR Imaging

None of the seven patients with schwannomatosis examined at the end of the follow-up period had intracranial tumors, but the patient with NF2 (Case 10) had multiple intracranial meningiomas, bilateral trigeminal tumors, and a unilateral vestibular schwannoma (Fig. 2), in addition to multiple intraspinal and peripheral nerve root tumors. In three patients with schwannomatosis (Cases 4–6) a small remnant of the primary or secondary spinal schwannoma was identified (Fig. 3 left), although in two of them the operation had been considered radical. One patient (Case 2) showed two previously undetected tumors at T-3 (Fig. 3 right) and L-5, and one patient (Case 4) had an asymptomatic tumor at L-4, which remained unchanged for 14 years (Fig. 3 left).

Histological Examination

A lobular grapelike architecture was observed in the tumors of four patients with schwannomatosis and in both patients with NF2 (Fig. 4 and Table 2). A large number of distinct Verocay bodies was seen in two and a moderate number in four of the nine schwannomatosis cases. In the 20 randomly selected sporadic schwannomas a lobular architecture was identified in one, and the number of Verocay bodies was large in two and moderate in four cases.

Molecular Analysis of the NF2 Gene

Sequencing of the coding region of the NF2 gene from peripheral blood lymphoblast DNA obtained from the seven patients with schwannomatosis (Table 1, Cases 1–7) showed no mutations. The sequencing was also negative for the patient (Case 8) in whom NF2 was diagnosed by means of radiological studies in the follow-up examination.

Discussion

Neurofibromatosis Type 2

Previously, patients with multiple nerve sheath tumors were mostly considered to have “neurofibromatosis.” With the recognition of the two different entities NF1 and NF2 and their underlying gene defects a more precise clinical characterization became possible. The NF2 gene on
and the NF1 gene on chromosome 17 are tumor suppressor genes and loss of their function carries a predisposition to tumor formation. Both conditions manifest themselves with multiple nerve sheath tumors, but the lesions are mostly schwannomas in NF2 and neurofibromas in NF1.

Definite NF2 is present in an individual who has bilateral vestibular schwannomas or in an individual who has a first-degree family relative with NF2, is younger than 30 years of age, and presents with unilateral vestibular schwannoma or two of the following: meningioma, glioma, schwannoma, juvenile posterior subcapsular lenticular opacities, and juvenile cortical cataracts. Presumptive NF2 is present in an individual who is younger than 30 years of age, who has a unilateral vestibular schwannoma and at least one of the following: meningioma, glioma, schwannoma, juvenile posterior subcapsular lenticular opacities, and juvenile cortical cataracts.

Most patients with NF2 present initially with symptoms caused by vestibular schwannomas and only a minority show symptoms attributable to spinal tumors. In familial NF2 in which two or more family members are affected, linkage analysis is an accurate method to identify carriers of the NF2 gene defect. However, approximately half of all NF2 cases are caused by new mutations that are only detectable by direct mutation analysis. Mutations are found at most in two-thirds of NF2 cases, and it seems that in mildly affected individuals the mutation detection rate is markedly lower.

Schwannomatosis and NF2 Mutations

A condition characterized by multiple schwannomas was first described in reports from Japan, as neurilemmomatosis or schwannomatosis. Many of these early reports included patients who nowadays would be classified as having NF2. In 1995 Honda, et al., identified a mutated NF2 gene in the tumor tissue and peripheral leukocytes in three of seven patients with multiple schwannomas. This indicated that germline mutations in the NF2 gene were the molecular mechanism of schwannomatosis, which in this sense would represent an incomplete form of NF2. Also, the molecular genetic studies of both sporadic and familial schwannomas support the two-hit mutation inactivation mechanism of the NF2 gene in all schwannomas.

MacCollin, et al., presented a series of 14 patients with schwannomatosis, composed of eight females and six males with a median age at onset of 26 years. Eight of the patients were followed for more than 10 years, including four who were adolescents. All patients in the study had been examined using cranial MR imaging but not all had undergone spinal MR imaging. These authors considered schwannomatosis to be a distinct clinical entity separate from NF2.

The patients with schwannomatosis in our series were middle-aged at presentation, which corresponds to the age at which most patients with sporadic schwannomas present, but is in clear contrast to NF2, in which the patients tend to become symptomatic before 20 years of age.

The vestibular schwannomas in NF2 often show a grapelike lobulated or nodular appearance, and foci of
increased cellularity and Verocay bodies are more common than in sporadic schwannomas. The same features were also seen in the schwannomatosis tumors in this series and by others. In this study none of the seven patients with schwannomatosis had a family history positive for the disease. This differs somewhat from the 23 patients with schwannomatosis presented by MacCollin, et al., and Jacoby, et al., of whom five were familial cases with dominant inheritance linked to the NF2 locus, although the tumors showed incomplete penetrance and expressivity. Surprisingly, no germline NF2 mutations were found in those familial cases although they were linked to the NF2 locus. This implies an inherited predisposition to NF2 gene somatic alterations with no changes of the coding region. Also, Evans, et al., described multiple nonvestibular schwannomas that were linked to the NF2 locus without mutations in the NF2 gene in five families. Somatic mosaicism of the NF2 germline mutation explains some cases of schwannomatosis, which makes the risk of inheritance more difficult to predict. Based on these data schwannomatosis seems sporadic in most cases, but a number of affected individuals will have an inherited form of the entity. We found no germline mutations on direct sequencing of the NF2 gene in the patients with schwannomatosis, although this may be a more efficient method to detect mutations and low-level mosaicism than the widely used single-stranded conformation polymorphism sequencing. The germline mutation in the patient with NF2 was not discovered, which is not surprising because direct sequencing reveals a mutation in only half of NF2 cases (M Sainio, unpublished data).

Secondary Tumors in Schwannomatosis

The presence of more than one schwanna indicates a risk of developing new ones, but the clinical follow-up results in our patients showed great variation: some were followed for two decades with no new schwannomas seen, whereas some developed new symptomatic tumors every few years. All tumors verified on radiological studies did not necessarily grow or become symptomatic, even during a long follow-up period. MacCollin, et al., also reported the emergence of new tumors, but a definite risk cannot yet be assessed from the sparse literature available. It seems that some patients with schwannomatosis will develop new tumors, and in this respect schwannomatosis behaves like NF2.

Conclusions

Of patients presenting with a schwanna, 3 to 4% are found to have multiple lesions. As suggested by Jacoby, et al., the diagnosis of schwannomatosis seems justified for adult patients presenting with two or more schwannomas in different anatomical locations who show no clinical or radiological signs of a vestibular nerve tumor and no meningiomas, ependymomas, or any other signs of NF2. Most cases of schwannomatosis seem to be sporadic, and the age of the patient at onset corresponds to that seen in cases of solitary, sporadic schwannomas. These patients may develop new schwannomas, but the long-term outcome is still favorable. The presence of intracranial tumors or a young age may indicate NF2, and these patients should be examined and followed closely with regular MR imaging of the head and spine.

Acknowledgments

The authors thank Ms. Hannele Pihlaja, Ms. Paula Kristo, and Mr. Sebbe Sebse Wolde for technical assistance.

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Manuscript received April 14, 1997.
Accepted in final form March 2, 1998.
This work was supported by grants from the Maire Taponen Foundation and the Helsinki University Hospital.
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