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Consensus-Based Best Practice Guidelines for the Management of Spinal Deformity and Associated Tumors in Pediatric Neurofibromatosis Type 1: Screening and Surveillance, Surgical Intervention, and Medical Therapy

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The authors declare no conflicts of interest.

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Abstract

Background: Spinal conditions, such as scoliosis and spinal tumors, are prevalent in neurofibromatosis type 1 (NF1). Despite the recognized importance of their early detection and treatment, there remain knowledge gaps in how to approach these manifestations. The purpose of this study was to utilize the experience of a multidisciplinary committee of experts to establish consensus-based best practice guidelines (BPGs) for spinal screening and surveillance, surgical intervention, and medical therapy in pediatric patients with NF1.

Methods: Using the results of a prior systematic review, ten key questions that required further assessment were first identified. A committee of 20 experts across medical specialties was then chosen based on their clinical experience with spinal deformity and tumors in NF1. These were nine orthopaedic surgeons, four neuro-oncologists/oncologists, three neurosurgeons, two neurologists, one pulmonologist, and one clinical geneticist. An initial online survey on current practices and opinions was conducted, followed by two additional surveys via a formal consensus-based modified Delphi method. The final survey involved voting on agreement or disagreement with 35 recommendations. Items reaching consensus (≥70% agreement or disagreement) were included in the final BPGs.

Results: Consensus was reached for 30 total recommendations on the management of spinal deformity and tumors in NF1. These were 11 recommendations on screening and surveillance, 16 on surgical intervention, and three on medical therapy. Five recommendations did not achieve consensus and were excluded from the BPGs.

Conclusion: We present a set of consensus-based BPGs comprised of 30 recommendations for spinal screening and surveillance, surgical intervention, and medical therapy in pediatric NF1.

Level of Evidence: Not applicable

Keywords

neurofibromatosis; NF1; spinal deformity; scoliosis; kyphosis; spinal tumors; screening and surveillance; magnetically controlled growing rods; Delphi process; best practice guidelines

INTRODUCTION

Neurofibromatosis type 1 (NF1) is an autosomal dominant disorder with pervasive orthopaedic manifestations, most commonly involving the spine. Approximately 10–60% of patients with the diagnosis develop spinal deformities.[1–3] These can be accompanied by a myriad of manifestations, including sagittal malalignment, dural ectasia, Chiari malformation, vertebral subluxation or dislocation, and spinal canal stenosis.[4] Cervical abnormalities are more rare, but risk for severe neurologic complications is higher than that associated with thoracolumbar deformities.[5,6] Soft tissue involvement is also prevalent, primarily manifesting as tumors with or without intraspinal components. For NF1-associated osseous manifestations, age-related disease progression is a key consideration;[7]

this emphasizes the importance of early detection and treatment of vertebral defects and spinal tumors in an effort to prevent the development of severe deformity, morbidity, or malignancy.

A recent systematic review from our study group emphasized the paucity of evidence available with regard to the management of spinal manifestations in pediatric patients with NF1.[8] Despite the known importance of early risk identification, there is currently no standardized spinal screening protocol for this population, with a lack of published consensus on appropriate screening initiation, interval, and modalities for assessment. Further, while magnetically controlled growing rods (MCGRs) and definitive spinal fusion have shown effectiveness for the correction of thoracolumbar and cervical deformities, respectively, there are limited studies assessing the considerations surrounding their utilization in children with NF1.[9–11] Similarly, there is little published evidence for the treatment of NF1-associated spinal tumors with surgical resection and medical therapy.[12–21] 8Given the limited evidence on these topics as determined by this systematic review,[8] we developed a follow-up study with the intention to minimize these gaps in knowledge. We sought to utilize the experience of a multidisciplinary panel of experts to establish consensus-based best practice guidelines (BPGs) for spinal screening and surveillance, surgical intervention, and medical therapy in pediatric patients with NF1 through a validated modified Delphi process.

