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The Immature Spine in Type-1 Neurofibromatosis

By Alvin H. Crawford, MD, Shital Parikh, MD, Elizabeth K. Schorry, MD, and Diane Von Stein, MD

Neurofibromatosis is a multisystem disease that primarily affects cell growth of neural tissue. The intent of this article is to identify the spinal complications in skeletally immature patients that are most commonly associated with neurofibromatosis and to present strategies for management.

Historical Review

The neurofibromatoses are a spectrum of multifaceted diseases involving not only neuroectoderm and mesoderm but also endoderm. These disorders present with a wide range of clinical manifestations that have in common the presence of schwannomas, neurofibromas, and/or *café au lait* spots. Clinically, this multisystemic, hereditary disease may manifest as abnormalities of the skin, nervous tissue, bones, and soft tissues. The primary pathology is believed to be a tumor-suppressor disorder. Previous reports have dealt primarily with specific entities, such as spinal deformity, paraplegia, hemihypertrophy with overgrowth phenomena of the extremities, soft-tissue tumors, neoplasia, and congenital tibial dysplasia and pseudarthrosis following extremity fractures. Scoliosis is the most common musculoskeletal complication of peripheral neurofibromatosis^{1,2}.

Diagnostic Problems

Most investigators now accept three clinical forms of neurofibromatosis: peripheral or type-1 neurofibromatosis (NF1), central or type-2 neurofibromatosis (NF2), and segmental neurofibromatosis (a mosaic form of NF1)¹. A recently described fourth form, schwannomatosis, consists of multiple deep, painful schwannomas and is thought to represent a mosaic form of NF2³. A variety of eponyms have been used in the past to describe all forms, although subsequent information has made these names technically inaccurate or incomplete. The most common type (NF1) was previously known as von Recklinghausen disease and is an autosomal dominant disorder that affects approximately one in 4000 persons; multiple hyperpigmented areas (*café au lait* macules) and neurofibromas are characteristic.

In their statement on neurofibromatosis, the 1987 Consensus Development Conference of the National Institutes of

Health concluded that the diagnosis of von Recklinghausen disease or NF1 can be considered established when two or more of the following diagnostic criteria are found: (1) six or more *café au lait* macules (>5 mm in widest diameter in prepubertal children and >15 mm in widest diameter in postpubertal individuals), (2) two or more neurofibromas of any type or one plexiform neurofibroma, (3) freckling in the axillary or inguinal regions, (4) optic glioma, (5) two or more Lisch nodules (iris hamartomas), (6) a distinctive osseous lesion (such as sphenoid dysplasia or thinning of the cortex of a long bone with or without pseudarthrosis, and (7) a first-degree relative (parent, sibling, or offspring) with NF1 identified by the above criteria⁴. Other disorders of pigmentation, such as McCune-Albright syndrome, can be confused with von Recklinghausen NF1⁵.

These diagnostic criteria are useful even in young children⁶. There seem to be two peaks of severe clinical problems for NF1 patients: one peak from five to ten years of age, and a second from thirty-six to fifty years of age. At the second peak, 75% of the clinical problems are related to malignant neoplasms⁷. The orthopaedic complications usually present early and include the spinal deformities of scoliosis and kyphoscoliosis.

Molecular Genetics

NF1 is one of the most common autosomal dominant inherited disorders. It affects at least one million persons throughout the world. It is seen in all racial and ethnic groups. Approximately one-third of patients with NF1 will have serious medical and social complications during their lifetime. The gene is large in size, in the range of 350,000 base pairs. In 1990, the gene locus of NF1 in humans was discovered on the long arm of chromosome 17, and its protein product, neurofibromin, was identified^{8,9}. Expression of neurofibromin is highest in neurons, oligodendrocytes, nonmyelinated Schwann cells, the adrenal medulla, leukocytes, and the testes. Exons 21 through 27a of the NF1 gene encode a 360 amino-acid domain in neurofibromin, which shows homology with a family of proteins called GTPase-activating proteins (GAPs), and the domain is termed GAP-related domain (GRD). This shared domain offers clues as to the function of neurofibromin. GRD

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Fig. 1-A

Figs. 1-A through 1-D Spinal instability following laminectomy in a very young child who had neck pain and decreased range of motion.

Fig. 1-A Lateral radiograph of the cervical spine, made at presentation, demonstrating slightly decreased lordosis.

down-regulates p21-Ras, a key signal transduction protein involved in gene regulation. *Ras* is an oncogene, which is activated when bound to GTP, and GAPs, including neurofibromin, catalyze its inactivation due to their GTPase activity. Thus, loss of neurofibromin, as in NF1, would lead to an inability to shut off activated p21-Ras, with subsequent aberrant growth-promoting signals. In this respect, the NF1 gene is a typical tumor-suppressor gene, and NF1 is one of the most common human cancer-predisposition syndromes.

Molecular Diagnostics

Despite the early identification of the NF1 gene, comprehensive genetic testing for NF1 has only recently become available on a clinical basis¹⁰. The process has been slowed by the large complex structure of the NF1 gene and the wide diversity of mutations. Protein truncation assay, which has been used for NF1 in the recent past, detects only 60% to 70% of NF1 mutations. Direct sequencing of the NF1 gene is now available clinically,

has a 95% sensitivity, and has become the gold standard for NF1 testing. Direct testing is helpful in establishing the diagnosis in uncertain cases, such as those involving young children with only *café au lait* spots, and in prenatal diagnosis¹¹. The multistep direct-testing method is performed on a fresh blood sample and takes four to six weeks to obtain the test results. The protocol includes protein truncation testing by fluorescence in situ hybridization analysis for total gene deletions, direct sequencing of the entire coding region for missense mutations or smaller in-frame deletions or insertions, long-range reverse transcriptase polymerase chain reaction and Southern blot analysis for smaller mutations, and finally, cytogenic analysis for large-scale rearrangements¹¹. Availability of this testing will further influence classification, patient care, counseling of families, and research.

Clinical Findings

Café au Lait Spots

Café au lait spots are present in more than 90% of all patients with NF1. The pigmentation is tan, macular, and melanotic in origin and is located in and around the basal layer of the epidermis; the lesions may vary in shape, size, number, and location. In relation to NF1, these spots are frequently found in areas of the skin that are not exposed to the sun. Some patients may have very large *café au lait* spots that involve a large segment of the body, including a “bathing trunk” distribution.



Fig. 1-B

T1-weighted magnetic resonance image illustrating extradural neurofibromatosis as well as spinal cord indentation at C3-C4.

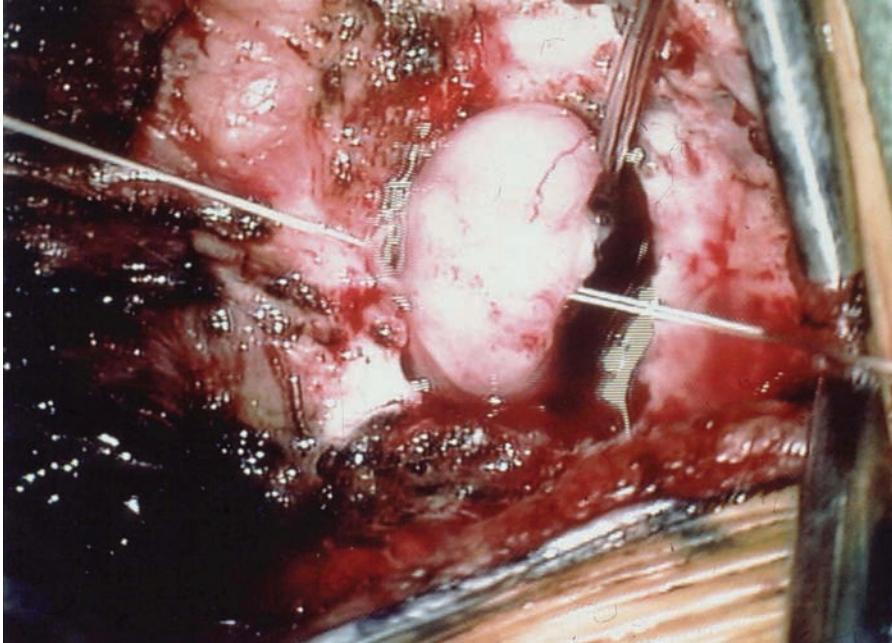


Fig. 1-C
Operative view during excision of the neurofibroma.

Axillary and Inguinal Freckling

Freckles—diffuse, small, hyperpigmented spots as much as 2 to 3 mm in diameter found in the axillary and inguinal region and other skin folds (areas not usually exposed to sunlight)—are helpful diagnostic criteria for NF1.

Lisch Nodules

Lisch nodules, or pigmented hamartomas of the iris, are present in 94% of patients with NF1 who are six years of age or older; 28% of younger patients have them¹². They increase in number with age, but they do not become symptomatic. The lesions appear to be specific for NF1; they are not commonly seen in non-NF1 individuals.

Neurofibromas

Neurofibromas mostly involve the skin, but they may be seen in deeper peripheral nerves. They may be nodular and discrete or diffuse with interdigitation with surrounding tissues. Highly vascular plexiform neurofibromas may cause segmental or localized hypertrophy. Puberty or pregnancy may cause an increase in the size and number of the lesions¹³.

