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Genetic Basis and Clinical Management of Schwannomatosis

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Schwannomatosis (SWN) is now recognized as a broad classification that includes neurofibromatosis (NF) type 2, reflecting their shared genetic and phenotypic characteristics. Previously, SWN and NF type 2 were considered distinct clinical entities; however, the 2022 classification revision has unified them under the umbrella of SWN, with NF type 2 now referred to as NF2-related SWN. SWN arises from mutations in *NF2*, *SMARCB1* (SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily b, member 1) or *LZTR1* (leucine zipper like transcription regulator 1). Recent diagnostic criteria for SWN incorporate molecular classification, including "NF2-related SWN", "SMARCB1-related SWN", "LZTR1-related SWN", "22q-related SWN", "SWN-not otherwise specified", or "SWN-not elsewhere classified". NF2-related SWN is a genetic condition where all individuals with a germline or constitutional *NF2* mutation are destined to develop the disease. The pathogenesis of SMARCB1- or LZTR1-related SWN follows a three-step, four-hit model. This involves retention of the mutated germline *SMARCB1* or *LZTR1* allele in the tumor, loss of the wild-type chromosome 22, and somatic mutation in the *NF2* gene. Clinically, NF2-related SWN involves bilateral vestibular schwannomas, with treatment options including microsurgery, radiotherapy, and bevacizumab, each with specific benefits and limitations. Patients with SWN frequently present with chronic pain caused by schwannomas, which often does not correlate with tumor size, location, or burden. Management of SWN is primarily symptom-based. Surgical intervention is reserved for symptomatic lesions, particularly in cases of spinal cord compression or significant functional impairments. Multidisciplinary approaches to pain management are critical for enhancing quality of life. Although malignant transformation of schwannomas is a potential risk, the life expectancy of individuals with SWN is nearly normal. Despite advancements in understanding SWN, further research is necessary to elucidate the underlying genetic mechanisms and to develop targeted therapeutic strategies for this complex disorder.

Key Words : Schwannomatosis · Neurofibromatosis 2 · Classification · Disease management.

INTRODUCTION

In 2022, the classification of schwannomatosis (SWN) was revised to incorporate neurofibromatosis (NF) type 2, acknowledging its genetic and phenotypic similarities with NF type 2[12,13]. This revision was based on the shared predisposition for schwannoma formation and the involvement of mutations in the *NF2*, *SMARCB1* or *LZTR1* genes[13,33]. As a result, the term "neurofibromatosis 2" is no longer in use[25], and SWN is now classified under several subtypes, including "NF2-related schwannomatosis", "SMARCB1-related schwannomatosis", "LZTR1-related schwannomatosis", "22q-related schwannoma-

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Table 1. Revised classification and diagnostic criteria of schwannomatosis subtypes[13,26]

Schwannomatosis subtype	Diagnostic criteria
NF2-related schwannomatosis (NF2-SWN)	1. Presence of bilateral VS 2. Identification of an identical *NF2* pathogenic variant in at least two anatomically distinct NF2-related tumors 3. Fulfillment of either two major criteria or one major criterion with two minor criteria Major criteria : 1) unilateral VS; 2) a first-degree relative (excluding siblings) with NF2-SWN; 3) two or more meningiomas (a single meningioma qualifies as a minor criterion); and 4) detection of an *NF2* variant in unaffected tissue (blood or saliva) with a variant allele fraction below 50% indicating mosaic NF2-SWN Minor criteria : 1) ependymoma, meningioma, or schwannoma (If unilateral VS is used as a major criterion, at least one schwannoma must be dermal) and 2) minor criteria that can only be counted once include : juvenile subcapsular or cortical cataract, retinal hamartoma, and epiretinal membrane diagnosed before age 40
SMARCB1- or LZTR1-related schwannomatosis (SMARCB1- or LZTR1-SWN)	1. Presence of at least one pathologically confirmed schwannoma or hybrid nerve sheath tumor 2. Identification of a pathogenic *SMARCB1* or *LZTR1* variant in unaffected tissue (blood or saliva). If the variant allele fraction is below 50%, the diagnosis should be classified as mosaic SMARCB1- or LZTR1-SWN 3. Identification of a shared pathogenic *SMARCB1* or *LZTR1* variant in two separate schwannomas or hybrid nerve sheath tumors
22q-related schwannomatosis (22q-SWN)	1. Does not fulfill criteria for NF2-, SMARCB1-, or LZTR1-SWN 2. Exhibits both : 1) loss of heterozygosity at the same chromosome 22q loci in two anatomically distinct schwannomas or hybrid nerve sheath tumors and 2) a distinct *NF2* pathogenic variant in each tumor, which is not detectable in unaffected tissue
Schwannomatosis-not otherwise specified (SWN-NOS)	1. Genetic testing has not been conducted or results are unavailable 2. Presence of two or more lesions on appropriate imaging studies consistent with non-intradermal schwannomas 3. Histopathological confirmation of at least one schwannoma or hybrid nerve sheath tumor
Schwannomatosis-not elsewhere classified (SWN-NEC)	Genetic testing of unaffected tissue and at least two anatomically distinct tumors fails to identify a pathogenic variant in any known genes associated with SWN or related conditions

