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A Review

Neurofibromatosis Type 2: A Review of Pain Management Options

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Neurofibromatosis is a chronic and painful disease process that can cause significant morbidity. The development of central and peripheral lesions is the primary source of acute and chronic pain. The pain associated with this condition is difficult to treat, but there are a number of options to make the lives of these patients more comfortable.

A review of current literature and research data was used to compile a detailed list of treatment options for patients with neurofibromatosis type 2 (NF2). Key points on physiology and pain, as well as current and potential treatment options, are discussed.

There are a number of articles, case reports, and studies regarding the treatment options for pain in patients with NF2. However, there is a lack of well-controlled randomized trials that demonstrate the superiority of one treatment modality. There are novel treatment plans being tailored to work at a genetic level, but these still require further research before implementing in daily practice.

The management of chronic pain in NF2 is a difficult challenge for the medical community. Novel treatment options are currently being researched to improve the quality of life in these patients. Using a multimodal approach to pain control will improve the chances of a successful outcome.

Key words: Neurofibromatosis type 2, schwannomatosis, neurofibromatosis type 1, chronic pain, pain management, neurofibroma, analgesics

Neurofibromatosis is an incurable genetic disorder characterized by the growth of tumors in the nervous system. These growths can be associated with significant acute and chronic pain secondary to nerve and soft tissue compression. This condition can be classified into 3 main types, depending on the manifestation of the disease. Neurofibromatosis type 1 (NF1) is typically characterized by cafe-au-lait spots, freckling of the intertriginous area of the axilla or genitalia, scoliosis, neurobehavioral disorders, epilepsy, as well as the presence of Lisch nodules, which are pigmented dome-shaped papules found on the iris. These individuals also develop benign nerve sheath tumors of the peripheral nervous system known as neurofibromas. The development of optic gliomas before the age of 6 can also be seen, which can lead to serious vision abnormalities (1).

The second type of neurofibromatosis is called schwannomatosis. It is characterized by the growth of multiple schwannomas, which are benign nerve sheath tumors of the myelin-producing Schwann cells. These tumors can form on peripheral, spinal, and cranial nerves, which can lead to significant nerve compromise. Signs and symptoms of this disease usually present in early adulthood as a chronic pain that can affect any part of the body. Other clinical presentations depend on which nerves are affected, but usually include numbness, weakness, paresthesias, and headaches. The features of schwannomatosis appear to be similar to those of

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neurofibromatosis type 2; however, schwannomatosis almost never includes vestibular schwannomas. Another distinguishing feature is that while NF1 and NF2 typically involve the development of other kinds of tumors, schwannomatosis is almost strictly only schwannomas (2).

The final classification is neurofibromatosis type 2 (NF2), which is also known by the acronym MISME (multiple inherited schwannomas, meningiomas, and ependymomas) (3). It is an autosomal dominant disorder that is characterized by the growth of primarily benign tumors in the peripheral and central nervous system (4,5). The hallmark of this disease is the development of bilateral vestibular schwannomas. The first signs and symptoms of NF2 usually appear during adolescence with most patients presenting with loss of hearing, tinnitus, and disequilibrium secondary to tumor formation along the vestibulocochlear nerve (5,6). It has been estimated that NF2 has an incidence of 1 in 33,000 people worldwide (5,7). A mutation in the NF2 gene, located on chromosome 22q, is what has been consistently linked with the abnormalities found in this disease (7). This gene is responsible for the production of a tumor-suppressive peptide known as merlin or schwannomin. When this peptide is absent or defective, it can lead to tumor formation caused by cells growing in a rapid and uncontrolled manner. While many patients inherit the disorder from their parents, more than half represent a new sporadic mutation. Many patients with NF2 tend to be mosaic, meaning that different cells in the same individual have different numbers or arrangements of chromosomes (8). Truncating mutations (nonsense and frameshift mutations) seem to cause the most severe form of the disease and are the most common germ line mutation (6). An often overlooked aspect of this form of neurofibromatosis is the potential presence of tumors of the skin, spinal cord, and meninges. This includes peripheral nerve schwannomas, intracranial and intraspinal meningiomas, as well as occasional ependymomas (6). While vestibular schwannomas are typically not painful, the other types of tumors in these individuals can lead to significant morbidity secondary to pain and loss of function.

In contrast to the gliomas seen in NF1, there is a predominance of schwannomas and meningiomas in NF2. Being that NF2 is a relatively rare disease compared to NF1 and now recognized as a distinct entity, there is not as much research analyzing its medical complications when compared to NF1 (1). This paper will focus on the sources of pain in patients with NF2 as well as review current and future treatment options for pain management.

TYPES OF PAIN IN NEUROFIBROMATOSIS TYPE 2

The presence and type of pain in NF2 is correlated with the phenotypical expression of the patient. Depending on the types and locations of the tumors, pain can manifest itself to varying degrees. Patients can present with a spectrum of symptoms, from debilitating spine pain, ophthalmalgia, and peripheral neuropathic pain to no pain at all.

