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Management Strategies of Neurofibromatosis Type 2 in Pediatric Patients : Challenges and Emerging Therapies

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Neurofibromatosis type 2 (NF2) is a rare genetic disorder caused by mutations in the *NF2* tumor suppressor gene, characterized by bilateral vestibular schwannomas and other central and peripheral nervous system tumors. Pediatric patients often present with more aggressive disease, greater tumor burdens, and increased morbidity compared to adults. Management requires a multidisciplinary approach that balances tumor control with functional preservation. While surgery and radiosurgery remain key treatment options, they carry risks such as hearing loss and malignant transformation of existing tumors. Bevacizumab and emerging therapies like gene therapy show promising therapeutic effects but are limited by variability in efficacy. Comprehensive care, including psychosocial support, is essential to improve clinical outcomes and quality of life for children with NF2.

Key Words : Neurofibromatosis 2 · Pediatrics · Neoplasms · Schwannoma · Therapeutics.

INTRODUCTION

Neurofibromatosis type 2 (NF2) is a rare autosomal dominant disorder resulting from mutations in the *NF2* tumor suppressor gene located on chromosome 22q12.2[1,2]. This tumor predisposition syndrome is characterized by the development of various tumors in the central and peripheral nervous systems, with its hallmark being bilateral vestibular schwannomas (VSs)[2,10]. In pediatric patients, the clinical presentation of NF2 is highly variable and often unrecognized, leading to frequent delays in diagnosis[1]. While adults with NF2 typically present with hearing loss and tinnitus caused by VSs, pediatric patients are more likely to exhibit visual disturbances, spinal cord compression, or other neurological symptoms[9,22]. Additionally, children with NF2 tend to have a greater tumor burden and face higher levels of morbidity and mortality compared to adults. Consequently, managing NF2 in the pediatric population is particularly challenging and requires long-term follow-up with tailored management strategies.

Until recently, NF2 was considered a distinct disease separate from schwannomatosis (SWN). However, as the genetic background of NF2 and SWN became better understood, molecular classification led to revised diagnostic criteria and nomenclature in 2022[41]. The condition previously referred to as 'NF2' was integrated into a unified category of SWN and renamed 'NF2-related SWN'. Consequently, 'NF2' is now considered a historical term and is no longer recommended for use. However, since inconsistency in terminology still remains, this paper

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will use 'NF2' as an abbreviation for the updated term 'NF2-related SWN'. This review highlights the current management strategies and major challenges for pediatric NF2, with a focus on VS.

NF2-RELATED INTRACRANIAL TUMORS

NF2-related tumors are frequently multifocal, arising from distinct clonal events and multiple second-hit mutations in the *NF2* gene[21]. This results in the formation of multiple intracranial tumors, including schwannomas, meningiomas, gliomas, and ependymomas[2,9]. These tumors often show a saltatory growth pattern, although some may exhibit linear or exponential growth[10]. New tumors can continue to develop throughout a patient's lifetime. The clinical presentation and course of NF2 are highly variable, with a significant risk of bilateral hearing loss over the natural disease course, even with careful monitoring and treatment[22,23]. Early diagnosis of NF2 and tumor monitoring are crucial, particularly to prioritize functional preservation- most notably hearing preservation.

Schwannoma

Bilateral VSs are the hallmark of NF2, affecting 90–95% of patients[2,10]. In the general population with VSs, approximately 4–7% of individuals have NF2[15,21]. While NF2 typically manifests as bilateral VS, it can present as unilateral VS with additional NF2 features in up to 15% of cases[21]. A study evaluating 18 VSs in 12 patients with NF2 found that all tumors displayed growth, with 46.7% displaying a saltatory growth pattern[1]. Increased morbidity was observed in patients with NF2-related VSs compared to those with sporadic VSs, partly due to the increased growth rate of tumors[35]. In children with NF2-related VSs, a higher growth rate of the tumor was significantly associated with increasing age, tumor volume, tumor size, and constitutional truncating mutations in the *NF2* gene[22]. Additionally, patients with unilateral VS were found to have a significant risk of developing bilateral VSs, with a mean delay of 6.5 years. In pediatric NF2 patients, the interval for the development of the second VS was even shorter, with a mean delay of 3.3 years for radiological detection of tumors and 7.3 years for the occurrence of bilateral hearing loss[14].