NF2 : neurofibromatosis type 2, SMARCB1 : SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily b, member 1, LZTR1 : leucine zipper like transcription regulator 1, VS : vestibular schwannoma

tosis", "schwannomatosis-not otherwise specified", or "schwannomatosis-not elsewhere classified" (Table 1)[13,26].

SWN was previously recognized as a distinct clinical entity, separate from NF type 1 and type 2. Traditionally, SWN was diagnosed based on the presence of multiple schwannomas without bilateral vestibular schwannomas, which are characteristic of NF type 2[10]. However, due to radiological features, SWN has often been misdiagnosed as NF type 1, particularly when schwannomas or hybrid nerve sheath tumors were misclassified as neurofibromas[25].

Therefore, a clear understanding of the current classification of SWN is essential for accurate diagnosis and appropriate clinical management.

DEFINITION AND DIAGNOSIS

The initial diagnostic criteria were established and published in 2005[17]. The criteria initially required the presence of at least two schwannomas, excluding vestibular schwannoma (VS), as confirmed by magnetic resonance imaging (MRI) after the age of 18. However, the application of these standards did not account for individuals with NF type 2 who presented non-VS symptoms at a younger age. Subsequent investigations revealed that, unilateral VS can occasionally occur in SWN[31], leading to further revisions of the initial diagnostic criteria. These revisions ultimately introduced a molecular classification following the identification of *NF2*, *SMARCB1* and *LZTR1* as causative factors for SWN[25]. The revision integrates NF type 2 and SWN into a unified category of SWN, distinguished by the specific gene involved or, in cases where the gene remains unidentified, by a descriptive label[13]. In the revised nomenclature published in 2022, SWN is classified under several terms, including "NF2-related schwannomatosis", "SMARCB1-related schwannomatosis", "LZTR1-related schwannomatosis", "22q-related schwannomatosis", "schwannomatosis-not otherwise specified", or "schwannomatosis-not elsewhere classified"[13,25]. NF2-related SWN was previously referred to as NF type 2. Other SWNs should be considered in cases where multiple non-intradermal schwannomas are present, with at least one confirmed by path-

ological examination, and in the absence of bilateral VS on high-resolution MRI. A family history of autosomal dominant inheritance of SWN supports the diagnosis[6]; however, the lack of a known family history does not exclude the condition[6]. Regarding the diagnostic criteria for SWN, molecular analysis is deemed clinically essential for all individuals with suspected NF type 2 or SWN. Consequently, patients suspected to having SWN should undergo comprehensive molecular genetic testing, which may require the analysis of various tissues, including tumor samples when available[10,13,25].

NF2-related Schwannnomatosis (NF2-SWN)

A diagnosis of NF2-SWN can be established if a patient meets one of the following criteria : 1) the presence of bilateral VS; 2) identification of an identical *NF2* pathogenic variant in at least two anatomically distinct NF2-related tumors; or 3) fulfillment of either two major criteria or one major criterion in combination with two minor criteria. The major criteria include : 1) unilateral VS; 2) a first-degree relative, other than a sibling, with NF2-SWN; 3) the presence of two or more meningiomas, noting that a single meningioma qualifies as a minor criterion; and 4) detection of an *NF2* variant in unaffected tissue, such as blood or saliva, where a variant allele fraction clearly below 50% indicates a mosaic NF2-SWN diagnosis. The minor criteria, which can be counted more than once of each type (e.g., two schwannomas are counted as two minor criteria), include : ependymoma; meningioma, or schwannoma, with the additional condition that if unilateral VS is used as a major criterion, at least one schwannoma must be dermal in location. Minor criteria that can be counted only once include : juvenile subcapsular or cortical cataract, retinal hamartoma, epiretinal membrane diagnosed before the age of 40[13].