Cutaneous Neurofibromas

Cutaneous neurofibromas, formerly called fibroma molluscum, are present in subcutaneous tissues and are typically found after puberty. They are usually manifestations of long-standing or adult disease and occur with low frequency (12%) in childhood. Recent electron microscopy studies have demonstrated that axons and Schwann cells are present in these tumors; therefore, it is appropriate that they be called dermal neurofibromas.

Plexiform Neurofibromas

Plexiform neurofibromas are neurofibromas that arise from



Fig. 1-D

Lateral radiograph of the cervical spine six months following laminectomy and excision of the neurofibroma, demonstrating marked kyphosis of the entire cervical spine and a dystrophic appearance of the vertebrae at the midportion of the apex.

large nerve roots and interdigitate with normal tissues. They have a ropy, “bag of worms” feeling. Their cutaneous involvement may cause decreased sensation, causing sores to develop under a brace or cast without the patient’s knowledge, or they may be hypersensitive. Underlying plexiform neurofibromas are often covered by an area of hyperpigmented skin and/or hairy patch. A plexiform neurofibroma has the potential for malignant degeneration⁵.

Elephantiasis

Occasionally, large soft-tissue masses are seen in NF1. These masses have been termed pachydermatocele or elephantiasis neuromatosa and are characterized by a rough, raised, villosus type of skin hypertrophy that presents an unmistakable appearance.

Optic Gliomas

Although optic gliomas account for only 2% to 5% of all brain tumors in childhood, as many as 70% of the cases are found in persons with NF1. They occur in about 10% of children with neurofibromatosis. In many NF1 patients, these tumors change little in size over many years, but a small percentage may enlarge rapidly, leading to exophthalmos and visual impairment. Gliomas involving the optic chiasm are the most likely to cause visual impairments and precocious puberty.

Verrucous Hyperplasia

Verrucous hyperplasia is an infrequently occurring and unsightly tremendous overgrowth of the skin, with thickening of a velvety-soft papillary quality. Many crevices form and tend to break down easily, with some weeping occurring in the skin folds.

Spinal Deformities

Spinal deformities have been noted to occur in NF1 but not NF2. The deformities include nondystrophic and dystrophic changes. The dystrophic changes may be intrinsic or associated with anomalies of the spinal canal secondary to abnormalities of the spinal-cord dura mater.

The relative incidence of spinal deformities in association with NF1 is unknown. The rate at which patients with NF1 have some disorder of the spine varies from 2% to 36%^{14,15}. Of the approximately 10,000 patients with scoliosis seen by Winter et al., only 102 were found to fit the traditional criteria for the diagnosis of NF1¹⁶. Functional scoliosis resulting from limb hypertrophy or long-bone dysplasia must be ruled out in patients with NF1. All preadolescent children with NF1 should be evaluated by scoliosis screening or the Adam forward-bend test to rule out the presence of a spinal deformity, which usually occurs earlier in children with NF1. The characteristic deformity tends to be a short-segmented, sharply angulated curvature; it usually involves four to six vertebrae¹⁷. Recently, investigators have suggested that there is no standard pattern of spinal deformity in NF1 and that the types of curvature are variable^{18,19}.

Scoliosis is the most common skeletal manifestation of

neurofibromatosis. The incidence of spinal deformities is reported to be between 10% and 60%^{15,20-22}. At our institution it is 23%. Spinal changes may occur throughout the course of the disease and are usually divided into soft-tissue and osseous abnormalities of the entire vertebral column. Some of the complications that can occur during the treatment of spinal problems may reflect a lack of understanding of the disease process on the part of the treating physician or may be related to the potential pitfalls of surgery. Other complications are inherent in the disease process itself. The goal is to prevent problems from occurring by understanding the unusual and unique characteristics of spine problems in NF1. It is imperative for the patient to understand the importance of careful follow-up observation to identify signs of progression of neurospinal disease as there is a very real, lifelong tendency for such progression to occur.

Management of Deformities

Cervical Spine

The cervical spine in patients with NF1 has not received much attention in the literature^{23,24}. Cervical abnormalities are more likely to be overlooked when scoliosis or kyphoscoliosis is present in the thoracolumbar region, which distracts the examiner’s attention to the more obvious deformity. Often the cervical lesion is asymptomatic. When the lesion is symptomatic, pain is the most common presenting symptom²⁵.

The most common abnormality is a severe cervical kyphosis (Figs. 1-A through 1-D), which is most often seen following surgery and is highly suggestive of the disorder¹⁷. Ogilvie reported on the surgical treatment of cervical kyphosis by anterior fusion with iliac-crest or fibular bone graft or both²⁵. He considered halo traction to be a useful preoperative step if the kyphosis was greater than 45°. When progressive cervical kyphosis is the presenting deformity, preoperative halo traction of flexible deformities, followed by posterior fusion, is the treatment of choice. If the deformity is rigid, then soft-tissue release followed by traction is believed to be safer. If sufficient bone stock is present, internal fixation with rods, wires, screws, or hooks may be used. Sublaminar wire fixation may be difficult secondary to dural ectasia and osseous fragility. If there is osteolysis with poor bone stock of the vertebral body, combined anterior and posterior fusion is needed²⁵ and postoperative immobilization with use of a halo vest is recommended. Yong-Hing et al. reported on fifty-six patients with NF1, of whom seventeen patients (30%) were found to have cervical abnormalities²⁴. Of these, seven patients were asymptomatic (the rest had either limited motion or pain in the neck) and four patients had neurologic deficits, which probably could be attributed to cervical instability. Four of the seventeen patients required fusion of the cervical spine. Curtis et al. described eight patients with paraplegia and NF1²⁶. In four of these patients, the paraplegia was due to cervical spine instability or cervical intraspinal pathology.

Attention should also be paid to the C1-C2 region. Isu et al. described three patients with NF1 who had a C1-on-C2



Fig. 2-A



Fig. 2-B

Figs. 2-A and 2-B This thirteen-year-old boy with NF1 underwent multiple laminectomies for decompression of a large neurofibroma at the C5-C6 level. He subsequently presented with a severe kyphosis of the mid-to-lower cervical spine. **Fig. 2-A** Frontal radiograph showing enlargement of the neural foramen at the C7-C8 junction. **Fig. 2-B** Lateral radiograph illustrating severe kyphosis at the C6-C7 level following laminectomy. The loss of the posterior (tension) supporting structures has allowed each involved facet joint surface to slide and subluxate on its opposing surface, producing an increased compressive force on the anterior portion of the vertebral bodies. There has been an unhinging of the posterior articular facets, resulting in complete disengagement.

dislocation with a neurologic deficit, all three of whom improved after decompression and/or fusion²⁷. It is worthwhile to note that no osseous changes in the C1 to C2 relation were seen on the flexion-extension radiographs in any of these patients²⁸. Therefore, relying only on these views to detect instability is unwise. Most of the problems that we have seen in the cervical spine were those that occurred after excision of tumors, the operations for which included resection of the laminae and posterior elements (Figs. 2-A and 2-B). Postoperatively, the spine is unstable and tends to develop progressive kyphosis. Therefore, it is important to be aware of the patient with NF1 who presents with a scar in and about the neck and gives a history of having a mass removed in the past. Recently, we developed a collaborative effort with our neurosurgery colleagues to stabilize the spinal column after removal of tumors from the spinal canal.

Anteroposterior and lateral cervical radiographs should be made for all patients with NF1 who (1) undergo surgery, (2) require endotracheal anesthesia, (3) require cranial traction, or (4) present with neck tumors. If there is any suspicion of subluxation, computed tomography or flexion-extension magnetic resonance imaging scans are appropriate studies. Other reasons for obtaining radiographs of the cervical spine in the patient with NF1 include ruling out the presence of torticollis or dysphagia²⁹. Because we have seen patients with erosive defects in the skull, it is important to obtain skull radiographs prior to applying halo or Gardner-Wells tong traction pins. Stabilization of these patients has been improved by the addition of pedicle screw anchors when laminectomy has been necessary. A reformatted computed tomography scan is extremely helpful to evaluate the osseous anatomy of the cervical spine.



Fig. 3-A

Figs. 3-A and 3-B Two thirteen-year-old adolescents with NF1 and scoliosis. One child (Fig. 3-A) has the nondystrophic type of scoliosis that is occasionally seen with neurofibromatosis, and the second child (Fig. 3-B) has the characteristic dysplastic scoliosis that is believed to be associated with NF1. **Fig. 3-A** This adolescent presented with multiple *café au lait* spots and was referred by her pediatrician because of a positive result on the Adam forward-bend test. This is a nondysplastic idiopathic-appearing curvature of 45°. It was recommended that she have corrective surgery. (Reprinted, with permission, from Crawford AH. Pitfalls of spinal deformities associated with neurofibromatosis in children. *Clin Orthop Relat Res.* 1989;245:32.)

