Early-Onset Spinal Deformity in Neurofibromatosis Type 1

Natural History, Treatment, and Imaging Surveillance

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Abstract

» Early-onset scoliosis (EOS) or kyphosis is common in patients with neurofibromatosis (NF) and is characterized by rapid progression of deformity.

» Traditional growing rods provide good functional and deformity outcomes in patients with NF and EOS; magnetically controlled growing rods (MCGRs) also provide good deformity correction, although high rates of revision have been reported after their use.

» Among patients with NF type 1 (NF1), morphologic characteristics of the spinal deformity are different in those with paraspinal neurofibromas than in those without paraspinal tumors.

» Patients with NF1 are at low risk for developing malignant peripheral nerve sheath tumors during childhood (<1%) and their lifetime (8% to 12%), and routine imaging surveillance for malignancy in the absence of symptoms should be clinically directed.

» Further investigation is needed to standardize screening for EOS in children with NF1 and to develop guidelines for ideal imaging modalities, including their frequency and a timeline.

Natural History of Early-Onset Spinal Deformity in Patients with Neurofibromatosis Type 1

Neurofibromatoses are a distinct set of genetic disorders that cause tumors (typically noncancerous) to grow in the brain, nerves, and spinal cord. Of the 3 types of neurofibromatosis, type 1 (NF1) causes skeletal deformity and has an estimated prevalence of 1 in 2,500 individuals[1]. Skeletal manifestations of NF include decreased bone density in as many as 50% of patients, long-bone dysplasia in 3% to 4% of patients, and early-onset scoliosis (EOS) (defined as a spinal curvature of >10° in the coronal plane in patients who are <10 years of age)[2]. Early-onset spinal deformities have been reported to occur in 10% to 60% of patients with NF1 and are classified as dystrophic or nondystrophic[3-8]. Of the 2, dystrophic deformities are less common but more likely to progress rapidly[9-11]. Dystrophic spinal curves are characterized by the following radiographic findings: enlarged intervertebral foramina, rib penciling, spindling of the transverse process, vertebral rotation, vertebral scalloping, vertebral wedging in the sagittal or coronal plane, and widened interpedicular distance[12]. In contrast to the long segmental curves that are seen in nondystrophic spinal curvature, dystrophic deformity in patients with NF presents as substantial angulation of 4 to 6 vertebral segments in prepubescent children and can lead to severe deterioration of pulmonary and neurologic function[13]. Additionally, dystrophic deformity is strongly associated with dural ectasia[14]. For nondystrophic curves, it is

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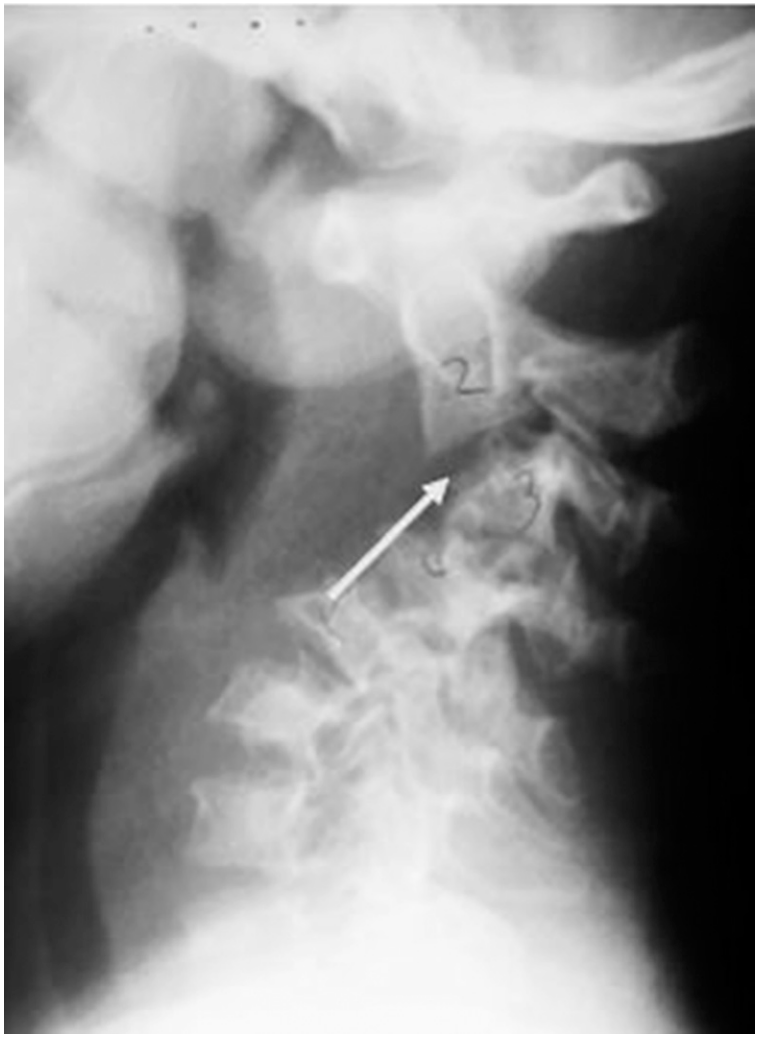