MATERIALS AND METHODS

Prior to conduct of this study, the primary authors performed a systematic review summarizing published literature on the management of spinal deformities and tumors in pediatric patients with NF1.[8] The present study is an extension of the cited systematic review. Knowledge gaps were identified, and key questions were formulated on spinal screening and surveillance, surgical intervention, and medical therapy that would benefit from further refinement. The authors subsequently surveyed a multi-disciplinary group of experts with substantial experience treating patients with NF1 for current practices and opinions pertaining to the key questions. Responses were compiled and disseminated to consensus participants, at which point the modified Delphi method was employed to establish recommendations to be included in the consensus-based BPGs. The Delphi method is a validated avenue for developing consensus for a defined clinical problem where there is little to no evidence in the literature.[22] It involves sequential administration of surveys that are iteratively refined, which allows participants to change their response to recommendations in subsequent iterations based on discussion or suggest modifications to recommendations. The method utilized in this study is considered “modified” because the process began with a set of selected items. Consensus was defined as a ≥70% agreement between respondents, a validated parameter utilized in previous Delphi-based studies.[23] The present study was conducted between April 2021 and December 2022.

Survey of Current Practices and Opinions

Thirteen experts across medical specialties were selected based on their clinical expertise in managing spinal deformity and tumors in pediatric patients with NF1. These experts

were identified based on their involvement in national organizations and research on the NF1 spine, the primary authors' knowledge of their clinical practices, and their willingness to participate in the modified Delphi process. An online questionnaire comprised of free-response prompts to our ten key questions was generated using the Google Forms platform (Google, Alphabet Inc, Mountain View, USA) (Table 1). The summative results of the systematic review and survey were then distributed via email to determine current practices and opinions of the expert panel. Respondents were encouraged to provide contact information of additional experts to partake in the study as consensus participants.

Modified Delphi Method: Consensus Round 1

Following the conclusion of the primary survey on current practices and opinions, a virtual conference was held by the primary study team with the expert committee to discuss results and allow for collaborative development of initial consensus-based BPG recommendations. Our initial expert committee identified seven additional NF1 experts who were added as consensus participants in the two-round modified Delphi process. Based on the primary results and live discussion, a 58-item online questionnaire comprised of multiple choice and Likert scale prompts was generated. The final questionnaire included 25 questions on spinal screening and surveillance, 28 questions on surgical intervention, and 5 questions on medical therapy. Given the differing expertise between surgeons and non-surgeons, two forms of the survey were created with appropriate inclusion of questions and disseminated to respective participants. At the end of each section, respondents were given the opportunity to elaborate on their choices, propose additional criteria, or suggest changes to the consensus items.

Modified Delphi Method: Consensus Round 2

Once all responses were received, results of the second questionnaire were collated and summarized electronically. Recommendations were then modified and condensed based on respondent feedback, and a 35-item final voting survey was generated asking for agreement or disagreement with each item. The summary data and survey were distributed to all consensus participants, with an opportunity for final comments or criticisms offered at the end. Respondents were directed to omit voting on recommendations for which they feel they do not have enough expertise. All statements with ≥70% consensus were included in the BPGs.

RESULTS

Expert Committee Characteristics

Thirteen of our 20 experts (65%) on spinal deformity and tumors in pediatric patients with NF1 participated in the initial survey on current practices and opinions. The response rate was 100% for the subsequent modified Delphi method rounds. The following pediatric medical specialties were represented on our expert committee: orthopaedic surgery (N=9, 45%), neuro-oncology/oncology (N=4, 20%), neurosurgery (N=3, 15%), neurology (N=2, 10%), pulmonology (N=1, 5%), and clinical genetics (N=1, 5%). Median time in practice at time of final voting was 11 years (range 3–45). Expert committee characteristics are displayed in Table 2.

Survey of Current Practices and Opinions

Free-text responses to the identified ten key questions on current practices and opinions are summarized in Supplementary Table 1. To be included, recommendations had to be mentioned in some capacity by at least one expert. Those with common themes were then condensed into the statements displayed in the referenced table. Ten recommendations were provided by ≥70% of experts, nine by 30–69% of experts, and 12 by <30% of experts.

Modified Delphi Method

The results of the first consensus round are displayed in Supplementary Table 2. After modification and abridgment based on respondent feedback, 30 recommendations reached consensus in the second consensus round and were included in the BPGs. These were 11 recommendations on screening and surveillance, 16 on surgical intervention, and three on medical therapy (Table 3). Five recommendations did not achieve consensus – three items on contraindications to MCGRs and two on specific drugs for medical treatment of spinal tumors – and thus were excluded from the BPGs (Table 4).