Thoracolumbar Deformities

Nondystrophic Curves

Peculiar to NF1 is the concept of dystrophic and nondystrophic spinal changes. Nondystrophic scoliosis is the most common spinal deformity in NF1; the findings, treatment, and complications are similar to those of a normal idiopathic curve with the following exceptions^{19,29,30}: (1) patients with neurofibromatosis present earlier than their idiopathic counterparts, (2) a somewhat worse prognosis can be anticipated for progression, and (3) there is a higher pseudarthrosis rate after spinal fusion³¹. These differences may be due to a process termed modulation (see below) in which a nondystrophic curve takes on the characteristics of a dystrophic curve^{31,32}.

Treatment for nondystrophic curves: If the patient's curve measures 20° to 25° and has less than three of the dystrophic characteristics, treatment is by observation. Bracing is used when progression has been demonstrated or the patient is skeletally immature and presents with a curve >25°. Deformities exceeding 40° need posterior spinal fusion with segmental instrumentation (Fig. 3-A). Curves >55° to 60° are treated with anterior release with bone-grafting, followed by an instrumented posterior spinal fusion³¹. This is necessary because the curve is usually more rigid than is a similar-

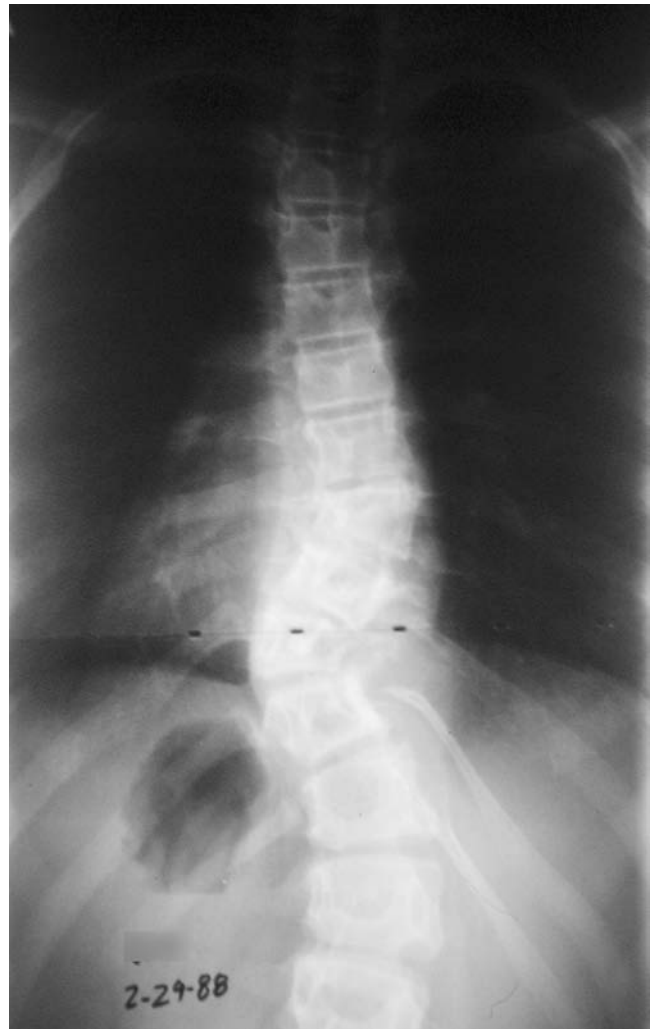


Fig. 3-B

This adolescent was known to have NF1 and a scoliosis deformity. She was being monitored for progression and, subsequent to this radiograph, was scheduled for surgery. This deformity typifies the characteristic, short-segmented, sharply angulated, dysplastic spinal deformity of neurofibromatosis in a young child. In this patient, there was a progression of the curvature of approximately 25° over a thirty-month period. (Reprinted, with permission, from Crawford AH, Gabriel KR. Dysplastic scoliosis: neurofibromatosis. In: Bridwell KH, DeWald RL. *The textbook of spinal surgery.* 2nd ed. Philadelphia: Lippincott-Raven; 1997. p 276-98.)

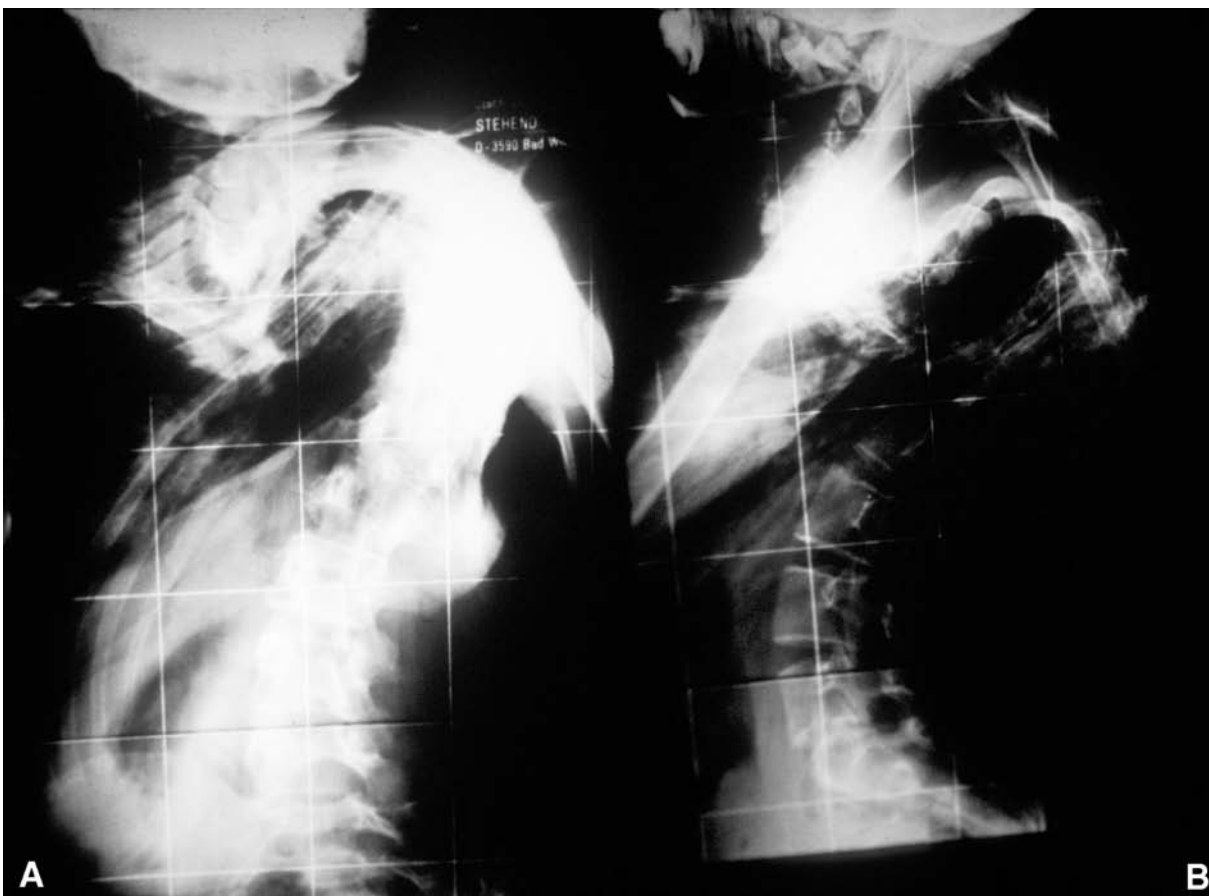


Fig. 4

Radiograph of a twenty-one-year-old patient who had a scoliosis with severe rotation and angulation. A: Coronal radiograph showing marked hairpin coronal-plane curvatures, which are more than likely a manifestation of the substantial kyphosis and rotatory deformity in this child. B: Sagittal radiograph showing the striking kyphosis (photographs courtesy of Dr. Klaus Zielke, Badwildengen, Germany).

sized curve in idiopathic scoliosis. We recommend postoperative orthotic immobilization, although others have managed these patients without postoperative immobilization, with good early results¹⁹. Assessment of the fusion mass by tertiary imaging (e.g., bone scan, computed tomography, magnetic resonance imaging) at six months after surgery is highly recommended.

Dystrophic Curves

The concept of dystrophic curves is based on radiographic findings that can be detected at three years of age (Fig. 3-B)²¹. The patient may present with a true scoliosis, with a normal kyphosis, or, frequently, with a kyphoscoliosis, with a severe kyphotic curve of $>50^\circ$.