Fig. 1-A

Figs. 1-A and 1-B Example of cervical kyphosis in a 3-year-old girl with NF1. **Fig. 1-A** Preoperative lateral radiograph demonstrating a kyphotic curvature of 67° between C2 and C3 (arrow).

important to monitor the evolution of the deformity because these curves transition to dystrophic types in 25% of patients with NF1 after the age of 7 years[10] and in 81% of patients who are younger than 7 years old. This transformation from nondystrophic to dystrophic curve types is a unique feature of EOS in patients with NF1.

Moreover, NF1 may be associated with cervical kyphosis; however, the specific incidence of cervical kyphosis in this patient population is unknown[15] (Figs. 1-A and 1-B). Yong-Hing et al. reported that 30% of patients with NF1 in their series had associated cervical spine abnormalities, although most patients were asymptomatic[16]. They noted that cervical spinal deformity in patients with NF1 was more common (44%) in those with concurrent dystrophic deformity or thoracic scoliosis[16]. Because a large proportion of patients are asymptomatic, we recommend cervical spine radiographs at the initial evaluation for all patients with NF1, but especially those who are undergoing instrumented fusion of the thoracic or lumbar spine, halo traction, or general anesthesia. Manipulation of the spine in the presence of unrecognized cervical lesions can result in neurologic changes[10,16]. Routine cervical radiographs are not recommended if the initial radiographic evaluation is negative.

Treatment and Surgical Management of EOS in Patients with NF1

For nondystrophic curves in skeletally immature patients, bracing can delay deformity progression in patients with NF1 with moderate spinal curvature of 20° to 40°[10]. In patients with curves that are <20°, clinical observation every 6 months is recommended. For nondystrophic curves, curves that are greater than approximately 45° may benefit from early spinal fusion or growth-friendly spinal instrumentation[10]. In contrast, bracing is less successful in treating dystrophic curves because of their tendency to progress rapidly. Dystrophic curves of <20° can be managed with observation at 6-month intervals, with progression being a relative indication for surgical intervention. In patients with NF1[10,11,17,18] and dystrophic or nondystrophic scoliosis (with or without neurologic symptoms) who are being considered for surgery,

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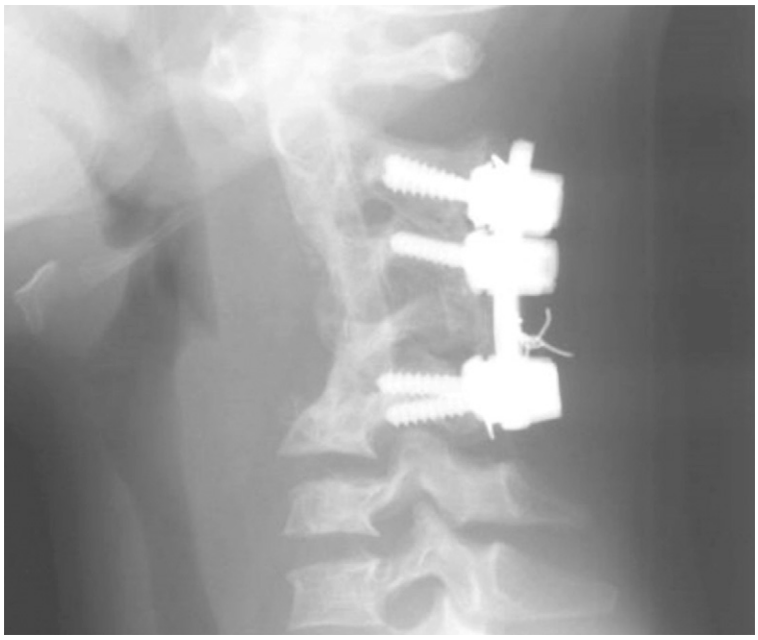