In a study done by Mautner et al, it was reported that spinal tumors were found in 65 of the 73 patients studied who had NF2. Even though spinal tumors were seen in the majority of the population being studied, initial symptoms of a spinal tumor were only seen in 22 (30%) of these patients (9). Another study by Asthagiri et al (4) reported that spinal tumors were found in 33 of the 49 patients studied with NF2. Even though spinal tumors were seen in the majority of the population being studied, initial symptoms of a spinal tumor were only seen in 13 of these patients. These symptoms include radiating pain, paresthesias, atrophy, muscle weakness, gait unsteadiness, and pronation of the foot. In a different study done by Mautner et al (10), spinal neurological symptoms were only seen in 2 out of 48 patients, while 90% of these patients had spinal tumors on imaging. In summary, it is typically difficult to discover spinal tumors based on clinical manifestations alone, and in most cases, spinal tumors are found incidentally on screening MRI.

Optic nerve sheath meningiomas are another disease manifestation that can generate pain in NF2. They have been found in up to 27% of patients with NF2. While benign, these tumors can lead to compression or vascular compromise of the optic nerve, resulting in color and progressive vision loss, optic atrophy, disc swelling, and eye pain (11).

Pain secondary to peripheral neuropathy in NF2 has been shown to be much more frequent than

in NF1 (12). The development of painful peripheral neuropathy in NF2 can be secondary to compressive effects, schwannosis, and local toxic or metabolic determinants from pathological cells (13).

TREATMENT OPTIONS

Opioids

Although opioids carry the stigma of abuse and addiction, they are very effective medications to relieve acute pain. Their use for chronic non-cancer pain remains more controversial, as there is no definitive proof of long-term benefits (14). Opioid utilization for chronic pain associated with NF2 carries the same risks as using opioids to treat other painful conditions. One of the major concerns that most providers have is the potential for misuse and diversion of these controlled substances. Patients are also at risk of overdose if they do not understand how to properly take these medications or if they intentionally use them for purposes other than pain control. Physicians who are trained in the management of chronic pain should be consulted to help treat these patients. Before starting opioid therapy, realistic treatment goals should be established and then the patient should be reevaluated intermittently to determine if there is a clinically meaningful improvement that outweighs any risks to the patient. If a prescription drug monitoring program is available, this should be referenced prior to continuing opioid prescribing. Providers should also consider urine drug testing at the initial visit and at least yearly to evaluate for compliance (15). Ultimately, opioid therapy can be generally safe and effective in selected patients (14).

Bevacizumab

Kollar et al (17) studied the effects of bevacizumab on pain relief in a patient with NF2. Bevacizumab is a monoclonal antibody that works by directly binding to vascular endothelial growth factor (VEGF) extracellularly to prevent interaction with VEGF receptors on the surface of endothelial cells. This may inhibit VEGF's angiogenic activity and a resulting inflammatory cascade. Kollar's study showed that after one infusion (5 mg/kg) of bevacizumab, a patient with NF2 received total pain relief. Prior to this infusion, the patient was on opioids, gabapentin, and metamizol, all of which were able to be discontinued a few days after the patient's first bevacizumab infusion. The treatment was continued for 18 months on a biweekly basis, which is the standard regimen for this dose of bevacizumab. The patient remained pain-free until about 5 months after the last infusion. Bevacizumab was then re-dosed and the patient was again pain-free within 2 weeks (17). In a study by Xu and Lawrence, 5 patients with NF2-associated chronic pain received 13 cycles of bevacizumab with 4 out of 5 patients reporting a decrease in subjective pain and were able to decrease their opioid use. All patients who had pain relief had a relapse of pain symptoms when the dose was reduced or infusions were paused (18).

Although bevacizumab is a promising agent for treating pain associated with NF2, it does have possible adverse reactions that need to be considered. This agent's most common side effects include epistaxis, headache, hypertension, rhinitis, proteinuria, taste alteration, dry skin, rectal hemorrhage, lacrimation disorder, back pain, and exfoliative dermatitis. It has been reported that, across all studies, bevacizumab was discontinued in 8.4% to 21% of patients because of some of these adverse reactions (19).

Relaxation Techniques

In a pilot study by Vranceanu et al (20), researchers found that a relaxation response resiliency program in patients with NF2 was effective in improving stress, depression, posttraumatic growth disorder, and overall life satisfaction. They also found positive trends for sleepiness and somatization. Pain improvement was seen in a subsample of patients who did not undergo any medical procedures during the course of the study (20).

While no randomized prospective studies could be found that specifically discussed cognitive behavioral therapy (CBT) as an effective treatment for the pain in NF2, CBT has shown promising results for other chronic pain syndromes. In a study by Glombiewski et al (21), it was shown that CBT was superior to other psychological treatments when it came to decreasing pain intensity.

