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REVIEW

Optimal Delivery of Pain Management in Schwannomatosis: A Literature Review

Utaro Hino[1], Ryota Tamura[2], Masahiro Toda[2]

[1]Department of Neurosurgery, Saiseikai Yokohamashi Tobu Hospital, Kanagawa, Japan; [2]Department of Neurosurgery, Keio University School of Medicine, Tokyo, Japan

Correspondence: Ryota Tamura, Department of Neurosurgery, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo, 160-8582, Japan, Email moltobello-r-610@keio.jp

Abstract: Non-NF2 schwannomatosis is a rare syndrome characterized by multiple benign schwannomas that primarily affect nerve sheaths, with chronic, treatment-resistant pain as the most common symptom. No protocol has been established for pain management, and pharmacotherapies, including molecular target therapies, are being evaluated. Neuromodulation therapies such as scrambler therapy and surgical options are also employed; however, surgery may lead to persistent or recurrent pain caused by nerve damage or tumor recurrence. The lack of accurate animal models hampers understanding of pain mechanisms and tumor development, necessitating further basic research and clinical trials to improve treatment strategies.

Keywords: schwannomatosis, pain, surgery, medication, neuromodulation

Introduction

Traditionally, schwannomatosis is a syndrome characterized by the development of multiple schwannomas, distinct from neurofibromatosis type 1 and 2 (NF2).[1] In 2022, the nomenclature of NF2 and schwannomatosis was revised and defined by pathogenic mutations in multiple genes on chromosome 22.[2,3] Previously known as schwannomatosis, this syndrome is now called non-NF2 schwannomatosis, which is characterized by mutations of the tumor-suppressor genes *SMARCB1* and *LZTR1* and the loss of heterozygosity on chromosome 22q.[3–7] Non-NF2 schwannomatosis is a syndrome characterized by the occurrence of multiple benign schwannomas that primarily affect the nerve sheaths, with a lower incidence of vestibular schwannomas than NF2-schwannomatosis. It is an exceedingly rare disorder, with an annual incidence of 0.58 per million, approximately half that of NF2 schwannomatosis.[8,9] Most cases of non-NF2 schwannomatosis occur sporadically, although familial cases account for 13%–25%.[8,10,11]

Patients with non-NF2 schwannomatosis most frequently and initially complain of pain.[11–13] It is typically resistant to treatment, chronic, and often accompanied by anxiety and depression.[14] Unlike NF2 schwannomatosis, patients' average life expectancy is not typically reduced;[9] however, malignant transformation and shortened survival are causes of concern in some cases.[13,15] The management of patients with schwannomatosis is primarily symptomatic, with observation as the principal approach for asymptomatic schwannomas. In symptomatic cases, chronic, intractable pain significantly affects the quality of life (QOL), making pain control the primary therapeutic goal.[3,12,16] This review summarizes the latest information on pain management in non-NF2 schwannomatosis.

Tumor Distribution

In non-NF2 schwannomatosis, tumors typically arise in subcutaneous tissues and peripheral, spinal; cranial, and sciatic nerves, within the pelvic region.[17,18] Given that tumors may be nonpalpable or asymptomatic, clinically assessing all tumors in patients with non-NF2 schwannomatosis is challenging. A study using whole-body magnetic resonance imaging (MRI) revealed that out of 51 patients with non-NF2 schwannomatosis, 36 had one or more internal tumors.[18] The median number of tumors in affected patients was 4 (range, 1–27), and the median total tumor volume

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was 39 mL (range, 7–1372 mL). Spinal schwannomas in patients with non-NF2 schwannomatosis tend to cluster in the lumbar region, which contrasts with sporadic schwannomas that are more commonly found in the cervical and thoracolumbar regions.[12,19] *LZTR1* mutations were reported to increase the incidence of spinal schwannomas.[20]

Mechanisms of Pain Development in Non-NF2 Schwannomatosis

Despite reports indicating a correlation between the total tumor volume and pain intensity,[20] pain is not strictly associated with tumor growth or mechanical nerve compression.[11] Pain may be localized to the tumor site or may spread beyond the tumor's location,[21] reflecting the presence of pain-inducing mechanisms beyond mechanical compression.