A dystrophic curve is characterized by a short-segmented (usually involving four, five, or six vertebrae), sharply angulated deformity, usually in the upper part of the thoracic spine (Fig. 4). There are nine radiographic characteristics of dystrophic spinal deformities (Table I). These include posterior, anterior, or lateral vertebral scalloping of the vertebral bodies, sharpening of the vertebral margins, severe rotation of the

apical vertebra, widening of the spinal canal or the intervertebral foramina, penciling of the ribs, spindling appearance of the transverse process, or a paravertebral mass^{17,33}. Apical vertebral rotation can become so severe that it rotates out of the support axis such that the vertebrae are approximated against one another in a complex three-dimensional pattern (Figs. 5-A and 5-B)¹⁶. On plain radiographs, this may occasionally be interpreted as a congenital deformity. Rib penciling is present when the width of the rib is smaller than that of the narrowest portion of the second rib. Vertebral scalloping is present when the depth of scalloping is >3 mm in the thoracic spine or >4 mm in the lumbar spine. Although scalloping is found in all planes, posterior scalloping is most consistent with the diagnosis of NF1. Scalloping may also be seen in patients with Marfan syndrome. The causes of these changes can sometimes be attributed to intraspinal pathologic processes, such as tumors, meningoceles, or dural ectasia; however, the changes may also occur in the presence of entirely normal intraspinal contents and with no localized abutment from the soft tissues. These dystrophic changes are attributed to primary bone dysplasia. Although all of these various features have been as-

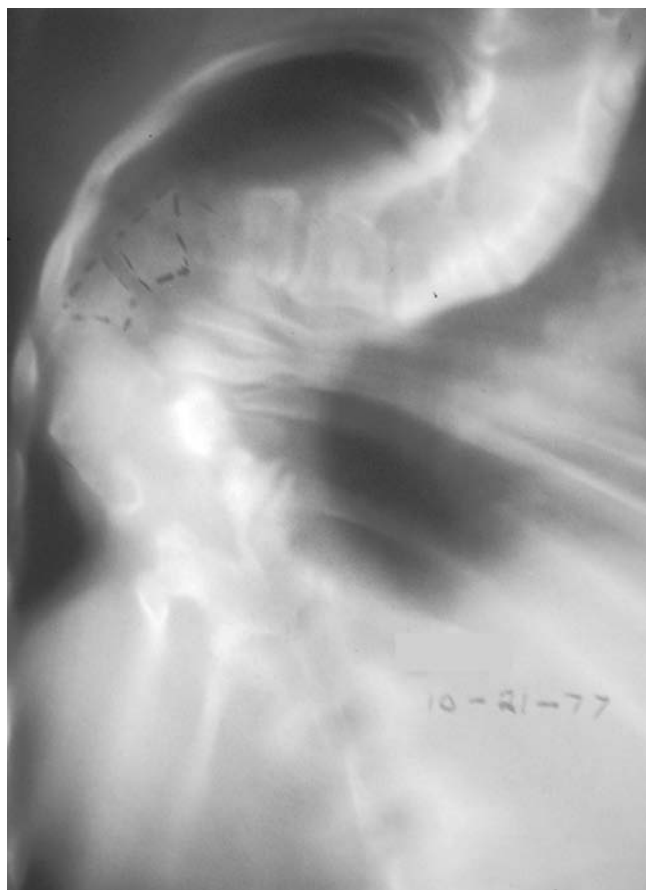


Fig. 5-A

Figs. 5-A and 5-B A sixteen-year-old adolescent with what was considered to be a short-segmented, sharply angulated curvature.

Fig. 5-A Anteroposterior polycycloidal tomograph shows the horizontal presentation of the upper apical portion of the curvature.

sociated with dystrophic deformity, a universally accepted diagnostic criterion does not exist. It is important to identify patients with a dystrophic curve because these types of curves are characterized by a rapid course of progression and a higher rate of pseudarthrosis following fusion.

A spinal deformity that has been diagnosed as idiopathic may show dystrophic changes at subsequent follow-up (Figs. 6-A and 6-B)^{18,31}. This condition is called modulation, a term that refers to the ability of a spinal deformity to transform by acquiring various dystrophic morphologic features. A nondystrophic curve can become dystrophic and a dystrophic curve can acquire further dystrophic changes. This condition is unique to spinal deformities in patients with NF1. These dystrophic changes may evolve slowly or aggressively. Progressively increasing dystrophic changes in a spinal deformity can, at a certain point, alter the behavior of the spinal curve and herald a course of rapid curve progression (Figs. 7-A and 7-B).

With the large number of characteristics found in dystrophic curves, it would be beneficial to the patient and clinician to determine if one or more of these findings may be more predictive of curves that are at greatest risk for progres-

sion. Funasaki et al., in 1994, found that the risk factors that were associated with substantial progression were early age of onset, a high Cobb angle at the first examination, an abnormal kyphosis, vertebral scalloping, severe rotation at the apex of the curve, location of the apex of the curve in the middle to caudal thoracic area, penciling of one rib or more on the concave side or on both sides of the curve, and penciling of four ribs or more²¹. In a recent study of ninety-one patients, the following observations were made: (1) Spinal deformity that develops before seven years of age should be followed closely so that any evolving dystrophic features (modulation) can be identified. (2) When a curve acquires either three penciled ribs or a combination of three dystrophic features, clinical progression is almost a certainty¹⁸.

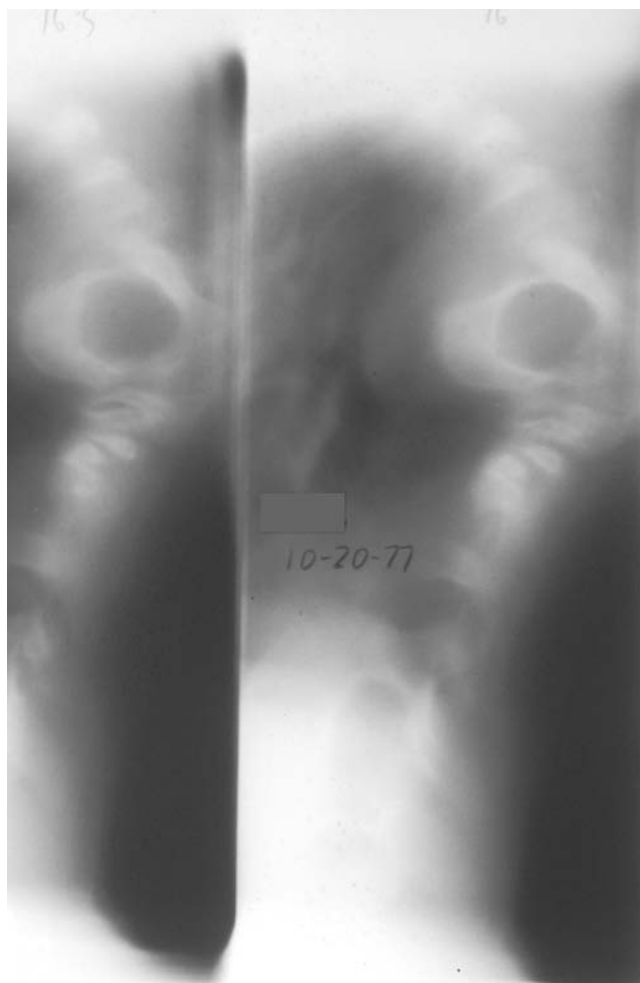


Fig. 5-B

These two lateral plain tomographs illustrate the horizontal alignment of the curvature by virtue of the fact that it is possible to see, in part, an axial view directly into the spinal canal. Even more impressive is the enlargement of the spinal canal secondary to dural ectasia. Note the inverse ratio of the widened canal; the anterior-to-posterior dimension of the vertebral body is reversed from its normal relationship. The anterior-to-posterior dimension of the vertebral body is usually up to twice the length of the canal.

Treatment for dystrophic curves: There is no justification to observe the dystrophic curve in NF1 because it always progresses^{2,30}. Studies have shown that curves treated with a Milwaukee brace progress at a rate similar to those that are left untreated. Early fusion is the best treatment. Fusion in the young individual stunts the growth of the truncal height only minimally because the curve is usually short and poor growth potential remains in the involved vertebrae. The use of subcutaneous growing rods, in theory, would allow for further growth, although Mineiro and Weinstein, in 2002, questioned their value on the basis of the small amount of growth achieved and the number of procedures required³⁴. However, only one of their patients had neurofibromatosis. More recent technological designs of universal instrumentation and localized fusion of anchor sites of growing rods may improve these results.

Despite meticulous planning and treatment, major complications may occur with surgical treatment even in patients without neurologic deficit³⁵. It is necessary to evaluate the contents of the spinal canal to minimize the possibility of neurologic injury during correction. High-volume myelography or magnetic resonance imaging can be used for identifying space-occupying lesions. Special attention should be

TABLE I The Nine Radiographic Characteristics of Dystrophic Deformity*

Dystrophic Features	(%)
Rib penciling	62
Vertebral rotation	51
Posterior vertebral scalloping	31
Vertebral wedging	36
Spindling of transverse processes	31
Anterior vertebral scalloping	31
Widened interpediculate distance	29
Enlarged intervertebral foramina	25
Lateral vertebral scalloping	13

*As seen in 457 children in the study by Durrani et al.¹⁸. Table reprinted, with permission, from Durrani AA, Crawford AH, Choudry SN, Saifuddin A, Morley TR. Modulation of spinal deformities in patients with neurofibromatosis type 1. Spine. 2000;25:69-75.