DISCUSSION

Given the high prevalence of NF1 (1 in 3,000 births) and of associated spinal manifestations, there is tremendous value in establishing guidelines for screening for and managing spinal deformity and associated tumors in these patients. To date, available evidence on management of the spine in NF1 has been largely informed by case series and reports.[8] The present study builds upon a recent systematic review conducted by the primary authors, which revealed substantial deficiencies in available best practices for the care of NF1-associated spinal conditions. Here, we leverage decades of multidisciplinary clinical expertise and established Delphi methodology to formulate a 30-item, consensus-based BPG for screening and surveillance, surgical intervention, and medical therapy of spinal deformity and tumors in pediatric NF1. We aim to expand overall knowledge available to the multidisciplinary teams that manage these complex patients and ultimately, improve the quality of care provided.

Perhaps most importantly, we established consensus for 11 recommendations on spinal screening and surveillance. If left untreated, NF1-associated spinal deformities and tumors are likely to progress and can result in severe, potentially irreversible neurologic and orthopaedic deficits.[24] For example, a natural history study by the National Cancer Institute noted a 10-fold increase in spinal neurofibromas in children aged 10–18 years compared to children <10 years.[25] Early detection is thus essential for maximizing the opportunity for timely intervention and the prevention of complications. There was consensus agreement to begin spinal screening with physical examination at diagnosis with NF1 or at first presentation to a healthcare system, with repeat screening performed at one-year intervals if initial physical examination is unremarkable. Comprehensive assessment should include general inspection, paraspinal palpation, Adam’s forward bend test, sensory and motor examination, and reflex testing. To limit radiation exposure in the pediatric population, there was consensus that diagnostic imaging should only be performed if clinical suspicion arises from patient history or physical examination. If spinal pathology is established,

both surveillance physical examination and imaging should be performed at six-month to one-year intervals to monitor progression. Furthermore, it is known that multiplanar thoracolumbar and cervical deformity, occult vertebral dysplasia, and paraspinal and intraspinal tumors frequently co-occur.[25–27] Our experts thereby agree that appropriate preoperative imaging should be pursued prior to these patients undergoing any spine surgery to assess for comorbid spinal manifestations. Of note, whole body magnetic resonance imaging (MRI) is cited as an excellent tool for the detection of initial tumor burden, but it may be less valuable for surveillance than focused cervical, thoracic, or lumbar MRIs. There is a trade-off between body area covered and detail, and small-scale changes may be difficult to identify on large field-of-view imaging.

Our consensus-based BPGs also include nine recommendations on the surgical correction of thoracolumbar and cervical deformity, including four contraindications for the use of MCGRs in this population. For children with NF1, the utilization of MCGRs has demonstrated significant postoperative improvements in major curve magnitude and spinal height gain over time,[9,10] outcomes which were agreed upon by our consensus panel. However, a known limitation of this technique is the resulting diminished visualization when imaging the postoperative spine. The ferromagnetic actuators within MCGRs induce circumferential artifact measuring nearly 30 cm from the magnets, with the greatest amount when dual MCGRs are implanted in a standard, offset configuration.[28] Accordingly, there was agreement that MCGRs are not recommended in children with NF1 who have a known spinal tumor burden which requires ongoing routine MRI surveillance, particularly in the setting of known intraspinal tumors. For these patients, alternative constructs should be utilized, such as traditional growing rods or a single MCGR with the magnet placed at the caudal end to limit MRI artifact. Alternative solutions can include use of a higher deformity threshold for surgical correction, greater consideration for simultaneous or staged resection of spinal tumors, or use of multidetector computed tomography for postoperative surveillance.[27,29] For significant cervical kyphosis, our recommendations are in line with the current literature, which strongly favors the use of combined anteroposterior arthrodesis rather than a posterior-only approach. This technique allows greater kyphosis angle correction, achieves optimal stability, and limits revision surgeries.[9,11] This study did not investigate questions regarding spinal fusion for thoracolumbar deformities due to the substantial evidence available on the topic.