Fig. 1-B

Three-month postoperative lateral radiograph. The patient had been treated with a C2-C5 anteroposterior fusion with posterior instrumentation and a rib autograft anteriorly. She had good correction of the cervical deformity.

magnetic resonance imaging (MRI) of the entire spine is typically recommended to (1) assess the spinal canal for associated intraspinal and paraspinal lesions, (2) identify any vertebral dysplasia and dystrophic characteristics, and (3) assist with preoperative planning. Often, MRI can help detect dystrophic changes that may have been missed on conventional radiographs[10].

For both dystrophic and nondystrophic types, growing rod (GR) instrumentation can control EOS in patients with NF1 while promoting lengthening of the spine[10,19]. Early fusion is a reportedly effective spinal deformity treatment in patients with NF1, despite the risks of the crankshaft phenomenon (progressive rotational and angular spinal deformity that may occur after posterior spinal fusion), growth restriction of the spine and thorax, and pseudarthrosis. In 1 retrospective study comparing early fusion (EF) versus GR procedures in patients with dystrophic EOS and NF1, early fusion produced similar final curve correction with fewer procedures[20]. However, the patients with GRs were younger and had larger curves at the time of surgery[20]. The EF consisted of anterior and posterior surgery in most cases, and still often required follow-up procedures for the crankshaft phenomenon or adding-on[20]. The study did not provide definitive indications for GRs versus EF but pointed out that EF may be a good choice for some patients[20]. For both dystrophic and nondystrophic curves, the use of autologous bone graft may be considered to improve osseous fusion because the rate of nonunion in patients with NF1 is greater than that in patients with idiopathic scoliosis[6,17].

During the past decade, the development of magnetically controlled GRs (MCGRs) has revolutionized growth-friendly management of EOS. Compared with traditional GRs, MCGRs allow for continuous growth using an external magnet for lengthening, which reduces the need for recurrent lengthening procedures and the risk of complications (Figs. 2-A through 2-D). Currently, the use of MCGRs is not well described in the literature, with 2 cases series reporting outcomes in pediatric patients with NF1. In a cohort of 5 patients with NF1, Mladenov et al. reported substantial improvements in coronal curvature following MCGR use, with a mean T1-T12 length gain of 7.3 mm per year[21]. However, the authors also reported that all 5 patients required revision surgery during the follow-up period. Similarly, in 2 pediatric patients with NF1, Nnadi et al. reported excellent correction of coronal curvature, with a mean T1-T12 length gain of 7.0 mm per year[22]. Other outcomes following MCGR treatment, including the extent of pulmonary function improvement and the mean T1-S1 and total height gains, have not yet been described in the NF1 population.

Regarding cervical kyphosis, Helenius et al. reported that although posterior fusion can be performed alone, anteroposterior fusion was associated with better deformity correction compared with isolated posterior fusion in patients with NF1, without a higher complication rate[15] (Figs. 1-A and 1-B). Complications in patients with NF1 who underwent cervical kyphosis correction included transient C5 neurologic deficits and junctional kyphosis. Fusion of all of the dysplastic levels may lower the rate of junctional kyphosis[15]. Interestingly, the risk of junctional kyphosis was lower in patients who underwent spinal fusion of ≥6 levels versus ≤5 levels[15].