Studies have reported that Schwann cells contribute to pain by secreting cytokines such as tumor necrosis factor-α and prokineticin 2, which sensitize nociceptors.[22,23] The nerve growth factor (NGF), initially identified as a neurotrophic factor, has increasingly been recognized as a key mediator, particularly in inflammatory and neuropathic pain.[24,25] NGF is also expressed in Schwann cells and is involved in the sustained hyperalgesia observed in non-NF2 schwannomatosis.[26–28] NGF expression has been detected in schwannomas resected from patients with non-NF2 schwannomatosis and in conditioned media from schwannoma cultures,[29] indicating its involvement in schwannomatosis-associated pain responses. Similarly, fibroblast growth factors are associated with neuropathic pain.[30,31] Schwannomas secrete high mobility group box 1, which stimulates surrounding dorsal root ganglion neurons, leading to CCL2 expression, macrophage recruitment, and interleukin (IL)-6 overproduction, a process implicated in pain generation.[32]

Patients with non-NF2 schwannomatosis carrying *LZTR1* mutations tend to experience more severe pain than those carrying *SMARCB1* mutations, indicating the potential association of germline mutations with pain severity.[20] The cause of the pain differences between these mutations is unclear but is hypothesized to be caused by the distinct functions of *SMARCB1* and *LZTR1*. *SMARCB1* is associated with the SWI/SNF human chromatin remodeling complex and is involved in the regulation of genome-wide gene expression,[33] whereas *LZTR1* functions as an adaptor protein for the Cullin-3 ubiquitin ligase complex, mediating the ubiquitin-dependent degradation of proteins such as epidermal growth factor receptor (EGFR) and anexelekto (AXL). LZTR1 mutations result in the abnormal accumulation of these proteins, leading to the aberrant activation of growth factor signaling. Schwannoma-like tumors have been shown to form in *LZTR1*-deficient mice.[34–36]

Pain Management

Medications

To date, no pharmacotherapy specifically for non-NF2-Schwannomatosis has been established, and medications commonly used for neuropathic pain, such as gabapentin, pregabalin, nonsteroidal anti-inflammatory drugs (NSAIDs), tricyclic antidepressants (such as amitriptyline), serotonin–norepinephrine reuptake inhibitors (such as duloxetine), anticonvulsants (such as topiramate and carbamazepine), and short-acting opioids, are also employed in managing pain in non-NF2 schwannomatosis.[37–42] In addition, the following drugs have been suggested to be effective in pain management in patients with non-NF2 schwannomatosis.

Cannabinoids

A case report indicated that the administration of tetrahydrocannabinol/cannabidiol crystals led to improvements not only in pain but also in the mood and QOL of a patient whose previous pain management, including opioids and antineuropathic drugs, had been completely ineffective.[38] Cannabidiol is thought to exert analgesic effects by acting on the transient receptor potential vanilloid subtype 1 receptors, which are primarily expressed on nociceptive neurons.[43,44] These receptors are nonselective nociceptive cation channels that take on a crucial role in pain transmission by promoting Ca2+ influx into peripheral sensory neurons.[45,46]

Bevacizumab

Bevacizumab, a monoclonal antibody against vascular endothelial growth factor A, has shown early promising results in clinical trials that target vestibular schwannomas in patients with NF2 schwannomatosis.[47] A study reported

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bevacizumab may reduce the tumor size and alleviate pain in non-NF2 schwannomatosis.[48] However, its use is associated with side effects, such as thrombosis, bleeding, visceral perforation, hypertension, and renal impairment.[49–51]

Brigatinib

Brigatinib, an inhibitor of anaplastic lymphoma kinase and several other tyrosine kinases, has demonstrated radiographic responses in multiple tumor types in NF2 schwannomatosis, with notable effects on meningiomas and nonvestibular schwannomas.[52] It has also demonstrated clinical benefits, including pain reduction. Given that *LZTR1* mutations are implicated in tumorigenesis through the dysregulation of tyrosine kinase pathways, including those involving EGFR and AXL,[35] brigatinib may exert similar effects on non-NF2 schwannomatosis. Its use is associated with side effects such as gastrointestinal symptoms (diarrhea and nausea), respiratory symptoms, hypertension, and hepatic dysfunction.[53–55]

Siltuximab

Siltuximab is a chimeric monoclonal antibody against human interleukin-6 (IL-6) and is currently used as a therapeutic agent for Castleman disease.[56,57] Given the influence of IL-6 in schwannoma-related pain, a Phase II trial (NCT05684692) has been initiated to evaluate siltuximab for pain relief in patients with non-NF2 schwannomatosis.[32] Side effects of siltuximab include lymphopenia, thrombocytopenia, neutropenia, anemia, upper respiratory infections, nausea, and headache.[56,58]