Meningioma

Meningioma is the second most common tumor in NF2 patients. NF2-related meningiomas tend to be of a higher grade compared to sporadic meningiomas[37]. In a study of 128 NF2-related meningiomas, 99.3% showed gradual growth during follow-up, with 60.9% exhibiting a saltatory growth pattern[1]. More rapid growth was identified in patients with a younger age at symptomatic onset. Some meningiomas have been found to grow more rapidly than schwannomas, although growth rates vary for tumor types. Constitutional NF2 mutations are recognized as the most common cause of meningioma in childhood[16]. NF2 has been identified in 28% of children with optic nerve sheath meningioma, a condition that can present early in life and may lead to complete vision loss[5].

Glioma, ependymoma, other cranial nerve schwannoma

Gliomas, ependymomas, and other cranial nerve schwannomas also occur in NF2 but are less common. These tumors contribute to the overall disease burden, particularly when they affect critical areas such as the spinal cord or brainstem. The prevalence of intracranial astrocytomas and ependymomas in NF2 patients ranges from 1.6% to 4.1% and 2.5% to 6%, respectively[1]. Their frequency is significantly higher in the pediatric NF2 population, reaching 24%[44]. These tumors are more commonly located in the lower brainstem and upper cervical cord compared to other regions but tend to cause symptoms less frequently than other tumor types[1].

Among spinal cord tumors associated with NF2, spinal ependymomas account for more than 75%[2]. Clinical symptoms vary depending on the size and location of tumors along the spinal axis, with symptomatic cases representing less than 20%. These tumors often remain quiescent and asymptomatic for many years, making observation the preferred management approach for asymptomatic cases. However, surgery is also effective and curative for symptomatic tumors. Schwannomas of the spinal nerve roots are frequently multiple and constitute nearly 90% of extramedullary spinal tumors in NF2.

MANAGEMENT

The highly variable clinical features and multifocal nature of NF2-related tumors make surgery and other interventions,

such as radiation therapy, more challenging and result in higher recurrence rates[21]. Effective management of NF2-related tumors requires balancing symptom relief with the preservation of neurological function. Surgical resection, while effective for symptom-producing tumors, is often challenging due to the multiplicity of lesions, surgical risks, and the possibility of functional impairment. For non-surgical tumors, stereotactic radiosurgery (SRS) has been widely used[13,31,43]. Advances in molecular genetics have also introduced novel targeted therapies into clinical practice[39,46]. Gene therapy is widely under preclinical investigation. A multidisciplinary, individualized approach is critical for treating NF2-related tumors, as these tumors can result in serious functional impairments, psychosocial challenges, and even life-threatening complications[22,23].

Surveillance in children with NF2

For children with NF2, annual history and physical exams, including audiology assessments, are recommended[17,24]. Ophthalmology reviews should be conducted every 2 years. Evaluation of brain magnetic resonance imaging (MRI) is recommended from the age of 10 years. Follow-up brain MRI is recommended annually if intracranial tumors are present, while MRIs every 2 years are recommended if no tumors are detected without symptoms. Evaluation of spinal MRI is also recommended from the age of 10 years. Follow-up spinal MRI is recommended every 2 to 3 years if tumors are present and every 5 years if no tumors are detected without specific symptoms. Spinal tumors are identified in 60–80% of NF2-related tumor patients, and 25–30% of symptomatic patients require surgical resection. However, there can be individual variations even within the same family. NF2-related tumors typically appear in late childhood or early adulthood. If the family history includes cases of early-onset tumors or severe NF2, imaging may need to begin earlier, depending on clinical symptoms or genetic findings. The approach should be personalized.

Surgery

NF2-related intracranial tumors frequently exhibit growth over time[10], though individual growth rates vary, making past behavior an unreliable predictor of future progression. Surgical resection is generally reserved for large, symptomatic tumors. For VSs, complete resection is achieved less frequently in NF2 patients than in those with sporadic tumors[29], presumably because NF2-related VSs tend to incorporate more nerve fascicles and adhere more strongly to surrounding nerves[25]. Surgery for NF2-related VSs carries a higher risk of hearing loss than surgery for sporadic VSs, even when performed by experienced surgeons using continuous electrophysiological monitoring[14,22]. As such, for large VS, surgery can be considered the primary treatment to remove a symptomatic lesion or potentially life-threatening mass effects[21]. Total or near-total resection can be attempted in deaf patients, while subtotal resection is preferred for others, aiming to preserve hearing with guidance from auditory evoked potentials (Fig. 1). A previous study indicated that tumor decompression could reduce tumor growth in children from 0.69 cm^3/yr to 0.23 cm^3/yr[22]. The surgical approach depends on hearing function, tumor characteristics, patient's preferences, and surgeon's expertise[21].