SMARCB1- or LZTR1-related SWN (SMARCB1- or LZTR1-SWN)

A diagnosis of SMARCB1- or LZTR1-SWN can be established when a patient meets one of the following criteria : 1) the presence of at least one pathologically confirmed schwannoma or hybrid nerve sheath tumor, coupled with the identification of a pathogenic *SMARCB1* or *LZTR1* variant in an unaffected tissue, such as blood or saliva. If the variant allele fraction is clearly less than 50%, the diagnosis should be classified as mosaic SMARCB1- or LZTR1-SWN and 2) the identification a shared pathogenic *SMARCB1* or *LZTR1* variant in two separate schwannomas or hybrid nerve sheath tumors[13,25].

22q-related SWN (22q-SWN)

A diagnosis of 22q-SWN can be established when an individual does not fulfill the criteria for NF2-, SMARCB1-, or LZTR1-SWN, and exhibits both of the following molecular features : 1) loss of heterozygosity at the same chromosome 22q loci in two anatomically distinct schwannomas or hybrid nerve sheath tumors and 2) a distinct *NF2* pathogenic variant in each tumor, which is not detectable in unaffected tissue[13,25].

SWN-not otherwise specified (SWN-NOS) and SWN-not elsewhere classified (SWN-NEC)

If genetic testing has not been conducted or the results are unavailable, a diagnosis of SWN-NOS may be established if the following two criteria are met : 1) the presence of two or more lesions on appropriate imaging studies that are consistent with non-intradermal schwannomas and 2) histopathological confirmation of at least one schwannoma or hybrid nerve sheath tumor.

In contrast, a diagnosis of SWN-NEC can be made if genetic testing of unaffected tissue, as well as at least two anatomically distinct tumors, fails to identify a pathogenic variant in any of the known genes associated with SWN or related conditions[13].

GENETICS AND PATHOGENESIS OF SWN

The genetic pathogenesis of SWN involves tumor suppressor genes *NF2*, *SMARCB1*, and *LZTR1*, all located on chromosome 22. NF2-SWN is a fully penetrant disorder, indicating that any individual who carrying a germline or constitutional *NF2* pathogenic variant will inevitably develop the disease[25]. SMARCB1- and LZTR1-SWN frequently exhibit loss of the wild-type chromosome 22, which harbors the intact *SMARCB1* or *LZTR1* genes. Furthermore, these tumors often acquire independent, tumor-specific somatic mutations that inactivate the *NF2* allele on the remaining chromosome 22. Consequently, schwannomas become hemizygous for genes located on chromosome 22, while being nullizygous for both *NF2* and *SMARCB1* or *LZTR1*[29]. This pattern of genetic alteration supports the development of a three-step four-hit model of oncogenesis in these tumors (Fig. 1)[24,29,33]. This sequence of events provides a framework for understanding the molecular mecha-

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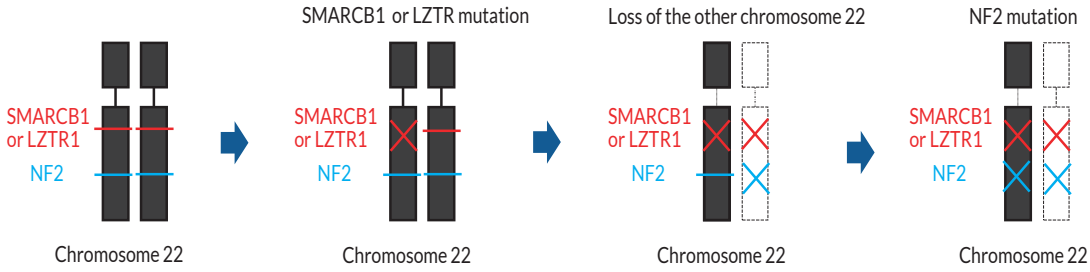