Fig. 6-A

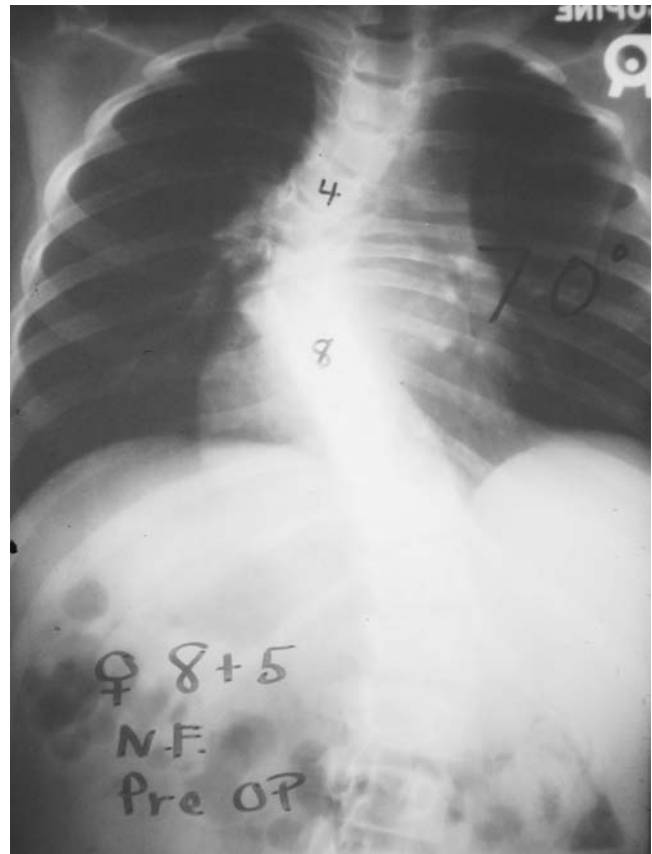


Fig. 6-B

Figs. 6-A and 6-B Progressive scoliosis in a very young child. **Fig. 6-A** Radiograph of the patient at age five years, eight months, showing a 46° thoracic curve. **Fig. 6-B** Radiograph of the same patient at age eight years, five months, showing a 70° deformity and more of the dysplastic characteristics. The curvature has modulated. The final deformity is short-segmented and sharply angulated, and the curve has progressed 24° over a 2.75-year period.

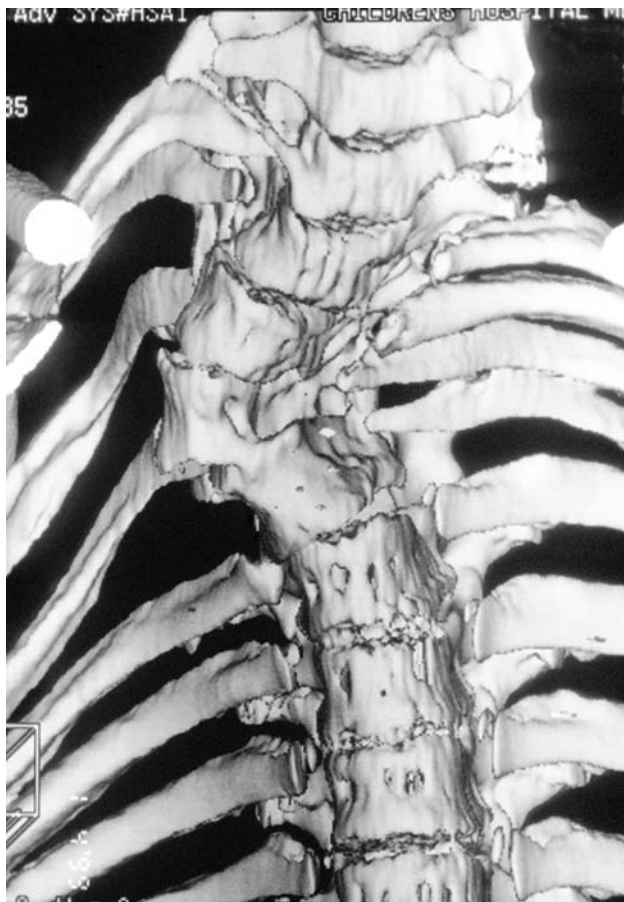


Fig. 7-A

Figs. 7-A and 7-B A nine-year-old child with dysplastic thoracic scoliosis who underwent anterior release and fusion with use of video-assisted thoracoscopic surgery. **Fig. 7-A** Three-dimensional reconstructed computed tomogram illustrating substantial rotation of the upper thoracic vertebra.

directed toward the neural foramen to rule out the presence of ribs protruding into the spinal canal^{36,37}.

We recommend that curves between 20° and 40° be fused posteriorly with the use of instrumentation from the neutral vertebra cephalad to the curve to the neutral vertebra caudad to the curve²⁹⁻³¹. If the curve is more than 40° or the kyphosis is greater than 50°, anterior surgery with discectomy and intervertebral fusion followed by posterior instrumentation and fusion is recommended²⁹.

Winter et al. reported that, in patients with a severe curve and a flexible kyphosis, preoperative traction improved pulmonary function, improved minor neurologic deficits, and diminished the curve size before fusion (Figs. 8-A through 8-D)³⁰. In 2002, Halmaj et al. reported their protocol for treating dystrophic curves of >60° by placing the patient in halo-vest traction for an average of three weeks before surgery¹⁴. They believed that this treatment would allow the paraspinal ligaments and tissues in the intervertebral spaces to become less tight and more hydrated, which would assist in derotating the spine, which in turn would decrease the rate of intraoperative neurologic complications. Careful neurologic monitoring, not just with an evaluation of motion but also with motor strength testing, should be documented during periods of traction. We recommend anterior release, nasojejunal tube alimentation, and craniofemoral traction for rigid curves of >90°. For curves >100° in any plane, anterior and posterior release is followed by nasojejunal tube alimentation and craniofemoral traction.

When posterior exposure is performed, careful decortication must be undertaken because erosion of the laminae is frequently seen due to dural ectasia. We dissect with electrocautery because of the potential of plunging an elevator through a weakened lamina³⁸. Dural ectasia, which can be identified by an increase in the width of the thecal sac due to an increase in hydrostatic pressure, is a process that causes expansion, erosion, and ligamentous instability to the spinal ca-

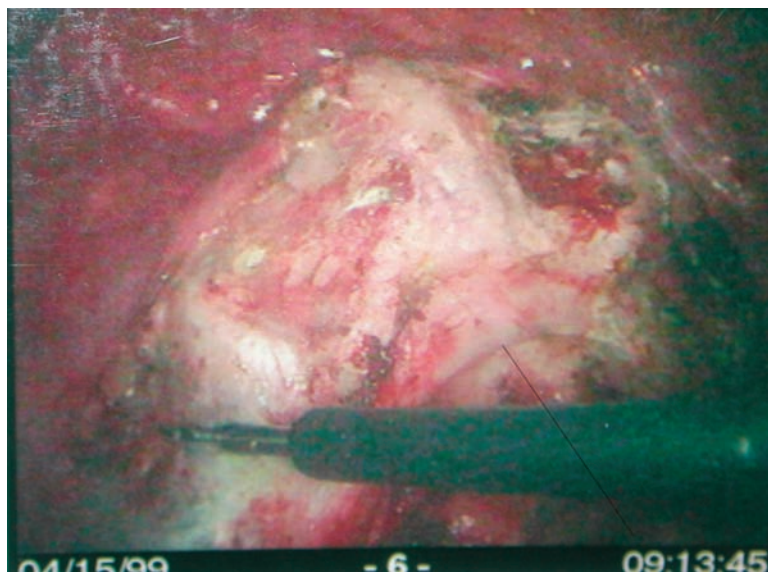


Fig. 7-B

Thoracoscopic view of the anterior apical vertebra. The anterior longitudinal ligament has rotated completely posteriorly on the concave side and is attached to the concave rib heads. The vertebra appears to have spun around toward the convex side.



Fig. 8-A

Figs 8-A through 8-D. This eleven-year-old child was referred to us with mild paraplegia after undergoing seven surgical procedures of the spine. The previous procedures were done with growing rods, which had been removed. **Fig. 8-A** Frontal clinical photograph of the child, showing appreciable *café au lait* spots as well as a plexiform neurofibroma over the inferior-anterior aspect of the left side of the rib cage.

nal and the costovertebral complex. Meticulous fusion after decortication must be carried out with use of abundant bone graft over a broad area. Care should be taken to remove all soft tissue from interposition in the area of the bone graft^{30,39}, and all of the facet joints should be taken down. The use of autologous bone graft is preferred to the use of bone from the bone bank. Instrumentation should be used when possible, but dystrophic vertebrae are not always good recipients for hooks because of osteoporosis and deformity of the posterior elements^{2,40}. Hook dislocation is therefore not infrequent. Pedicle screw anchors may provide the best foundation. In situ fusion

and immobilization in a brace or cast is rarely necessary and represents a poor alternative. The use of biologics such as bone morphogenetic protein or platelet-derived growth factor, when approved, may benefit these patients.