There was agreement for seven recommendations related to the surgical resection of spinal tumors. Across tumor types in NF1 (i.e., ganglioma, spinal or plexiform neurofibromas), resection can be an important adjunct to medical therapy and radiation, yet indications for surgery have not been previously well-defined. Our expert committee agreed on six indications for surgical resection. Objectives for surgical intervention include addressing neurologic symptoms from spinal cord compression, improving respiratory capacity, and stabilizing spinal deformity.[30,31] Based on clinical experience, resection of paraspinal and intraspinal tumors can be safely performed in the same procedure as deformity correction. Specifically, it is important to note that malignant peripheral nerve sheath tumors (MPNSTs) have poor outcomes when managed at later stages.[12,14,32] Thus, early detection and timely resection are critical if there is suspicion of malignant conversion.

Finally, the present study identified three recommendations on medical therapy for spinal tumors in pediatric patients with NF1. Early studies cited the use of various medical agents with mixed results.[12,14,18–21,33,34] In 2020, the MEK inhibitor selumetinib was approved by the Food and Drug Administration (and subsequently several regulatory agencies around the world) for the treatment of plexiform neurofibromas in children with NF1.[35–37] Several other MEK inhibitors (i.e., trametinib) have also shown efficacy or are in testing in phase II trials for both pediatric and adult patients with NF1.[38] These targeted agents have been shown to reduce tumor size, slow neoplastic growth, and may prevent worsening of spinal cord compression.[39–41] One expert reported that within their institution, there is currently movement toward recommending MEK inhibitors before performing surgery, when possible, for spinal neurofibromas. Thus, patients who meet the identified indications for resection should first be evaluated for candidacy in receiving MEK inhibitors if the presentation is not emergent. While long-term outcomes have yet to be reported, current data shows a limited adverse effect profile.[39] Consensus was unable to be reached for the use of drug agents other than MEK inhibitors for spinal tumors.

The recommendations included in our consensus-based BPGs must be interpreted in context of their limitations. First, the multidisciplinary nature of the committee is one of the present study's strengths, yet it also carries the limitation of a low number of experts representing non-orthopaedic surgery specialties. This distribution is secondary to the primary team's affiliation and knowledge of qualified experts who were invited to participate. Along a similar line, a lower experience threshold was accepted for expert qualification because of the highly specialized nature of the questions asked in this study. Physicians with only three or four years of experience were included because they trained underneath other NF1 experts and have practices with a high volume of patients with NF1 that allowed them to contribute meaningfully. Second, as mentioned above, there is an absence of strong evidence for many of the included items. The expert committee and modified Delphi method design were chosen to overcome this limitation. However, the BPGs should be strongly considered within the changing landscape of the field as more evidence becomes available through research, which may either support or refute our recommendations. Third, several of the final recommendations are subject to modification based on each patient's unique presentation. Providers must use their own clinical judgment to further specify or qualify these items to utilize the BPG most effectively in their own practice.

CONCLUSION

In the present study, we established consensus-based BPGs for spinal screening and surveillance, surgical intervention, and medical therapy in pediatric patients with NF1. This was achieved via an extensive modified Delphi process involving a multidisciplinary expert committee across orthopaedic surgery, neuro-oncology/oncology, neurosurgery, neurology, pulmonology, and clinical genetics. The final BPG includes eleven recommendations on screening and surveillance, sixteen on surgical intervention, and three on medical therapy that aim to improve quality of care for these complex patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Key Questions on Screening and Surveillance, Surgical Intervention, and Medical Therapy for Spinal Deformity and Tumors in Pediatric NF1

Key Questions
1. What screening practices are used for thoracolumbar spinal deformity?
2. What screening practices are used for cervical deformity?
3. What screening practices are used for intraspinal and paraspinal tumors?
4. What imaging surveillance protocols are used to monitor spinal tumors?
5. Has the use of MCGRs impaired ability to identify and follow spinal tumors?
6. What are the contraindications to using MCGRs in patients who would otherwise benefit from this intervention?
7. What techniques have been utilized and outcomes observed for cervical kyphosis correction?
8. What are indications for surgical resection for biopsy and removal of para-spinal/extra-spinal tumors?
9. What are indications for surgical resection for biopsy and removal of tumors in the spinal canal?
10. What is recommended for medical management of spinal or thoracic tumors?

