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What to know about schwannomatosis: a literature review

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ABSTRACT

Background: Schwannomatosis is a relatively rare disorder and is related to neurofibromatosis type 2. Although there is clinical overlap between schwannomatosis and neurofibromatosis type 2, these diseases have to be regarded as separate entities due to the genetic origin and course of the disease.

Methods: A comprehensive review of the literature was conducted for relevant studies using Pubmed and Cochrane databases to discuss the epidemiology, clinical presentation, diagnostic criteria, pathological and imaging features, treatment and genetics of schwannomatosis.

Results: Germline mutations *SMARCB1* and *LZTR1* together with the *NF2* gene play a role in the pathophysiology of schwannomatosis. The most common symptom is pain with affection of the spine and peripheral nerves in the majority of patients. High quality contrast enhanced MRI scan is the imaging modality of choice. Treatment is conservative if asymptomatic and surgical if symptomatic. The goal is symptom control with preservation of neurological function.

Conclusion: Schwannomatosis is a relatively rare disorder in which the main goal is to preserve neurological function.

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Schwannoma;
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NF2 gene

Introduction

The neurocutaneous disorders neurofibromatosis type 1 and 2 are very well known by neurosurgeons for decades. More recently related forms of these two disorders have been reported. Legius syndrome or NF1-like syndrome is caused by mutations in the *SPRED1* gene and is associated with similar multiple café-au-lait spots as neurofibromatosis type 1 but the tumoral phenotype is absent.¹ Schwannomatosis is a disease related to neurofibromatosis type 2 and is characterized by peripheral and spinal schwannomas in the absence of bilateral vestibular schwannomas.^{2–6}

Familial schwannomatosis is an autosomal dominant disorder characterized by heterozygous inactivating mutations in the tumor suppressor genes, *SMARCB1* and *LZTR1* in the majority of familial cases and in some sporadic cases of schwannomatosis.^{2–6}

It is clear that schwannomatosis must be distinguished from type 1 and especially from type 2 neurofibromatosis because the genetic origin, course of the disease and its repercussions are different. Although there is, in part, clinical overlap between schwannomatosis and especially the mosaic form of *NF2*, these diseases have to be regarded as separate entities.

In this review, we describe the characteristics of schwannomatosis relevant for the neurosurgeon.

Epidemiology

Schwannomatosis is a very rare disorder with an estimated birth incidence of 1/40000 to 1/70000 and an incidence of 0.58 cases per 100000 persons/year.^{2,5,7,8}

It is characterized by a predisposition for multiple schwannomas and less commonly meningiomas. In schwannomatosis patients, the diagnostic criteria for *NF2* are occasionally met. There are no bilateral vestibular schwannomas in schwannomatosis but unilateral vestibular schwannomas can be seen in patients with an *LZTR1* mutation.^{1,2,5–9}

The majority of schwannomatosis patients occur sporadically whereas familial cases occur in 13%–25% of cases.^{3,7,8}

Clinical presentation

In patients with schwannomatosis, schwannomas commonly affect the spine in 74% of cases and the peripheral nerves in 89% of cases. Cranial nerve schwannomas are uncommon and upon appearance they mostly affect the trigeminal nerve (present in 8% of cases).

In 33% of cases with schwannomatosis, the lesions are anatomically limited to a specific segment of the body: a single limb, several contiguous spinal segments or one half of the body.

Schwannomatosis patients mostly develop symptoms in the second or third decade of life with a diagnostic delay of more or less 10 years. There is no predilection for race or sex. Patients most commonly present with chronic pain in 46% of cases or a mass in 27% of cases. In 11% of patients the clinical presentation is a combination of both.

In schwannomatosis patients, depression and anxiety are common comorbidities resulting from chronic pain and affecting 17% to 39% of patients. Additional tumors such as lipomas and angioliipomas occur in 11% and 3% of patients respectively.

Meningeomas occur in 5% of patients with schwannomatosis, most often as a solitary lesion.