If kyphoscoliosis is present (kyphosis of $>50^\circ$), anterior and posterior fusion should always be performed^{29,31,41}. When anterior fusion is performed, thorough intervertebral disc-space exposure is extremely important. The fusion must be as long as possible, with the addition of strut-grafting. One should attempt to get the bone graft into the vertical weight-bearing axis of the torso³⁰. The recipient area should be well exposed (which is technically difficult because of the severe apical rotation), and the strut graft that is inserted should be in contact with bone because graft material surrounded by neurofibromatous soft tissue has a tendency to resorb. Multiple strut grafts should be used, and the fibula, being the strongest, should be placed most anteriorly. A rib graft swung on a vascular pedicle may also be helpful¹⁶. The exposure is extremely difficult from the concave side, however, and often the apical vertebra may be subluxated or so severely rotated that it is not in alignment with the rest of the spine⁴². Such malalign-

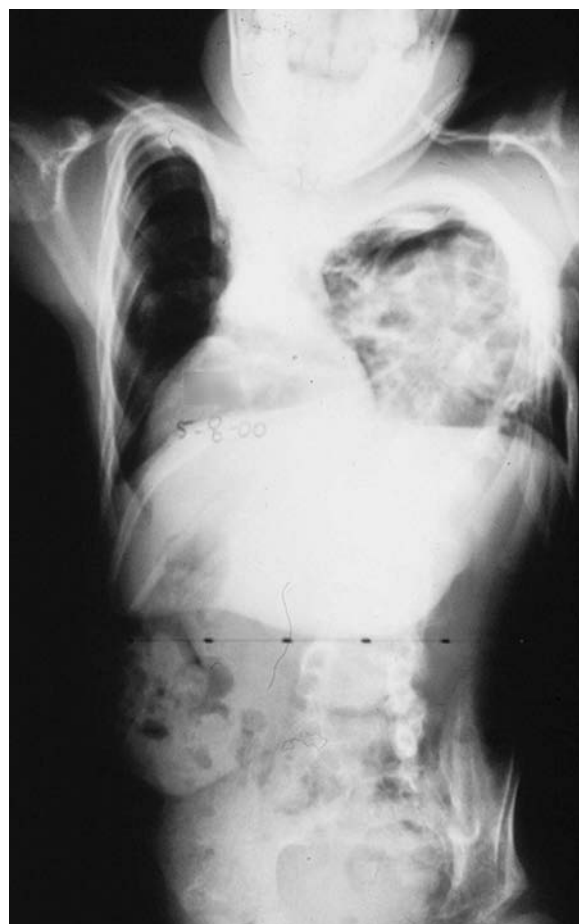


Fig. 8-B

Posteroanterior radiograph of the thoracolumbar spine, showing marked angular deformity in a hairpin turn of greater than 200° .



Fig. 8-C

Lateral clinical photograph, made with the patient bending over, illustrating the clinically significant kyphosis of the midthoracic spine. In addition, there is a very large plexiform neurofibroma at the base of the kyphosis.

ment makes it difficult to place the anterior strut graft in the concavity of the kyphosis. Shufflebarger believes that the anterior procedure should be undertaken from the concave side with multiple strut grafts and that a convex discectomy would destabilize the spine¹⁹. We agree completely, but we have not had a problem with the convex approach and continue to recommend it.

Since we began to perform anterior and posterior releases followed by craniofemoral traction for no less than ten days, the difficulty of obtaining correction has diminished. Because of the ability to gain more correction with extensive release and traction, we are more aggressive with the use of anterior intervertebral segmental fusion (than with the use of strong structural grafts), especially when it is reinforced with posterior fusion.

Even with rigid instrumentation, postoperative immobilization in patients with NF1 is always recommended in an effort to prevent pseudarthrosis³⁰. The external support should be maintained until a fusion mass with trabecular pattern is seen. Despite well-done surgery, pseudarthrosis with loss of correction is not infrequent, even in the hands of experienced spine surgeons. The reason for failure of the surgery is usually an inadequate anterior procedure. Crawford reported a 15% incidence of pseudarthrosis in forty-six patients²⁹, and Sirois and Drennan reported a 31% incidence⁴³. Winter et al. reported on eight patients who underwent a planned two-stage anterior and posterior fusion³⁰. Of these, five patients healed, one patient died of respiratory complications and paraplegia, and two patients developed a pseudarthrosis. The integrity of the fusion mass can be evaluated with use of bone scan, computed tomography, magnetic resonance imaging, or second-look surgery about six months after the initial surgery. Sirois and Drennan recommended planned six-month reexploration and augmentation procedures in patients with an isolated posterior fusion⁴³.

Another complication during surgery may be bleeding. Soft-tissue manifestations of NF1 may complicate an otherwise well-planned surgery⁴⁴. Excessive plexiform venous channels have been described around the vertebral bodies, making it difficult to access the vertebrae⁴³. Soft-tissue tumors from NF1 may be highly vascular; thus, postoperative hematoma is not uncommon and postoperative extradural hematoma causing paraplegia has been described^{30,43}. Therefore, meticulous hemostasis must be carried out during surgery and Hemovac drainage must be performed postoperatively.

Sirois and Drennan reported complications that required additional surgery in nine of twenty-three patients (39%) who underwent treatment of dystrophic curves⁴³. These included four reexplorations and augmentations six months postoperatively, two revisions for instrumentation dislocation, two extensions of the fusion mass for curve extension, and one multiple spinal osteotomy for increasing deformity despite the



Fig. 8-D

Standing lateral radiograph illustrating the severe kyphosis in this child. Note that, at the midportion of the apex, there is a lucency of the spinal canal as the view becomes cephalocaudal. This confirms the fact that the severe rotation has caused the midportion of the spine to be horizontally positioned on this radiograph.

presence of a solid fusion mass. In patients who are still growing, if anterior and posterior fusion is not done, there is an increased incidence of progression of the curve and the occurrence of the crankshaft phenomenon. Additional reported and not infrequent complications include urinary tract infection, dural leak, and thrombophlebitis. After anterior surgery, pulmonary problems with pneumonia, atelectasis, and hemothorax may be seen. Ileus is observed, especially during the period of time between staged anterior and posterior surgery, if the patient is kept in traction. We strongly recommend nasogastric tube placement and hyperalimentation for all patients who undergo staged anterior-posterior surgery.

Kyphoscoliosis

Kyphoscoliosis is defined as a curve with 50° or more of kyphosis. If kyphosis is present, appropriate dynamic radiographs (i.e., a hyperextension cross-table lateral view, made with the patient lying over a bolster) should be performed to evaluate

the flexibility of the curve. Paraplegia is not uncommon in patients with severe kyphosis. If a flexible kyphosis is causing paraplegia, the treatment should be craniofemoral traction (but with extreme caution), with close neurologic or evoked potential monitoring during the course of the traction^{29,45}. A magnetic resonance imaging scan is mandatory for all patients with paraplegia to rule out rib protrusion into the spinal canal^{36,37,46}. For patients with severe deformities, three-dimensional computed tomography scanning can be assistive in surgical planning.

If the kyphosis is flexible, the traction will correct some of the kyphosis and also reduce spinal cord compression and possibly improve the neurologic deficit (Figs. 9-A through 9-E)³⁵. Following traction, anterior release and spinal cord decompression (if needed) and fusion should be performed, followed by a posterior fusion. Because of the potential increase in bleeding that may occur once the patient is normotensive, deep Hemovac drainage is necessary for all patients who un-



Fig. 9-A



Fig. 9-B

Figs. 9-A through 9-E Preoperative and postoperative radiographs of a five-year-old child with severe dystrophic kyphoscoliosis. This child underwent anterior anular release through bilateral open “trapdoor” procedures of the anterior cervicothoracic region, a posterior soft-tissue release, and craniofemoral traction to achieve correction of the severe deformity. A posterior cervical thoracic fusion with use of growing rods was performed following two weeks of traction. **Fig. 9-A** A frontal radiograph illustrating the severe left cervical thoracic kyphoscoliosis. There was dural ectasia with widening of the thoracic canal and penetration of three ribs into the spinal canal. **Fig. 9-B** A standing preoperative lateral radiograph illustrating the severe kyphotic deformity in this child.

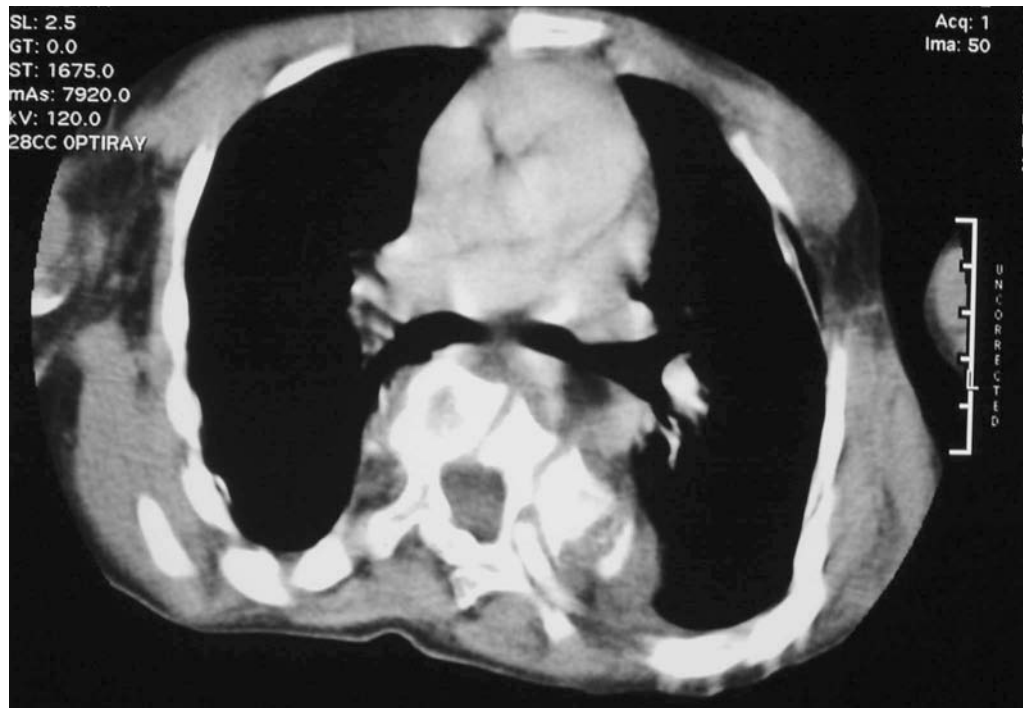


Fig. 9-C

A T2-weighted axial magnetic resonance imaging scan of the thoracic spine at the level of the midportion of the apex, illustrating severe deformity that includes three horizontal vertebrae (lateral projection) and the head of a rib in the spinal canal.

dergo anterior reconstructive surgery. Postoperatively, these patients should be observed carefully for the development of pseudarthrosis. Augmentation of the fusion mass should be performed at six months postoperatively if pseudarthrosis is suspected because of loss of correction.