Despite high variability in literature, surgery-related neurological deficits have been reported to be around 5–11%[21,47]. It was reported that rates of hearing preservation were up to 50% over 3 years postoperatively[19]. Among a cohort of 35 children with NF2, a total of 47 VS resections were performed between 1992 and 2004, achieving hearing preservation at 70 dB in 55% of cases, a rate comparable to the 48% reported in another study[45]. In another study involving 29 pediatric patients (23 of whom had NF2), hearing preservation was achieved in only 30% of cases. Resection of larger tumors was associated with a higher risk of hearing loss and facial nerve damage[2,6]. Preserving the cochlear nerve is another key surgical objective, as it enables the use of cochlear implants, which can provide stable and functional hearing for at least 8 years in most patients[34]. The risk of persistent facial palsy ranged from 3% to 46%[47]. It also depends on the individual tumor, but approximately 15–20% of patients have been reported to experience moderate to severe facial paralysis following surgery[26]. Strategies for improving cosmetic outcomes in cases of facial nerve damage have been proposed[40]. To improve the rate of functional preservation, intraoperative monitoring is essential for the surgery of VS[21,32]. Microsurgery generally achieves satisfactory tumor mass reduction, but the risk of surgical complications should be considered[11,30].

Radiosurgery

SRS, such as Gamma Knife radiosurgery (GKRS), has been widely used for the treatment of VSs and meningiomas. Prospective studies have shown that SRS is superior to microsurgery for VS, which is smaller than 3 cm in preserving facial

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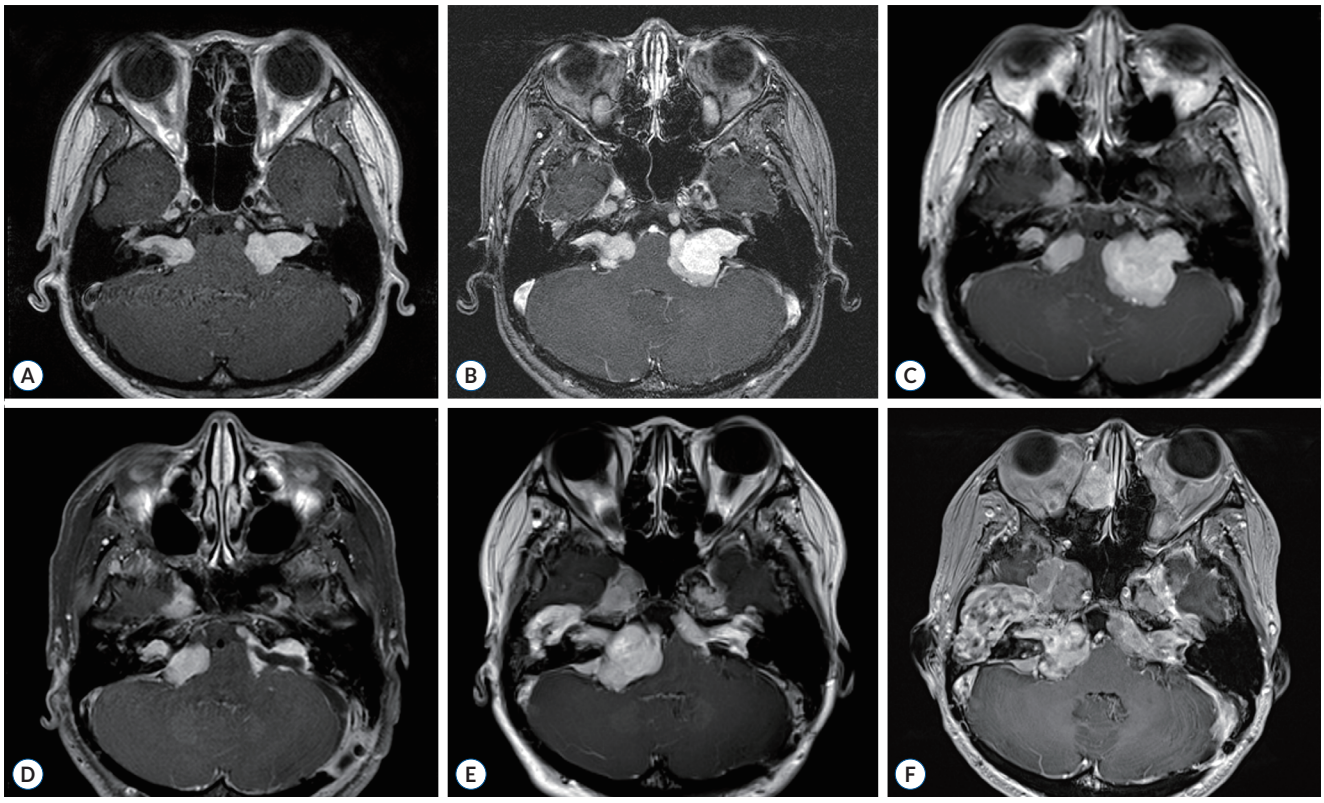