Tanezumab

Tanezumab is a humanized monoclonal antibody designed to inhibit NGF. It was developed primarily to treat chronic pain conditions such as osteoarthritis and chronic low back pain.[59–61] NGF is involved in the sensitization of nociceptors, which are nerve cells responsible for transmitting pain signals to the brain. By inhibiting the interaction between NGF and tropomyosin receptor kinase A, tanezumab is believed to prevent nociceptor sensitization and suppress the transmission of pain signals.[62] Its efficacy in alleviating pain associated with non-NF2 schwannomatosis is currently being investigated in a Phase 2, randomized, double-blind, placebo-controlled study (NCT04163419).[63] The results of this trial could offer a new therapeutic option for pain management in patients with non-NF2 schwannomatosis.

Paresthesia, arthralgia, hypoesthesia, and peripheral edema are common adverse events of tanezumab.[61,64,65] The primary safety issues with tanezumab are rapidly progressive osteoarthritis and the increased likelihood of joint replacement surgery, particularly when used in combination with NSAIDs.[59]

Nerve and Ganglionic Block

Common non-pharmacological treatments for neuropathic pain include nerve and ganglion blocks.[66,67] Corticosteroids, neurolytic agents such as alcohol, and local anesthetics including lidocaine, bupivacaine, and clonidine are the agents of choice for nerve blocks.[68,69] Local anesthetics provide temporary analgesia by blocking sodium channels and may also exert long-term effects on chronic pain through modulation of NGF-mediated pathways, influencing neuronal growth and sensitization.[70,71] Reports indicate that nerve blocks can offer significant symptomatic relief for drug-resistant neuropathic pain, particularly following Schwannoma removal.[72,73]

Nerve blocks are associated with complications, including infection, hemorrhage due to vascular injury, and neurological impairments such as unintended sensory disturbances and motor dysfunction.[69,74] To minimize these risks, procedures are performed under ultrasound or fluoroscopic guidance.[68,75]

Neuromodulation

Scrambler therapy, a relatively new neuromodulation treatment, noninvasively alleviates neuropathic pain through transcutaneous electrical stimulation.[76,77] Its mechanism is attributed to the replacement of endogenous “pain” signals with artificial “non-pain” signals transmitted along the same neural pathways. These artificial signals are conveyed through local electrical stimulation channels that interact with surface receptors on C-fibers.[76,78,79] Typical treatment involves daily sessions of 30–45 min for 10 consecutive days[76,80] to induce neuroplastic changes in the spinal and cerebral pain pathways, resulting in prolonged analgesic effects even after the treatment sessions.[76,77] A study using MRI suggested that scrambler therapy induced changes in cerebral blood volume in specific brain regions associated with pain processing, such as the frontal lobe, precentral gyrus, and postcentral gyrus, indicating its central effects.[81] Furthermore, studies have reported that scrambler therapy led to significant reductions in the levels of inflammatory neuropeptides, such as NGF, in the blood.[82] This therapy alleviates neuropathic and cancer-related pain resistant to other treatments, and studies have reported its efficacy in alleviating pain in non-NF2 schwannomatosis.[83]

Surgery

Surgery is indicated for symptomatic schwannomas, such as those causing refractory pain, localized neurological deficits, or spinal cord compression, and tumor resection is often associated with significant pain relief.[84,85] The complete excision of schwannomas outside the tumor capsule is associated with a higher risk of postoperative complications related to nerve function. Therefore, intracapsular resection, which relieves tumor-induced compression and preserves the nerve, is generally preferred for better preservation of neurological function.[86,87] However, some patients experience persistent or recurrent pain postoperatively, which may be caused by preoperative nerve damage from tumor compression, iatrogenic nerve injury during surgery, postoperative soft tissue scarring, or tumor recurrence.[85,88] In non-NF2 schwannomatosis, given the multifocal nature of schwannomas, patients may require an average of 3.4 surgical procedures in 10 years.[11]

Ongoing Clinical Trials

Table 1 presents the ongoing trials that focused on molecular target therapies. These include the humanized monoclonal antibody tanezumab, which inhibits NGF, and siltuximab, a human-mouse chimeric monoclonal antibody that binds to human IL-6. These studies aim to provide valuable insights into the pain mechanisms in non-NF2 schwannomatosis and explore potential therapeutic options.