The risk of malignancy is low and patients with schwannomatosis in general do not have a decreased life expectancy. But there seems to be an increased risk for malignant peripheral nerve sheath tumors in patients with a *SMARCB1* mutation.¹⁰

In contrast to neurofibromatosis type 2, vestibular schwannomas are rare and the occurrence of bilateral vestibular lesions must prompt the search for an alternative diagnosis. Unilateral vestibular schwannomas however may occur in schwannomatosis patients. On the other hand, intradermal schwannomas, ependymomas, gliomas, neurofibromas, eye abnormalities, skinfold freckling, greater than 6 café-au-lait spots and Lisch noduli which all typically seen in type 1 and/or type 2 neurofibromatosis do not occur in schwannomatosis.

Diagnostic criteria

Since research criteria were published in 1997 and MacCollin et al. postulated the first consensus diagnostic criteria for schwannomatosis in 2005, revisions of these criteria were published onto a background of an evolving genetic knowledge of this disease.

Currently, the diagnosis of schwannomatosis is based on molecular and/or clinical diagnostic criteria according to Plotkin et al. and Ostrow et al.¹¹

These criteria, together with exclusion criteria, are summarized in Table 1.

Pathological features

A schwannoma arises from Schwann cells. It is a benign tumor that is encapsulated by epineurium and grows eccentrically to the underlying nerve, thereby displacing the nerve fibers. In schwannomas, Schwann cells form fascicles with a wavy aspect of the cytoplasmic processes. Vessels with prominent hyaline walls are often seen (Figure 1(A)). Antoni A and Antoni B regions can be found. Antoni A regions are characterized by high cellularity and spindle-shaped nuclei arranged in palisades separated by nuclear-free zones. Antoni B regions are less cellular than Antoni A regions and have a more disorganized matrix. Degenerative features like myxoid/cystic degeneration, inflammation and fibrosis are not rare in longstanding tumors ('ancient' Schwannoma). Whatever it looks like, Schwannomas are always diffusely positive for S-100 protein (Figure 1(B)).

Schwannomas are as such clearly different from neurofibromas which are located centrally in the nerve with a diffuse infiltration between the axonal structures.

Imaging features

High quality MRI-scan with 3 mm thick slices through the internal auditory canal is the cornerstone of radiologic evaluation for vestibular schwannomas and as such the imaging modality of choice.

Schwannomas present as discrete well-defined round-to-oval lesions situated along the course of the nerve.

On MRI the lesions are low-to-intermediately intense on T1-weighted imaging (Figure 2(A,B)) and hyperintense on T2- and STIR-weighted sequences (Figure 3). They show an intense contrast enhancement and have a typical dumbbell-shape.

On CT, schwannomas are hypo- to isodense with a variable degree of contrast enhancement.

Treatment

Management of patients with schwannomatosis is symptom-oriented.

The rule is observation for the asymptomatic schwannoma patient. Surgical excision is only indicated for spinal cord compression and for symptoms clearly related to the schwannoma such as pain or a cumbersome mass.

The goal of treatment should be symptom control with preservation of neurological function.

In schwannomatosis patients there is no defined role for radiotherapy or chemotherapy. Radiotherapy should be reserved for life-threatening enlarging schwannomas that cannot be addressed surgically or for the very rare patient with a malignant schwannoma. Individual reports debate on the efficacy of bevacizumab. This however has not been tested in clinical trials, but

Table 1. Diagnosis of schwannomatosis based on molecular and/or clinical diagnostic criteria according to Plotkin et al.⁶ and Ostrow et al.¹¹

| | |
|---|--|
| Clinical diagnosis | |
| ≥2 non-intradermal schwannomas, 1 pathologically confirmed schwannoma and absence of bilateral vestibular schwannomas | |
| or | |
| 1 pathologically confirmed schwannoma or intracranial meningioma and 1 affected first-degree relative | |
| Combined molecular and clinical diagnosis | |
| ≥2 pathologically confirmed schwannomas or meningiomas | ≥2 tumors with 22q LOH and 2 different somatic NF2 mutations |
| or | |
| 1 pathologically confirmed schwannoma or meningioma | Germline <i>SMARCB1</i> or <i>LZTR1</i> pathogenic mutation |
| Exclusion criteria | |
| Germline pathogenic <i>NF2</i> mutation | |
| Diagnostic criteria for NF2 fulfilled | |
| First-degree relative with NF2 | |
| Schwannomas occur exclusively in a region of previous radiation therapy | |

there are a number of anecdotal reports suggesting a beneficial effect of bevacizumab in schwannomatosis patients.

Genetics

The genetics of schwannomatosis is not yet entirely unraveled.