Spinal Tumors and Deformity Progression in Patients with NF1

The reported prevalence of spinal tumors in patients with NF1 varies

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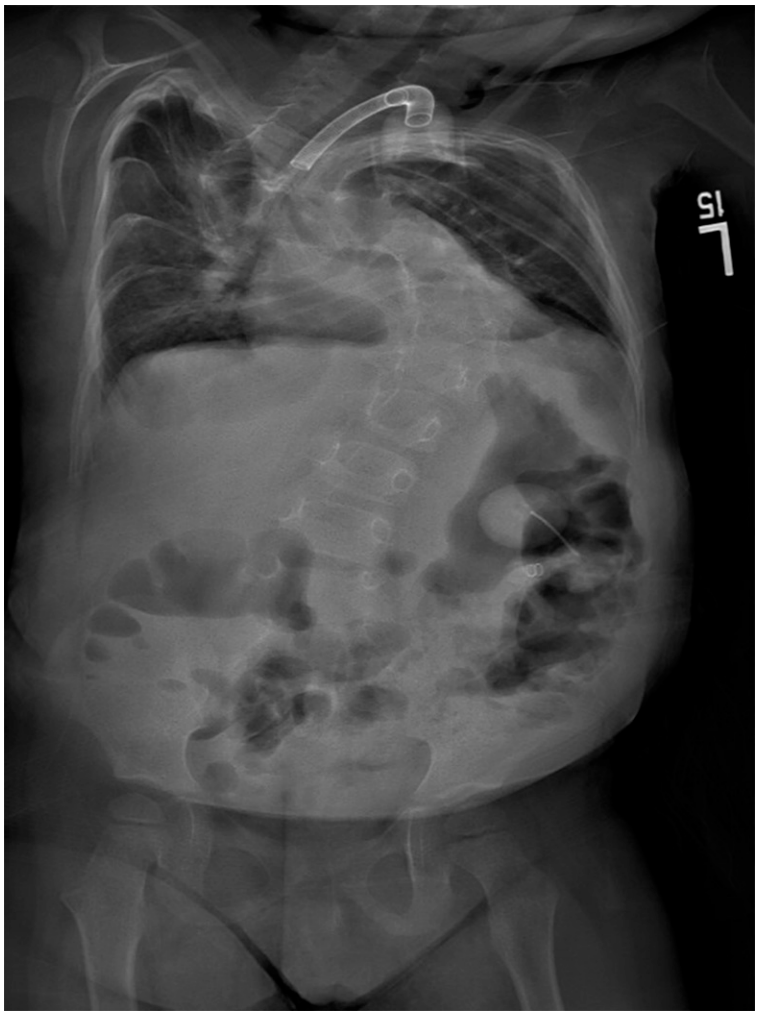

Fig. 2-A

Figs. 2-A through 2-D MCGRs in a 3-year-old girl with NF1. **Fig. 2-A** On initial evaluation, the preoperative anteroposterior radiograph showed major dystrophic changes with sharply angulated curvatures.

widely, from 1.5% to 24.0%, with most tumors located in the cervical or lumbar region, although thoracic tumors also occur[23]. Of these tumors, approximately 57% are intraforaminal, 33% are intraspinal extramedullary, and 6% are intramedullary[23]. Although approximately 40% of patients with NF1 and spinal tumors are asymptomatic, 96% of patients with NF1 and neurologic deficits have spinal tumors on MRI[14,23]. In patients with symptomatic plexiform neurofibromas, intraspinal involvement can cause spinal cord compression, resulting in neurologic deficits, pain, and functional disability. Interestingly, in patients with NF1 and scoliosis, paraspinal neurofibromas are associated with different morphologic features of the spinal deformity compared with those without paraspinal neurofibromas, including increases in apical vertebral rotation and in the prevalence of rotatory subluxation[24]. Paraspinal neurofibromas are typically nonmalignant. Reports have described cases of paraspinal malignant peripheral nerve sheath tumors (MPNSTs) in children with NF1, although this is extremely rare[25]. In patients with NF1, the overall risk of MPNST is <1% in childhood and 8% to 12% in a lifetime[26-28]. Most MPNSTs develop from plexiform neurofibromas, which can transform into atypical neurofibromatous neoplasms of uncertain biologic potential and then into MPNSTs. Atypical neurofibromas are considered premalignant because they represent a transition from benign nodular plexiform neurofibromas to MPNSTs. This risk of malignant transformation is especially high in patients with >1 atypical neurofibroma, and total-body MRI is often recommended to identify nodular neurofibromas with rapid growth rates[26,27]. No association exists between spinal deformity and concomitant malignancy[14].

Imaging Surveillance in Patients with NF1

The need for imaging surveillance in patients with NF1 without associated scoliosis is determined by clinical evaluation and the presence of symptoms. Routine surveillance for malignancy is not currently recommended, with the exception of screening for optic glioma every 6 to 12 months until 8 years of age[27]. Patients should be assessed with