Future Direction

Although pain does not affect survival, it is associated with non-NF2 schwannomatosis is chronic and refractory, significantly impairing the QOL of patients. No treatment protocol has been established for pain management in non-NF2 schwannomatosis, and therapy is typically tailored to the clinical situation using a combination of the aforementioned methods (Figure 1) based on the discretion of individual institutions. Despite reports of *LZTR1*-deficient, *SMARCB1*-deficient, and patient-derived xenograft model mice that develop schwannoma-like tumors, currently, no animal model faithfully replicates the tumor formation and pain mechanisms of non-NF2 schwannomatosis.[32,35,89] Thus, new animal models are anticipated. Further elucidation of the detailed molecular mechanisms and large-scale clinical trials for various treatment options are needed.

Putting in Perspective

Non-NF2-Schwannomatosis is a rare disorder causing chronic, treatment-resistant pain that significantly impacts patients' quality of life. This review highlights the roles of NGF and IL-6 in pain mechanisms, with emerging therapies like Tanezumab and Siltuximab offering promise. Non-invasive approaches, such as Scrambler Therapy, also show potential.

Table 1 Ongoing Clinical Trials for Pain Related to Non-NF2 Schwannomatosis

ClinicalTrials.Gov Identifier	Initiation date	Responsible Party	Estimated Enrollment	Age	Treatment Strategy
NCT04163419	April 2020	Massachusetts General Hospital	46	≧18	Tanezumab
NCT05684692	August 2023	Massachusetts General Hospital	40	≧18	SiltuximabErenumab-Aooe

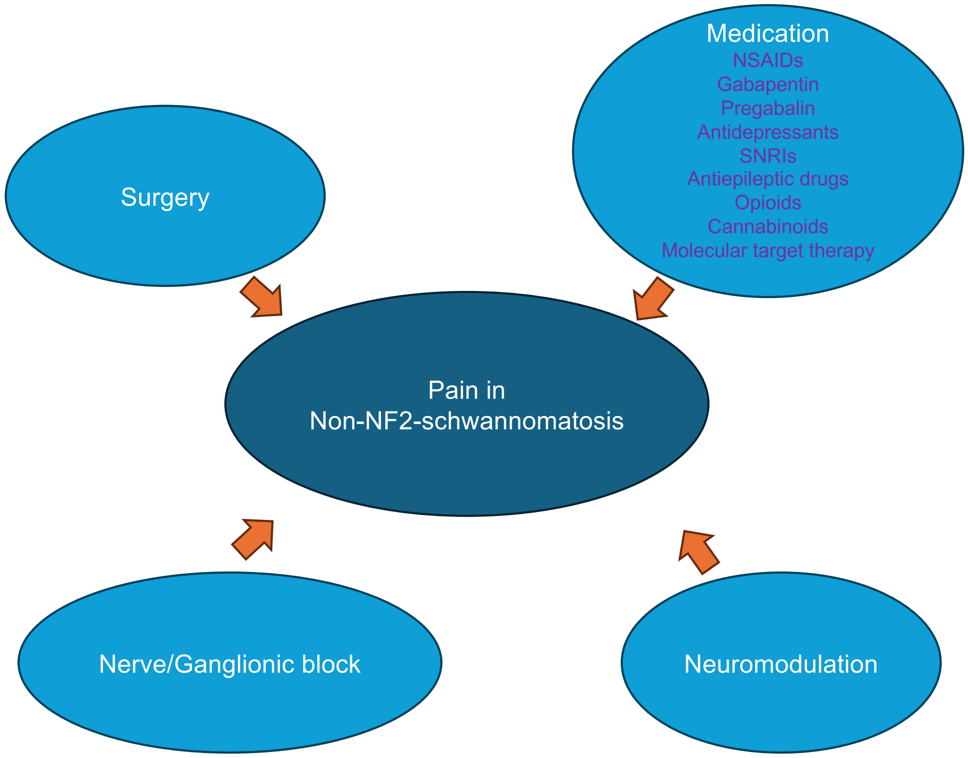

Figure 1 Multidisciplinary treatment using a combination of several methods.

However, the lack of accurate models and limited treatment options remain challenges. Future research should focus on uncovering pain mechanisms and developing effective therapies. This review provides a foundation for advancing treatment strategies and improving patient outcomes.

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Disclosure
The authors report no conflicts of interest in this work.

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