If the kyphosis is rigid, traction should not be used⁴⁵. Traction in these patients stretches the mobile spinal segments that are located cephalad and caudad to the kyphosis, increasing the tension and point compression on the spinal cord at the midportion of the apex, which may cause further damage. Therefore, direct anterior release, disc excision, and intervertebral fusion followed by seven to ten days of traction, followed by posterior spine fusion, are recommended.

The vertebral bodies are occasionally extremely porotic and will tend to bleed freely from their cancellous surfaces. The end plate is the strongest portion and should be protected with a meticulous anular and discal release. The disc space should be packed with bone. Sufficient bone graft needs to be available.

Because of the association between paraplegia and kyphoscoliosis, there is a tendency to perform laminectomies to relieve pressure on the spinal cord. Laminectomy only for spinal cord compression and kyphoscoliosis is contraindicated, however^{29,45}. Occasionally, a neurologic improvement may be seen after a posterior decompression of the dura, which may temporarily release pressure on the spinal cord. However, laminectomy does not truly decompress the spinal cord because the compression arises anteriorly and removal of bone

posteriorly destabilizes the spine, potentially increasing the kyphosis. Furthermore, laminectomy alone also removes valuable bone stock that will be required for a posterior spinal fusion. Occasionally, paraplegia is related to protrusion of a rib into the spinal canal³⁷. This will usually be evident on a computed tomography or magnetic resonance imaging scan. Removal of this protrusion should prevent progression of neuropathy. When a rib protrusion is noted prior to surgery, osteotomy with a 2.5 to 5-cm resection is recommended at the time of posterior fusion.

In conclusion, dystrophic thinning of the posterior elements and the possible presence of dural ectasia of the spinal canal make the planning of instrumentation to correct the deformity a challenge. We recommend the use of a titanium universal rod system with hooks, wires, and pedicle screw anchors as needed. We have on occasion used bone morphogenetic protein (off-label) to supplement the fusion, but we have no data to support an increase in fusion rate.

Spondylolisthesis

Spondylolisthesis in patients with NF1 is rare⁴⁷⁻⁵⁰. Spondylolisthesis is usually secondary to increased anteroposterior diameter of the spinal canal, with elongation and thinning of the pedicles, causing a pathologic forward progression of the anterior elements of the spinal column. The causes of pathologic instability are frequently dural ectasia, meningocele, and neurofibroma. Magnetic resonance imaging or computed tomography and/or contrast scans are absolutely nec-

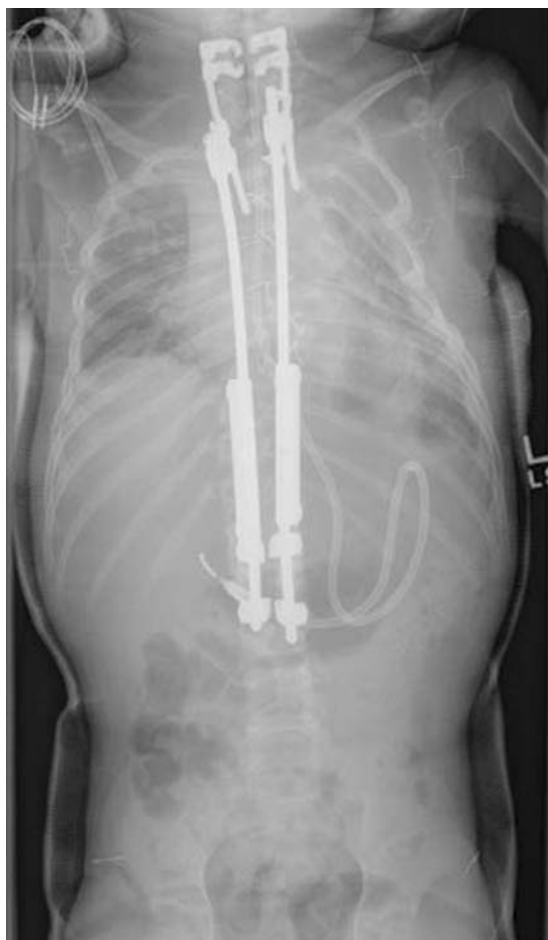


Fig. 9-D
Postoperative posteroanterior radiograph of the spine, illustrating the instrumentation construct as well as the nasogastric tube being used to provide hyperalimentation for this child.

essary for preoperative evaluation. The treatment in severe spondylolisthesis is anterior and posterior spinal fusion. Fusion is difficult to obtain because of the mechanical alignment of the lumbosacral region and poor bone formation. We recommend at least an L4-to-sacrum anterior and posterior fusion with lumbosacral instrumentation. Postoperative immobilization is strongly recommended.

Paraplegia

Paraplegia is not an infrequent complication of spine deformities in NF1²⁶. The neurologic compromise may be related to spinal deformity, instability of the costovertebral complex causing direct protrusion of a rib into the spinal cord, vertebral angulation, tumor, or dural ectasia. Paraplegia presenting in skeletally immature children is frequently caused by spinal deformity, and, in skeletally mature children, by tumor. Paraplegia that occurs after corrective surgery is often due to the compression exerted on the spinal cord by tumors occupying the intraspinal space. Rarely reported is the patient who pre-

sents with paraparesis due to rib displacement. This type of paralysis may have an insidious onset or may occur after trauma³⁶. Rib osteotomy should be carried out before instrumented correction in these patients, lest the correction cause the rib to impale the spinal cord. Osseous dysplasia, intervertebral foraminal enlargement, and rotation of vertebral bodies all may contribute mechanically to allow the heads of the ribs to displace in the canal. In patients with spinal deformity, it seems that kyphosis is the most frequent cause of paraplegia. Increased kyphosis leads to excessive axial tension on the spinal cord and especially on the posterior dura, which compresses the spinal cord against the anterior vertebral body. Paraplegia is rare in a pure scoliotic curve; if present, a workup for intraspinal pathology should be done. If paraplegia is



Fig. 9-E
Standing lateral radiograph illustrating the instrumentation construct. Note the stainless-steel wire closures of the sternum following the "trapdoor" procedure and the nasogastric tube that is being used for hyperalimentation. The child was placed in a Minerva cast for immobilization.

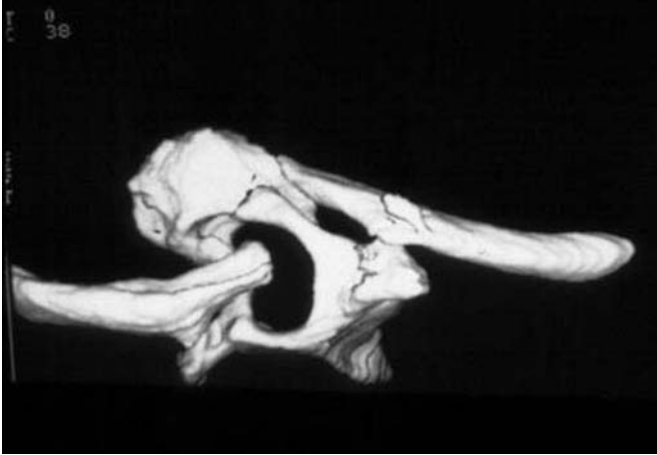


Fig. 10-A

Figs. 10-A and 10-B This patient has severe spinal deformity at the midthoracic level, including protrusion of the rib head into the vertebral canal and widening of the canal secondary to dural ectasia. **Fig. 10-A** Three-dimensional reconstructed computed tomogram showing the rib head protruding into the very widened spinal canal, which has been expanded secondary to dural ectasia. (Contributed by Stephen Tredwell, MD, Vancouver, British Columbia, Canada.)

present, magnetic resonance imaging or a computed tomographic myelogram is appropriate to find the cause of paraplegia. With a severe deformity, interpretation of these images can be confusing, however, and often inconclusive.

Radicular symptoms have been reported, as well, due to vertebral arteriovenous fistulas⁴⁴. The most common form is a dural arteriovenous fistula that is situated in the sleeve of the thoracolumbar nerve root. Kahara et al. recently reported a posttraumatic arteriovenous fistula that caused radicular symptoms due to a mass effect of the dilated epidural venous space⁴⁴.