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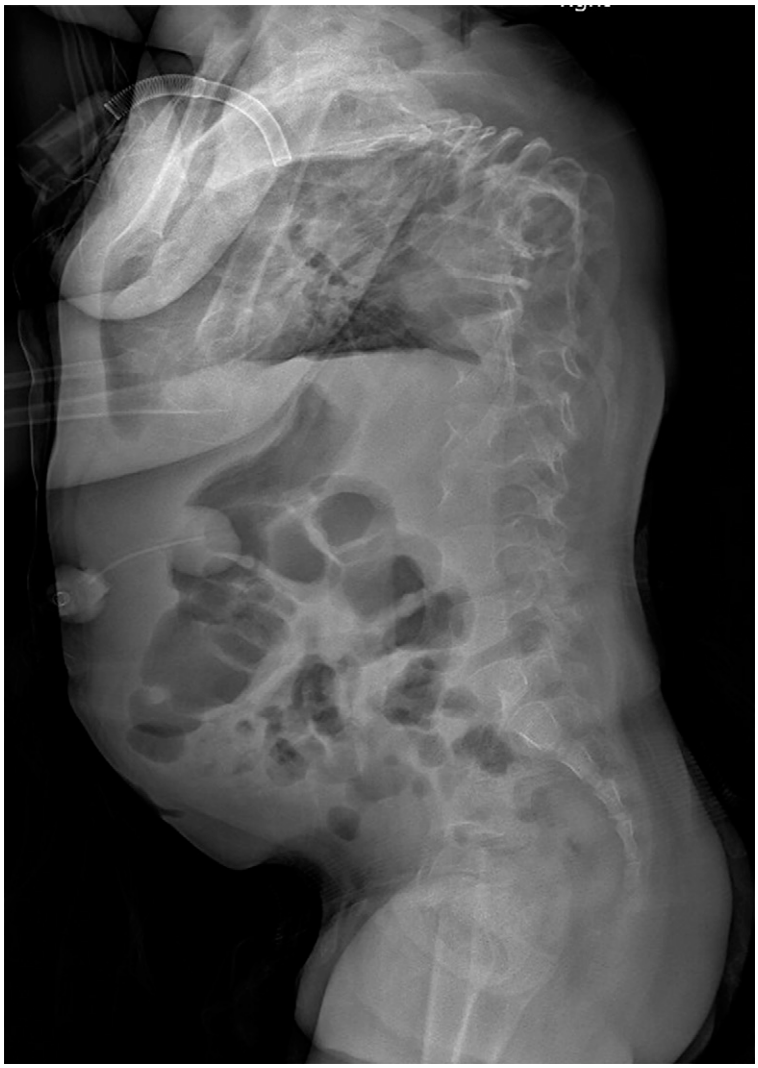

Fig. 2-B

The preoperative lateral radiograph showed the angulated kyphotic deformity in the upper thoracic spine.

an annual clinical examination, with a focus on symptoms and predictors for the development of spinal MPNST. These symptoms include pain that awakens the patient at night, change in consistency of the baseline pain level, focal neurologic deficit, and rapid growth of any nondermal neurofibroma[27]. Higher levels of surveillance may be recommended for patients who are at greater risk for malignancy, including those with a full gene deletion or those with a high tumor burden of plexiform neurofibromas[27]. Although genetic testing identifies approximately 95% of mutations in individuals, we recommend obtaining genetic testing in patients with NF1 who do not meet clinical diagnostic criteria because a positive DNA test result cannot predict the presence, the age at onset, or the severity of NF1 symptoms[29].

A single total-body MRI for all patients with NF1 has been recommended and can be performed as the patient enters adulthood (at age 16 to 20 years) to help determine the course of long-term follow-up[27]. In patients with identified spinal tumors, the authors recommended increased MRI surveillance to identify nodular neurofibromas with rapid growth rates, which can be a sign of malignancy[27]. Because patients with NF1 have a lifetime risk of MPNST of approximately 8% to 12% (substantially higher than that of the general population), we recommend a single total-body MRI to identify patients who may require closer surveillance. In patients with NF1 with symptoms that suggest spinal involvement or in those with known spinal tumors, advanced imaging modalities, including MRI and positron emission tomography (PET), can help further differentiate plexiform neurofibromas, paraspinal neurofibromas, and MPNSTs[1]. PET and computed tomography (CT) imaging can guide a biopsy of anatomically accessible tumors. For surveillance of spinal tumors in the NF1 population, multidetector CT has been reported to be superior to MRI, particularly in patients with surgical instrumentation,

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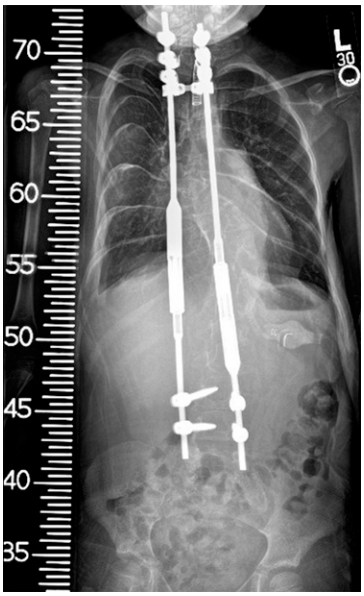