To date, germline mutations in 2 genes have been identified in schwannomatosis patients: *SMARCB1* and *LZTR1*. These are tumor suppressor genes located on chromosome 22, centromeric to *NF2*. Germline *SMARCB1* mutations account for 48% of familial and 10% of sporadic schwannomatosis patients. Germline *LZTR1* mutations on the other hand explain 38% of familial and 30% of sporadic schwannomatosis cases. The genetic cause is unknown in 14% of familial cases and in 60% of sporadic cases. Recent data show that there are still undiscovered genes for familial schwannomatosis and this is the topic of

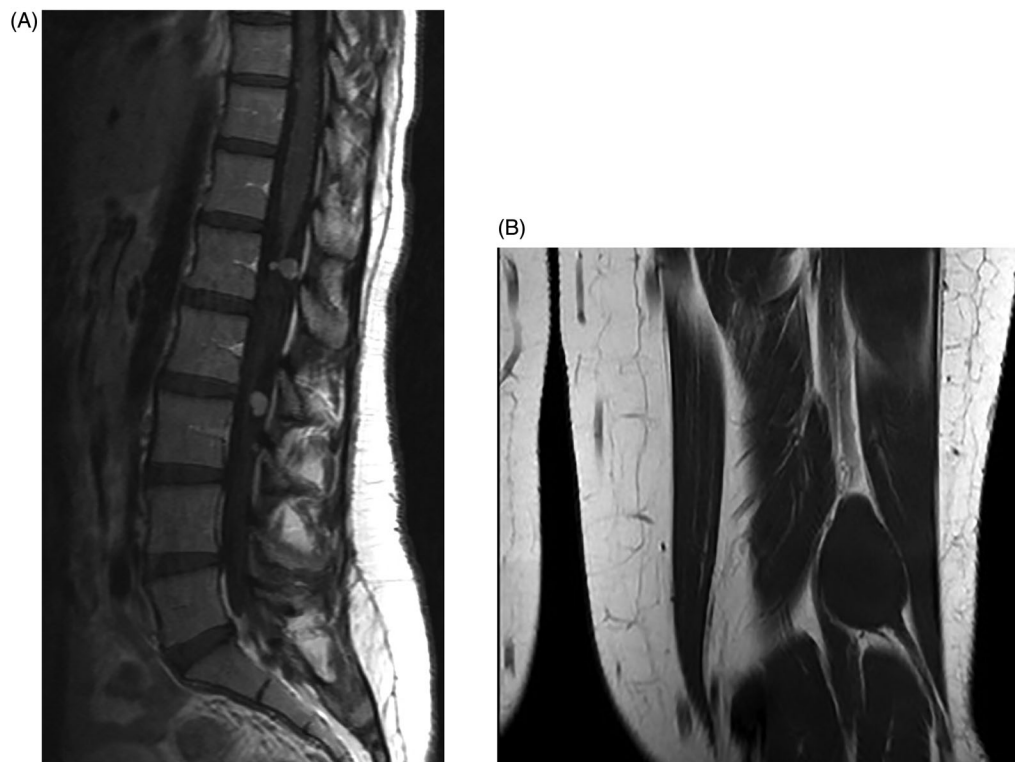


Figure 2. (A) T1-weighted MRI scan with contrast demonstrating the contrast enhanced schwannomas. (B) T1-weighted MRI scan without contrast.

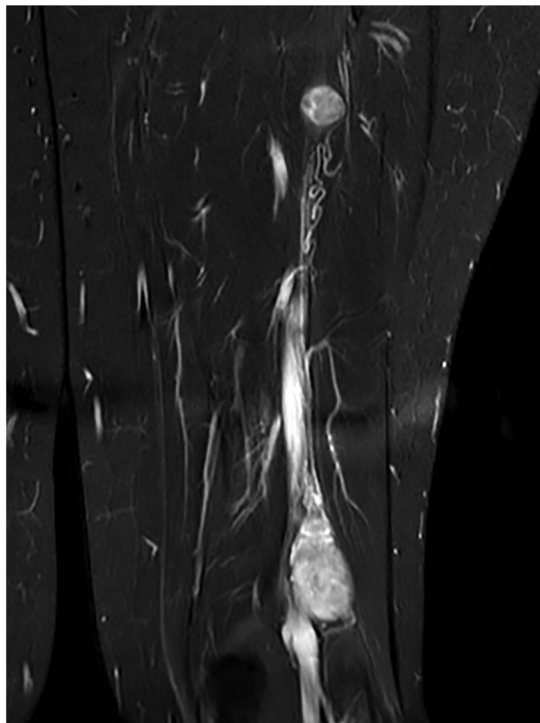


Figure 3. Hyperintense lesions on T2-weighted MRI scan without contrast.