Resection

Currently the most common approach to treating symptomatic lesions is surgical resection. Bilateral vestibular schwannomas, the hallmark of the disease,

can cause progressive hearing loss and can also lead to death by progressive brainstem compression. Surgical resection remains the main treatment option used to achieve tumor control, however this can frequently lead to iatrogenic hearing loss secondary to damage of the vestibulocochlear nerve. Even with complete resection, 20% of lesions will recur at the same location (22).

In a study by Peyre et al (23), it was shown that if a patient has bilateral vestibular schwannomas compressing the brainstem, the tumor growth rate of the remaining vestibular schwannoma increases after surgery of the contra-lateral tumor. Patients should be made aware of this before the initial surgery since an enlarging tumor could further damage their hearing, significantly impacting their daily life (23). These tumors can also become large enough that they reach the trigeminal nerve and can mimic trigeminal neuralgia (24).

Radiation Therapy

Although surgical resection of symptomatic tumors remains the mainstay of treatment for NF2, radiation therapy also plays an integral part in the treatment process. In patients who are nonsurgical candidates or have particularly aggressive tumors, radiation therapy is an important treatment method (7). It can also be a good choice in older patients or those in poor health who may not be able to handle traditional microsurgery. Even though this modality has proven to be helpful in symptom management, there are a number of concerns to keep in mind with this form of treatment. In some situations, radiation is not effective and even if there is a reduction in tumor mass, there is a potential for regrowth. Radiation therapy can also change the consistency of the tumor's mass and can make any subsequent surgical removal more difficult. Another issue is that even if the tumor responds to treatment, there is often a swelling of tissue in the area, which can potentially cause compression-related side effects. In addition, radiation itself poses the risk of creating additional tumors or increasing the growth of existing tumors in the surrounding area. When treatment involves exposure of the brain to radiation it can cause cognitive impairments such as decreased attention, working memory, and processing speed, as well as changes in auditory and visual processing, logic and reasoning, and long-term memory. Other issues that may be seen with radiation include nerve damage, hearing implant damage, and hair loss (25).

POTENTIAL FUTURE THERAPIES

There are a few drugs that are being studied as possible treatments for tumors; these drugs could secondarily help with pain control.

Gleevac

Based on in vitro studies, Gleevac, a tyrosine kinase inhibitor, may also be useful in the treatment of vestibular and spinal cord schwannomas. Nevertheless, further research is needed on this intervention (26).

Erlotinib

Erlotinib is an epidermal growth factor receptor inhibitor and antineoplastic agent that has also shown some promise as a treatment modality by decreasing tumor size along with improving auditory function. Again, further research is needed before this agent can be recommended on a routine basis (27).

In the future, the development of tailored drug therapies aimed at the genetic level is likely to provide vast improvements for treatment options. There is significant progress being made in cellular research and in the analysis of the pathways in which the NF2 gene products interact. This research is raising new hope for potential targeted therapy. Drugs such as bevacizumab, lapatinib, elotinib, and sorafenib that have the potential to target the ERK1/2, AKT, PDGFRbeta, integrin/focal adhesion kinase/Src/Ras signaling cascades; and VEF-F, phosphatidylinositol 3-kinase/protein kinase C/Src/c-Raf pathways may prove to be beneficial (7).

PROGNOSIS

The average age at onset of NF2 is 20 years; however, diagnosis is often delayed on average for 7 years (28). The range of disease progression and severity is highly variable, but many patients will eventually become deaf secondary to vestibular schwannoma's and/or need wheelchair assistance. Unfortunately, despite the improvements made in microsurgery along with radiation therapy, most people affected by

NF2 will suffer complete hearing loss at some point in their lifetime. The schwannomas seen in NF2 are more difficult to treat compared to sporadic unilateral vestibular schwannomas as they are often multifocal, appearing “like a bunch of grapes” and thus difficult to resect (6).

Prognosis is adversely affected by the number of meningiomas at time of diagnosis, early symptom onset, and the presence of a truncated mutation (6). All of these findings are associated with a heightened risk of early mortality. In a cohort study done in 1992 involving 150 patients with NF2, the mean survival age was 62 years, however more than 40% of these patients were expected to die by age 50. Since that time, the 15-year mean actuarial survival from time of diagnosis has extended due to advances in treatment (4).

CONCLUSION

NF2 continues to be a disease that is challenging for both patients and physicians. The symptoms remain difficult to manage with most patients facing significant pain, morbidity, and shortened life expectancy. Current management continues to focus on surgical resection, with radiation therapy and conservative methods used as adjunctive treatment (6). Depending on the tumors’ location and size, surgical resection or radiation may not be an option. In these cases, the treatment goal is pain control via psychotherapy and pharmacological methods. Several studies are currently being conducted to tailor the development of drug therapies at the genetic level in the hopes of generating a cure for this often disabling disease (6). Using a multimodal approach and a multidisciplinary team to treat and manage this disease can lead to successful outcomes and an improvement in the quality of life of these patients.

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