Fig. 1. A 15-year-old female presented with multiple subcutaneous neurofibromas. A : Bilateral VSs were identified on MRI, and NF2 was diagnosed. B : Over the next 3 years, the VS increased in size, accompanied by a decline in hearing function. Fractionated GKRS (4 Gy×4) was performed on the left VS. C : The tumor remained stable for a period, but after 3 years, it began to regrow, resulting in the loss of left hearing function. D : The left VS was surgically resected in a subtotal fashion. E : Over the following 6 years, the left VS remained stable, but the right VS gradually increased in size. Fractionated GKRS (6 Gy×5) was performed on the right VS. F : Over the subsequent 6.5 years, five additional GKRSs were performed on multiple intracranial tumors, including the bilateral VSs. VS : vestibular schwannoma, MRI : magnetic resonance imaging, NF2 : neurofibromatosis type 2, GKRS : gamma knife radiosurgery.

nerve and hearing function[21]. There are no established criteria for the upper size or volume limit of the tumor, but large tumors generally require fractionation. In the general NF2 population, SRS achieves tumor control rates of 60–80% at 5 years, which is significantly better than the natural course of the disease[31]. Hearing preservation rates in patients with serviceable hearing were reported at 73% after 1 year, 59% after 2 years, and 48% after 5 years, with lower risks of facial nerve injury (5–12%) and trigeminal nerve injury (2–7%)[31,43]. Better hearing at the time of radiosurgery (Gardner-Robertson grade 1 compared to grade 2) was significantly associated with a higher rate of serviceable hearing preservation[38]. However, long-term outcomes in NF2-related VSs were less favorable than those observed in sporadic VSs[4]. In a pediatric case series, hearing preservation following SRS was compared favorably with adult patients, with rates of 67% at 1 year and 53% at 5 years (n=11 tumors). However, tumor control was notably poor, with a control rate of only 35% at 3 years (n=17 tumors)[9].

Although SRS has advantages in treatment, concerns remain regarding the increased risk of malignant transformation of existing tumors and the development of secondary tumors within the irradiated field in patients with NF2[3,12]. Radiation-associated malignant transformation was estimated to occur in 4717 per 10^5 in the NF2 population. The inherent tumor susceptibility of NF2 patients has been linked to a 6% increased risk of malignant transformation or new tumor growth within the irradiated tissues[13]. Some authors have estimated that exposure to radiotherapy increases the risk 10-fold[49]. NF2 patients comprise approximately 7% of VS cases treated with SRS, but they account for nearly half of the reported cases of malignant transformation. Although SRS is a widely used and effective treatment method, this highlights the need for cautious use

of this treatment modality in the NF2 population[2,12].

Pharmacotherapeutic management

Targeted therapies are increasingly being explored as alternatives to surgery or radiotherapy, particularly for tumors that are less symptomatic[8]. Bevacizumab, a monoclonal antibody that targets vascular endothelial growth factor (VEGF), has demonstrated potential in reducing tumor size and improving hearing function in a subset of patients[11,20,46,51] (Fig. 2). In a recent study analyzing 17 patients who received 7.5 mg/kg bevacizumab for 7.1 months, 93% of patients experienced hearing preservation (40% improved, 53% stable)[13]. Similar responses were found for tumor size, as 31% of the target tumors exhibited regression, and 69% remained stable. However, common adverse events included hypertension (82%) and fatigue (29%), and severe adverse events led to treatment discontinuation in 29% of the patients. In a recent meta-analysis analyzing 200 patients with bevacizumab (dose, 2.5–10 mg/kg), the pooled radiographic response rate (RR) was 38% (95% confidence interval [CI], 31–45%), and the pooled hearing response rate (HR) was 45% (95% CI, 36–54%)[8]. The most frequent bevacizumab-related toxicities were hypertension and menorrhagia. Nephrotoxicity is another well-known side effect of bevacizumab. Previous studies have shown that proteinuria occurs in approximately 5–12% of pediatric patients treated with bevacizumab. While severe renal toxicity is rare, it has been documented in case reports, highlighting the need for careful monitoring[28,33]. On the other hand, there showed no differences in radiographic and hearing responses according to the dose of bevacizumab, which suggests the possibility of reducing toxicity with lower dose therapy[8]. A recent prospective study involving 20 patients treated with bevacizumab (5 mg/kg every 3 weeks for 18 months) demonstrated that freedom from hearing loss in the target ear was 95% at 48 weeks, 89% at 72 weeks, and 70% at 98 weeks. Additionally, freedom from tumor growth in the target tumor was 94% at 48 weeks, 89% at 72 weeks, and remained 89% at 98