current research. Sporadic cases are often clinically indistinguishable from mosaic neurofibromatosis type 2.⁹

The schwannomas of patients with a *SMARCB1* or *LZTR1* germline mutation frequently show loss of the chromosome 22 in

the tumor harboring the wild type *SMARCB1* or *LZTR1* gene. In addition independent tumor specific somatic mutations inactivating the *NF2* allele on the remaining chromosome 22 are frequently found in these schwannomas, meaning that these schwannomas are hemizygous for chromosome 22 genes and nullizygous for the *NF2* gene AND the *SMARCB1* or *LZTR1* gene. This led to the three-step, four-hit model of oncogenesis (Figure 4).⁶

The fact that somatic *NF2* mutations often coexist with constitutional *SMARCB1* or *LZTR1* mutations in schwannomatosis patients demonstrate that the classical 2-hit model of tumorigenesis is insufficient to account for the development of schwannomas in schwannomatosis. Genetic testing is possible on blood- and tumor-derived DNA and a comprehensive mutation analysis of *LZTR1*, *SMARCB1* *NF2* should be performed in patients with schwannomatosis.

It is important to point out here that mutations in the *SMARCB1* gene can be responsible for schwannomatosis but also for pediatric atypical teratoid/rhomboid tumors and rare cases of Coffin-Siris syndrome, a syndromic form of intellectual disability. The three different syndromes are usually associated with a specific set of mutations in *SMARCB1* but some overlap exists and a case of Coffin-Siris syndrome with schwannomatosis has been reported¹² and we are also aware of one unreported case (unpublished data: EL).

On the other hand mutations in *LZTR1* have been reported in schwannomatosis but also in patients with Noonan syndrome, a syndromic form of short stature and learning disabilities.¹³ Schwannomatosis is genetically heterogeneous because mutations in more than one gene can cause the disease.

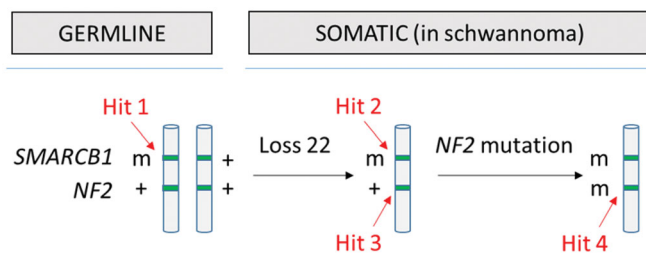


Figure 4. The four-hit, three-step model for tumorigenesis in schwannomatosis (here shown for *SMARCB1*): germline mutation in *SMARCB1* (hit 1), loss of a region of chromosome 22 (hit 2 and 3) and pathogenic mutation in remaining WT *NF2* allele (m=pathogenic mutation; += WT). The same mechanism has also been demonstrated for germline *LZTR1* mutations.

Conclusion

Schwannomatosis is a very rare disorder which has to be distinguished from the other, better known, neurofibromatosis. To date, germline mutations in *SMARCB1* and *LZTR1* have been identified in schwannomatosis however there most probably is also a role for the *NF2* gene.

The most common symptom in schwannomatosis patients is pain and the spine and peripheral nerves are affected in the majority of patients. In schwannomatosis there can be no diagnostic criteria for *NF2* in general and no (bilateral) vestibular schwannomas as well as no first-degree relatives with *NF2* and no known constitutional *NF2* mutation in particular.

High quality contrast enhanced MRI-scan is the imaging modality of choice.

Treatment of schwannomatosis patients is symptom-oriented with observation for the asymptomatic patient and with surgical excision for spinal cord compression and for symptoms clearly related to the schwannoma such as pain or a cumbersome mass.

The goal of treatment is symptom control with preservation of neurological function. Radiotherapy or systemic therapy are reserved for lesions non-accessible for surgery or for malignancy.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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