Fig. 2-C

At 3 years after the MCGRs had been inserted, the anteroposterior radiograph showed good correction of the coronal curvature.

because CT allows better visualization of osseous structures[30]. Fluorodeoxyglucose PET can be used to differentiate between benign plexiform tumors and MPNSTs, which is extremely useful because MPNSTs are often heterogeneous, and a biopsy of small sections of tumor may not accurately characterize the tumor as a whole[1].

Areas for Future Investigation

Despite our understanding of deformity progression and spinal tumors, as well as advancements in growth-friendly treatments for patients with NF1, many unanswered questions remain. Early identification of spinal deformity, including cervical kyphosis, is critical for the prevention of curve progression; however, standardized practice guidelines to determine the timing of routine spinal screenings in young children are limited. Recently published health management guidelines for children with NF1 recommend an annual clinical bone and scoliosis examination beginning in early childhood (at ages 1 to 5 years) but do not make recommendations regarding imaging of the spine[31]. Furthermore, a clinical threshold for pursuing growth-friendly treatment versus definitive fusion for deformity correction is unclear in children with NF1. Although there is great variability among patients, it may be possible to define parameters in which growth-friendly intervention may not produce any additional health benefits or height gain. Identification of specific patient factors, such as skeletal maturity, dystrophic deformity, presence of concurrent spinal tumors, and short-segment curves, may favor early fusion as opposed to growth-friendly intervention. Questions also remain regarding the use of MCGRs in patients with NF and their effect on the surveillance of spinal neurofibromas. MCGRs may reduce the ability to detect spinal tumors on MRI. Although MRI is the "gold standard" for diagnosing and monitoring neurofibromas with rapid growth rates, MCGRs contain magnets and ferromagnetic materials that produce major scatter and image distortion in the areas within 20 cm of the actuator[32-34]. Scatter from MCGRs reduces resolution and impairs visualization in critical areas of the trunk, reducing the ability to monitor neurofibroma growth using MRI and to assess the potential for MPNST. Therefore, before MCGR placement, patients may need additional screening to assess for thoracic lesions and spinal tumors or syrinx, although these guidelines have not been established. These concerns regarding MCGRs and spinal tumor surveillance have implications for clinical trials of NF1 medical therapy. For example, it is unclear whether patients who are enrolled in a clinical trial of medical treatment for NF1, such as MAPK (mitogen-activated protein kinase) inhibitor therapy, could undergo placement of MCGRs because artifacts on imaging can preclude accurate surveillance of tumor regression secondary to therapy.

Overview

Major advances have been made in understanding the natural history of EOS in patients with NF1, the outcomes of surgical treatment to limit deformity progression, and the characterization of spinal tumor development. With the increasing introduction of medical therapies to treat plexiform neurofibromas, including paraspinal neurofibromas in children with scoliosis, further investigation is needed to standardize EOS screening in young patients and develop guidelines regarding ideal imaging modalities, including their frequency and a timeline, as well as criteria for identifying candidates for MCGR treatment.

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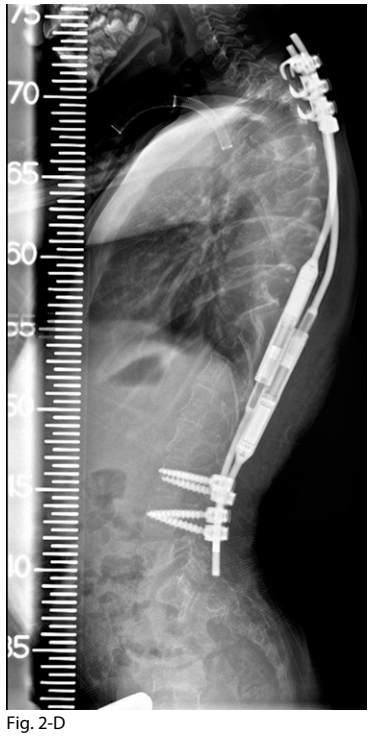

Fig. 2-D

The lateral radiograph showed restoration of thoracic kyphosis with resolution of the kyphotic deformity.

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