NF1, neurofibromatosis type 1; MCGRs, magnetically controlled growing rods

Table 2

Characteristics of Expert Committee on NF1

	N (%)
Experts	20 (100)
Gender	
Female	10 (50)
Male	10 (50)
Medical specialty (all pediatric)	
Orthopaedic surgery	9 (45)
Neuro-oncology/oncology	4 (20)
Neurosurgery	3 (15)
Neurology	2 (10)
Pulmonology	1 (5)
Clinical genetics	1 (5)
Practice geographic region	
East	12 (60)
Central	3 (15)
West	5 (25)
Years in practice *	11 (3–45)

NF1, neurofibromatosis type 1

* Data displayed as median (range)

Table 3

Final Best Practice Guidelines: Consensus Recommendations on Screening and Surveillance, Surgical Intervention, and Medical Therapy for Spinal Deformity and Tumors in Pediatric NF1

	Consensus (%)	
Recommendation	**Yes**	**No**
Guidelines on Screening and Surveillance		
Screening for spinal manifestations should be performed with physical exam of the TL and cervical spine at diagnosis/first presentation.	100	0
Imaging for spinal manifestations should be performed only when there is clinical concern.	85	15
Patients without prior abnormal screening should undergo routine physical exams annually.	90	10
Patients without prior abnormal screening should not undergo routine imaging.	100	0
If symptomatic or clinical suspicion arises for TL or cervical deformity, radiographs ± MRI should be performed.	95	5
If symptomatic or clinical suspicion arises for spinal tumor burden, MRI alone should be performed.	90	10
In patients with established spinal pathology, surveillance physical exam should be performed every 6 months to 1 year.	95	5
In patients with established spinal pathology, surveillance imaging should be performed every 6 months to 1 year.	95	5
Preoperative radiographs and MRI ± CT should be obtained to evaluate TL or cervical deformity prior to any spine surgery.	100	0
Preoperative radiographs ± MRI should be obtained to evaluate tumor burden prior to any spine surgery.	85	15
Whole body MRI can be excellent for initial screening of tumor burden and gross changes, but detail is limited for intraspinal tumors and adequate surveillance.	100	0
Guidelines on Deformity Correction and Tumor Resection		
MCGRs can severely limit detection or monitoring of spinal tumors (intraspinal > paraspinal).	95	5
MCGRs are not recommended for patients with high spinal tumor burden (intraspinal > paraspinal).	90	10
Contraindications for MCGRs:		
Suspicion for spinal tumor malignant transformation	95	5
Identified intraspinal tumors	77	23
Excessive kyphosis	77	23
Need for MRI surveillance	89	11
Combined anterior-posterior fusion is the recommended approach for cervical deformity correction to achieve optimal stability and limit revision surgeries.	100	0
Cervical deformity correction is recommended for kyphosis:		
≥50 degrees	93	7
30–49 degrees	86	14
Spinal tumors can be safely resected in the same procedure as thoracolumbar or cervical deformity correction.	86	14
Indications for surgical consideration both intra- and paraspinal tumor resection:		
Suspicion for spinal tumor malignant transformation	100	0
Neurological symptoms	82	18
Worsening thoracolumbar or cervical deformity	71	29
Chest crowding	73	27
Detriment to spinal cord health	94	6
Impaired spine access for surgery	82	18
Guidelines on Medical Therapy		

	Consensus (%)	
Recommendation	**Yes**	**No**
MEK inhibitors can effectively reduce tumor size, slow tumor growth, and relieve cord compression.	100	0
MEK inhibitors can be used for ≥2 years duration safely and with continued clinical benefit.	100	0
When on medical therapy for tumor burden, appropriate MRI surveillance should be conducted at Q3–6 month intervals.	100	0

NF1, neurofibromatosis type 1; TL, thoracolumbar; MRI, magnetic resonance imaging; CT, computed tomography; MCGR, magnetically controlled growing rods

Table 4

Items Not Reaching Consensus for Inclusion in Best Practice Guidelines on Screening and Surveillance, Surgical Intervention, and Medical Therapy for Spinal Deformity and Tumors in Pediatric NF1

	Consensus (%)	
Recommendation	**Yes**	**No**
Guidelines on Deformity Correction and Tumor Resection		
Contraindications for MCGRs:		
Identified extra- or paraspinal tumors	65	35
Small stature	56	44
High degree of spinal deformity	50	50
Guidelines on Medical Therapy		
Carboplatin/vincristine ± surgery can used as an alternative for intraspinal tumors.	50	50
Denosumab and Sirolimus can effectively reduce tumor size, slow tumor growth, and relieve cord compression.	33	67

NF1, neurofibromatosis type 1; MCGRs, magnetically controlled growing rods