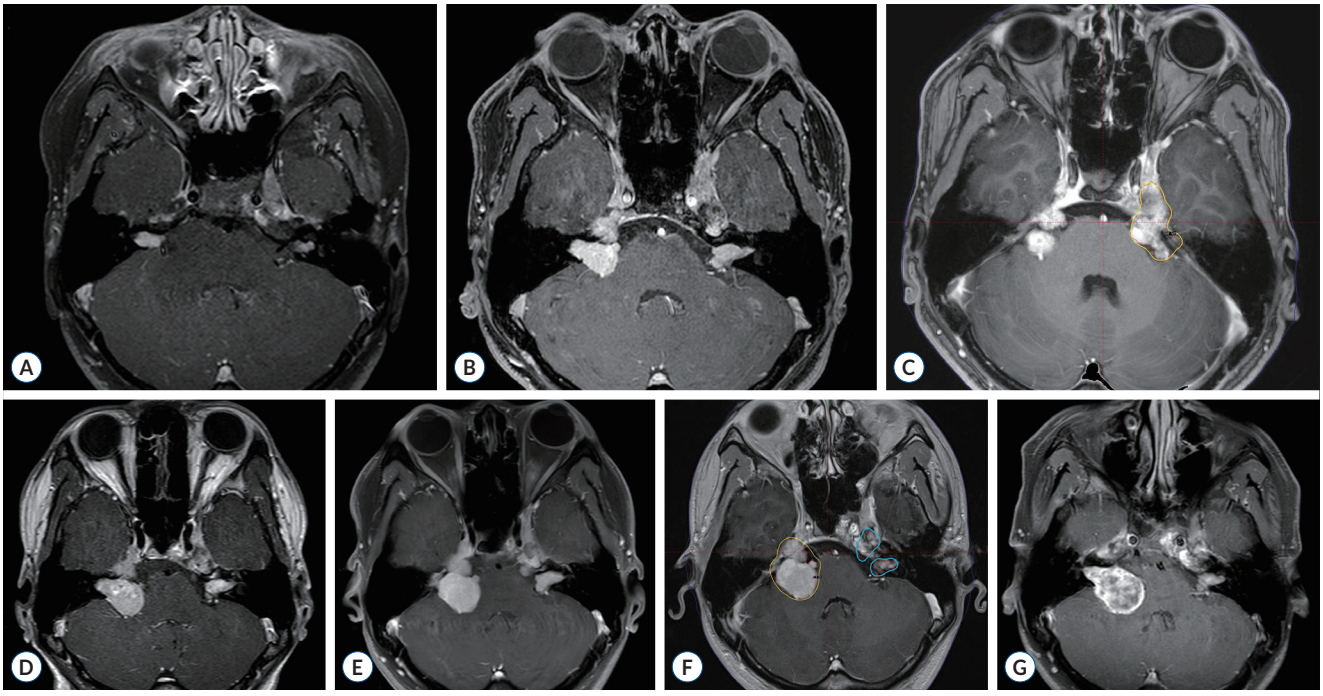

Fig. 2. A 6-year-old male first presented with left third nerve palsy. A : At the age of 12, bilateral VSs were identified on MRI, with normal hearing function. Genetic testing confirmed a diagnosis of NF2 (NM_000268.3:c.586C>T (p.Arg196Ter)). B and C : Over the next 4 years, the size of multiple cranial nerve tumors increased, including bilateral VSs and left cavernous sinus infiltrating tumors. Fractionated GKRS (5.5 Gy×4) was performed on the left VS and cavernous sinus tumors. D : For 2 years, the irradiated tumors remained stable. However, with increased tumor burden in untreated areas, bevacizumab treatment (5 to 7.5 mg/kg every 2 to 3 weeks) was initiated. E : After 1 year of bevacizumab treatment, there showed partial effects on other tumors, but no significant effect was observed on the right VS. Right hearing function declined as the size of the right VS increased. F : Fractionated GKRS (5.5 Gy×4) was performed on the right VS. G : One year later, the tumor size remained stable, and hearing function was similar to the prior evaluation. VS : vestibular schwannoma, MRI : magnetic resonance imaging, NF2 : neurofibromatosis type 2, GKRS : gamma knife radiosurgery.