Fig. 1. The tumorigenesis process in schwannomatosis (SWN) is described by three-step, four hit model. According to this model, the first event involves the retention of a mutated germline *SMARCB1* or *LZTR1* allele in the tumor (hit 1), Subsequently, chromosome 22, or at least a segment containing the wild-type alleles of *SMARCB1*, *LZTR1*, and *NF2*, is lost (hits 2 and 3). Finally, a somatic mutation occurs in the remaining wild-copy of the *NF2* gene (hit 4), completing the sequence of genetic alterations. SMARCB1 : SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily b, member 1, LZTR1 : leucine zipper like transcription regulator 1, NF2 : neurofibromatosis type 2.

nisms underlying the development of these tumors. The molecular pathogenesis of SWN is driven by a stepwise accumulation of genetic alternations, including germline mutations, chromosomal loss, and somatic *NF2* mutations. In 2007, *SMARCB1* was identified as the first familial gene associated with susceptibility to SWN[4]. Subsequently, in 2014, *LZTR1* was recognized as the second causative gene implicated in the development of SWN[23]. Some familial SWN do not exhibit germline variants in *SMARCB1* or *LZTR1*, indicating the potential involvement of additional genes in the pathogenesis of SWN. Among these, *DGCR8* has been proposed as a candidate gene. This hypothesis is supported by reports of a three-generation family and an unrelated sporadic case, both characterized by multiple schwannomas and multinodular goiter, in which a *DGCR8* variant on chromosome 22q was identified[21]. These findings highlight the need for further investigations in additional families to validate the role of *DGCR8* in the development of SWN.

SMARCB1

The *SMARCB1* gene has also been associated with a predisposition to meningioma development certain families; however, this tumor remains relatively rare even among individuals with SMARCB1-SWN[5,14]. Sporadic meningiomas that arise as isolated tumors without any other clinical features of SWN may harbor somatic *SMARCB1* variants that are absent in the germline[26,28]. *SMARCB1* functions as a tumor suppressor gene. Genetic variants of *SMARCB1* that elevate the risk of familial SWN are predominantly non-truncating[27]. Among these, mutations in exon1 and the 3' untranslated region have been identified as the most frequently reported alterations[32]. This observation contrasts with mutations identified in atypical teratoid/rhabdoid tumor (AT/RT), which primarily involve the central exons or result in deletions of all or significant portions of the coding sequence. The strong association between missense mutations and familial SWN, as opposed to AT/RT, underscores this distinction. Although truncating mutations are predominantly observed in AT/RT, they also occur in SWN, particularly in exon 1. These findings reinforce the hypothesis that mutations in AT/RT are linked to the complete loss of the *SMARCB1* protein, whereas SWN-associated mutations are more likely to be hypomorphic, leading to reduced expression levels or partial loss of function of the *SMARCB1* protein[32]. Furthermore, germline truncating variants of *SMARCB1*, exon deletions, or complete or large deletions of *SMARCB1* have been identified in 15–60% of individuals diagnosed with AT/RTs[3].

LZTR1

LZTR1 encodes a protein localized to the Golgi apparatus and is a member of the BTB-Kelch superfamily. This protein plays a role in polyubiquitination and the subsequent degradation of rat sarcoma (RAS) via the ubiquitin-proteasome system, thereby contributing to the sustained activation of the RAS/mitogen-activated protein kinase signaling pathway[1,20]. In up to 8% of individuals with Noonan syndrome (NS), a genetic multisystem disorder, *LZTR1* mutations have been implicated[15]. A single case of NS co-occurring with SWN has also been documented[35]. NS is characterized by developmental delays, distinctive facial features, congenital cardiac abnormalities and short stature[11]. Loss of *LZTR1* function, either through genetic mutations or deletions, impairs the self-renewal and proliferation of glioma stem cells. In sporadic glioblastoma, which manifests are isolated tumors without other clinical features of SWN, a somatic variants of

LZTR1 are not present in the germline.

CLINICAL FEATURES AND MANAGEMENT OF SWN

VSs

NF2-SWN is characterized by the development of bilateral VS[7]. Treatment options include microsurgery, radiotherapy, and pharmacotherapy with bevacizumab. Each approach has distinct advantages and limitations. Microsurgical resection is effective in reducing tumor volume; however, tumor recurrence and hearing loss occur in approximately 50% of the cases[18]. Radiotherapy provides good tumor control in most patients with NF2-SWN, yet it is frequently associated with hearing impairment and other nerve deficits[7]. Bevacizumab, a monoclonal antibody targeting vascular endothelial growth factor, inhibits tumor angiogenesis and has demonstrated the ability to halt or reverse tumor progression, particularly in schwannomas[7]. However, its use is associated with significant adverse effects, including hypertension, proteinuria, and hematologic disorders[7].