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weeks[39]. Bevacizumab provides an effective alternative to surgery or radiotherapy for VS and related symptoms. However, it still faces challenges in that the effect on target tumors is variable, different bevacizumab regimens and surveillance protocols are used across institutes, and the effect of dosage on reported efficacy and toxicity remains uncertain[8,13].

As growth stimulatory signaling pathways (RAS-MAPK and AKT-mTOR) are activated in NF2 patients, agents targeting these oncogenic pathways potentially improve the treatment of tumors[8,20,51]. A phase II clinical trial evaluating the efficacy of lapatinib (tyrosine kinase inhibitor, target : HER1 and HER2) showed response rates of 6% RR and 31% HR with delayed wound healing in 4.8% of participants as the only grade 3 toxicity based on common terminology criteria for adverse events system[8,27]. Also, another phase II trial investigating a VEGF receptor vaccine targeting VEGFR-1 and VEGFR-2 showed response rates of 29% RR and 40% HR with no grade 3 adverse events related to treatment[8,48]. More agents can be considered for future clinical trials, either as monotherapy or as combination therapy.

Gene therapy

Several preclinical studies have shown encouraging results with gene therapy as a potential treatment for NF2-related tumors[20]. Gene replacement therapy aimed to restore merlin expression, potentially providing an effective treatment for the disease[51]. Recently, adeno-associated virus (AAV)-based gene replacement therapy showed encouraging efficacy in a preclinical xenograft mouse model of NF2-related schwannomas. AAV vector serotype-1 was utilized to deliver interleukin β-converting enzyme, the pore-forming protein Gasdermin-D, apoptosis-associated speck-like protein containing a caspase recruitment domain, and functional merlin causing schwannomas regression in a xenograft mouse model[20,51]. Although gene therapy still faces specific challenges such as immunogenicity, delivery vector, manufacturing, and the long-term effects of treatments, it has shown potential in preclinical animal models and is moving to the clinic with a promising future.

Psychosocial management

NF2 significantly impacts the quality of life of affected individuals, particularly children and adolescents. Some patients may experience severe hearing loss, vision impairment, motor deficit, and other neurological deficits[7]. In a previous study, over 30% of NF2 patients showed elevated psychological distress, suggesting that their condition was likely to adversely affect their quality of life and interpersonal relationships[42]. Patients with NF2-related tumors showed a high prevalence of clinically relevant symptoms of depression (30%), anxiety (16%), and somatic burden (32%)[18]. Mental health showed a significant association with disease severity and health-related quality of life. Especially, most patients with bilateral VSs eventually experience complete hearing loss. The inability to communicate can lead to significant psychological distress, making it beneficial for these patients to learn sign language early, before their hearing is entirely lost. Additionally, an auditory brainstem implant or cochlear implant may provide significant benefits for suitable candidates[36,50]. Comprehensive psychosocial screening and support, including counseling, family education, and rehabilitation, is essential for managing the emotional and functional challenges of the disease.

CONCLUSION

NF2 in the pediatric population presents unique challenges due to its variable presentation, higher tumor burden, and increased morbidity. Early diagnosis, regular monitoring, and a multidisciplinary approach are essential for tumor control, functional preservation, and improved outcomes. Surgical intervention and radiosurgery remain key treatment options but carry notable risks regarding functional impairment and concerns about the malignant transformation of tumors, particularly in children. Targeted therapies, such as bevacizumab, offer promising alternatives, while emerging treatments, including gene therapy, hold future potential. Optimizing care for pediatric NF2 patients requires standardized protocols, ongoing research, and comprehensive psychosocial support to enhance their quality of life.

AUTHOR'S DECLARATION

Conflicts of interest

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 : JSL; Data curation : JSL; Methodology : JSL; Visualization : JSL; Writing - original draft : JSL; Writing - review & editing : JSL

Data sharing

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