Schwannomas and pain

Patients with SWN typically present with multiple schwannomas, which frequently develop in the spinal nerve roots, particularly in the lumbar spine - the most commonly affected region[16]. Schwannomas may also occur in the peripheral nerves throughout the body and, less commonly, in cranial nerves, including unilateral involvement of the vestibular nerve (histologically benign nerve sheath tumors)[9,10]. While schwannomas associated with SWN are histologically similar to their sporadic counterparts, certain features are more commonly observed in SWN-related schwannomas. These include whorling patterns, myxoid alterations, and evidence of nerve swelling and/or infiltration[2,13]. Furthermore, schwannomas in SWN patients often exhibit mosaic loss of *SMARCB1/INI1* expression, despite variability among lesions. Immunohistochemistry for *SMARCB1/INI1* is a reliable diagnostic marker for SWN and is used to determine whether a schwannoma is associated with predisposition syndrome. However, *SMARCB1/INI1* expression can also be detected in VSs associated with NF2-SWN, limiting its utility in distinguishing NF2-SWN from other forms of SWN[4,13].

Patients with SWN typically present with chronic pain, which is a hallmark feature of the disease. This pain may be localized or diffuse and frequently shows no correlation with the

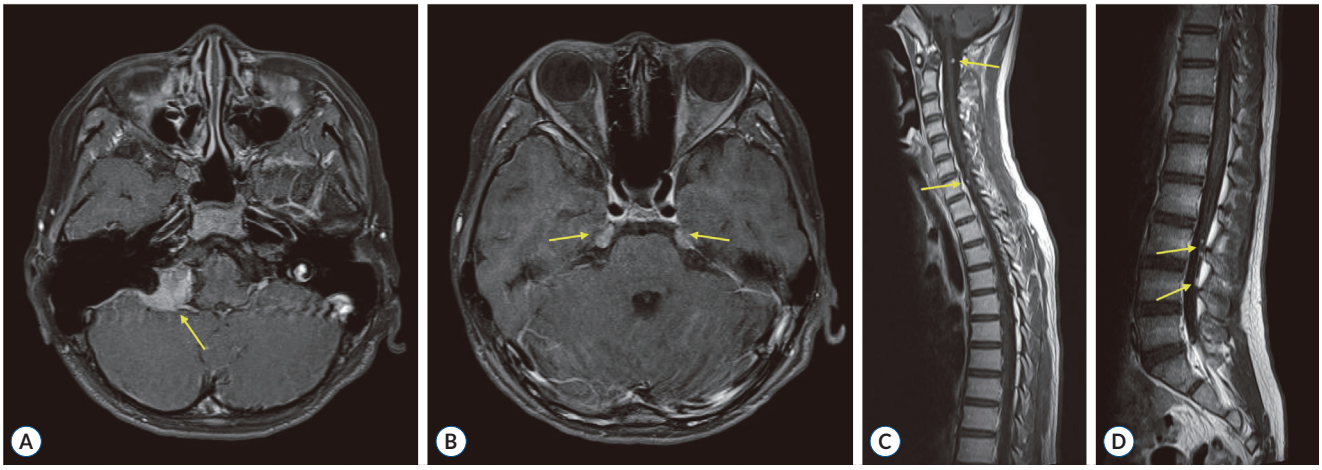

Fig. 2. A 12-year-old boy presented to the outpatient clinic with a 2-month history of persistent hoarseness and mild swallowing discomfort, though without significant aspiration. Neurological examination revealed intact extraocular movements, preserved facial sensory and motor functions, and normal visual and auditory function. However, uvular deviation to the left was observed. Brain magnetic resonance imaging (MRI) demonstrated a 3 cm-enhancing mass near the right jugular foramen (arrow) (A), along with smaller enhancing masses in the bilateral Meckel's caves (arrows) (B). Spine MRI revealed multiple small enhancing nodules along the cervical and thoracic spinal cord and the cauda equina (arrows) (C and D). There was no sign of vestibular schwannomas. These findings raised suspicion of a tumor-prone genetic syndrome, such as neurofibromatosis (NF) type 2. The patient had no family history of similar disorders or intracranial schwannomas. Germline genetic testing for the *NF2* gene revealed no pathogenic alterations. A diagnosis of probable SWN was made. The patient was managed with regular imaging follow-ups due to the stability of his symptoms. At a 4-year follow-up, the patient's hoarseness and mild swallowing discomfort remained stable, and all tumors showed no significant growth on imaging.

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tumor's size, location, or overall burden. Although schwannomas often develop during the second or third decade of life, a formal diagnosis is frequently delayed for several years due to the lack of a clear association between tumor characteristics and pain-related morbidity[33]. In contrast, neurological deficits and polyneuropathy are relatively uncommon among individuals with SWN[19,29].

The management of SWN is primarily symptom based (Fig. 2). Asymptomatic patients are generally monitored through observation. Surgical intervention is recommended only in cases of spinal cord compression or when symptoms such as pain or weakness are clearly associated with schwannomas. Surgical resection is advised for symptomatic lesions if the procedure can be performed without causing neurological deficits and by surgeons with expertise in nerve sheath tumor resection[10,29]. However, certain lesions may be inoperable, and surgical procedures are associated with a higher risk of morbidity[10]. Currently, no specific medical treatments are available for SWN. Management is largely focused on multidisciplinary approaches to pain relief, aiming to enhance quality of life, optimize functional capacity, and minimize complications. Given the neuropathic nature of the pain commonly associated with schwannomas, first-line pharmacological treatments typically include tricyclic antidepressants and gabapentin. For patients who do not respond to these treatments, second-line options may involve selective serotonin reuptake inhibitors or anticonvulsants, such as topiramate, carbamazepine, or oxcarbazepine[10,33]. Radiotherapy may increase the risk of malignant transformation in patients with SWN and is therefore reserved for cases of growing schwannomas that are not amenable to surgical treatment or for rare instances of malignant schwannoma[10,29]. Patients with intractable pain, which significantly impacts their quality of life, often experience substantial psychological distress. This pain may lead to severe emotional consequences, including an elevated risk of suicide. Therefore, psychological assessments are recommended during annual follow-up visits. Additionally, effective pain management may play a critical role in alleviating symptoms of anxiety and depression, thereby improving overall patient well-being[6,10,29].

Meningioma

Individuals diagnosed with an apparently isolated meningioma before the age of 25 should undergo further evaluation for potential tumor predisposition syndrome, given its significant implications and the possibility of familial disease. Among patients with a solitary meningioma, 40% were found to have NF2-SWN[22]. Studies have demonstrated that genetic mutations in *SMARCB1* are associated with an increased risk of developing multiple meningiomas[5,34]. Among the patients diagnosed with other SWNs, approximately 5% were reported to have meningiomas[30].

Malignancy and prognosis

The malignant transformation of schwannomas remains a potential risk in individuals with SMARCB1-SWN[8]. Rapid growth of schwannomas and intractable pain should prompt suspicion of possible malignancy. Despite this risk, the life expectancy of individuals with SWN appears to be near normal, with an average of 76.9 years. This is notably higher than the mean life expectancy of patients with NF2-SWN, which is 66.2 years[9].

CONCLUSION

SWN is a rare genetic disorder that must be distinguished from NF type 1. Germline mutations in *NF2*, *SMARCB1* and *LZTR1* have been identified as critical contributors to the pathogenesis of SWN. A revised molecular classification and nomenclature for SWN, proposed in 2022, underscores the importance of molecular analysis in the accurate diagnosis of this condition. The most common clinical manifestations of SWN include the development of VSs, multiple schwannomas, and chronic pain. The management of SWN is primarily symptom-based, with asymptomatic patients typically monitored through observation. Surgical intervention is indicated in cases involving spinal cord compression or when schwannomas are associated with significant symptoms, such as severe pain or debilitating masses. Effective symptom control is a cornerstone of SWN management, and pain management is particularly critical in alleviating associated symptoms, including anxiety and depression, thereby improving overall patient quality of life.

AUTHOR'S DECLARATION

Conflicts of interest

Ji Hoon Phi has been editorial board of JKNS since October 2024. He was not involved in the review process of this original

article. No potential conflict of interest relevant to this article was reported.

Informed consent

This type of study does not require informed consent.

Author contributions

Conceptualization : SN, JHP; Data curation : SN, JHP; Funding acquisition : JHP; Methodology : JHP; Project administration : JHP; Visualization : JHP; Writing - original draft : SN; Writing - review & editing : JHP

Data sharing

None

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None

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