Prior to surgery, the source of paraparesis, paraplegia, or radiculopathy needs to be thoroughly investigated so that the surgeon is prepared to perform the necessary surgery and have the appropriate assistance available.

Pseudarthrosis

Pseudarthrosis occurs more commonly following an attempt at spinal fusion in patients with dystrophic or nondystrophic curves than it does in patients with idiopathic scoliosis. The incidence is higher in patients who have a kyphosis of $>50^\circ$. Prior to the use of universal spinal instrumentation and anterior-posterior combined surgery, reexploration and rebulking was routinely used for patients with neurofibromatous spinal de-

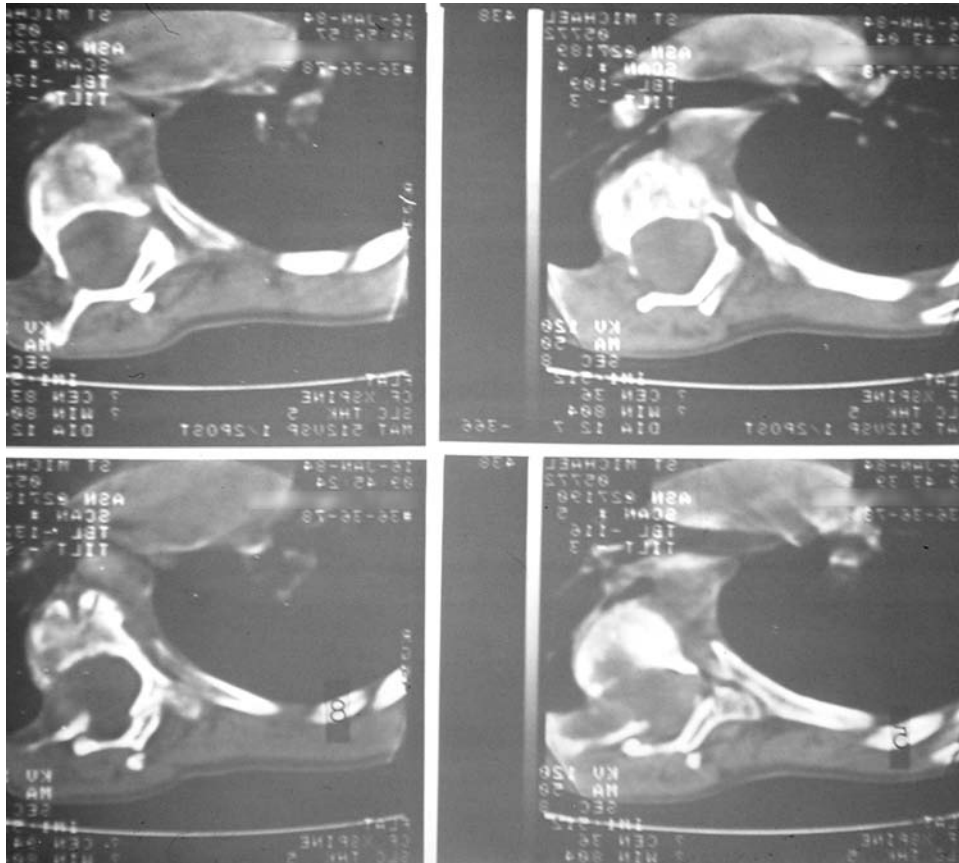


Fig. 10-B

Several axial high-volume computed tomographic myelograms show the erosive effects of dural ectasia. There is appreciable widening of the spinal canal and erosion of the lamina, transverse processes, and pedicle on the right, with consequent displacement of a rib into the canal.

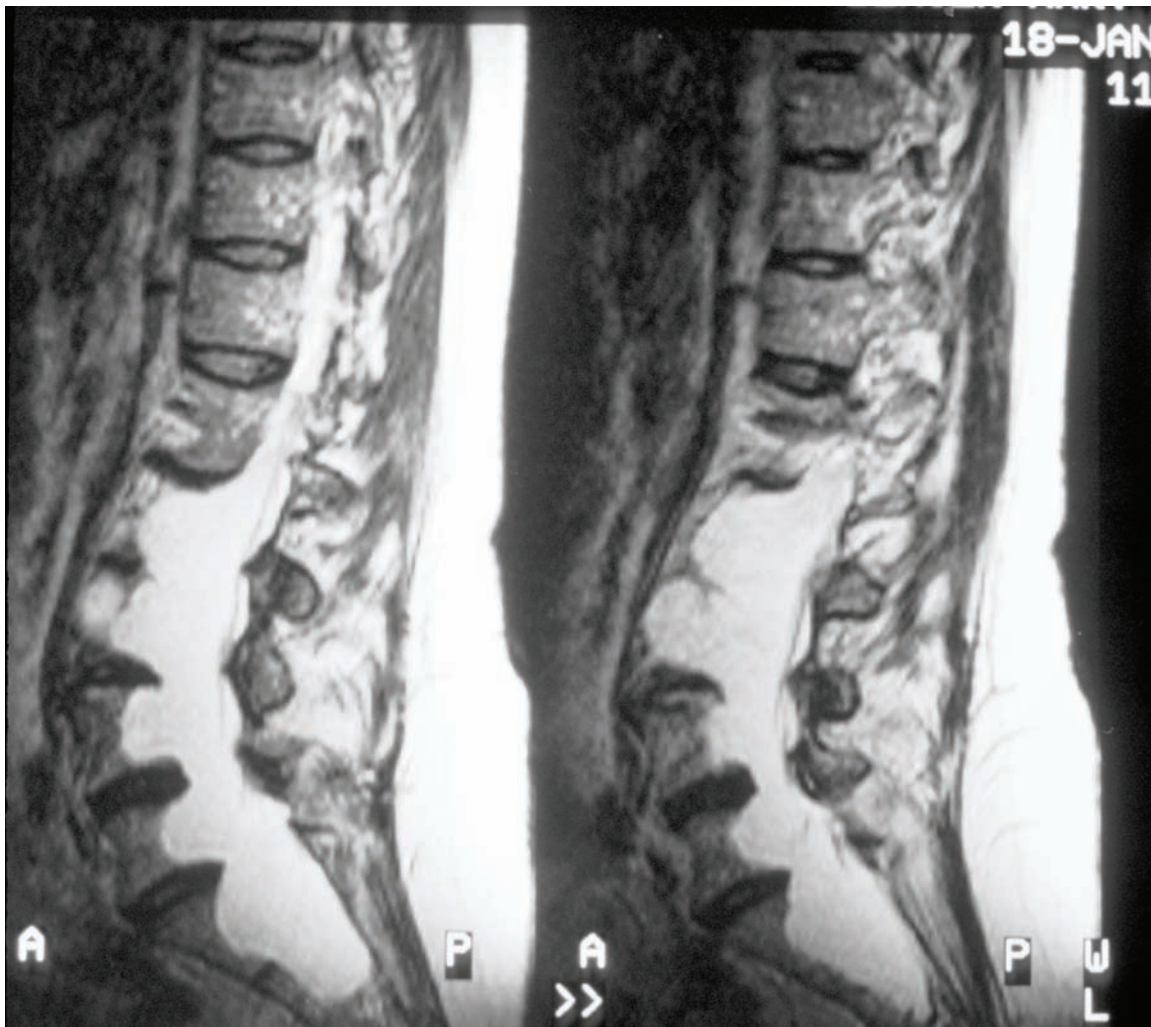


Fig. 11

Multiple T2-weighted magnetic resonance images of a forty-seven-year-old patient with low-back pain, illustrating severe erosion of the lower lumbosacral spine as a result of dural ectasia. (Courtesy of Dr. Courtney Brown, Denver, Colorado.)

formities. The best results are obtained by planning a double (anterior and posterior) arthrodesis right from the start. Even the increased strength of current instrumentation is insufficient to obtain stability at the time of surgery when dealing with some of these deformed, dystrophic elements.

Spinal Canal Pathology

Dural Ectasia and Intrathoracic Meningocele

A unique finding in NF1 and Marfan syndrome is dural ectasia. This is an expansion of the dural sac from an unknown etiology⁵¹. Magnetic resonance imaging or high-volume computed tomographic myelography may distinguish dural ectasia from tumor (Figs. 10-A and 10-B). The expanding dura may cause erosion of the vertebral body and later, destabilization of the spine, with possible spontaneous dislocation (Fig. 11)⁵²⁻⁵⁵. Dural ectasia may in some cases expand the spinal canal so much that the spinal cord is not injured, even if spine dislocation has occurred.

A meningocele is a protrusion of the spinal meninges through the intervertebral foramen or through an erosion of the vertebral body⁵⁵⁻⁶¹. It contains a subarachnoidal space filled with cerebrospinal fluid and causes a paravertebral cystic swelling. It is usually located in the thoracic spine. Meningocele and dural ectasia are a variation of the same phenomenon, with meningocele being more localized. Meningocele may often be an incidental finding on chest radiographs or may be associated with symptoms such as pain or neurologic compromise. If an intrathoracic meningocele expands, causing pressure on adjacent structures, it may cause coughing or dyspnea⁶¹. A massive, symptomatic meningocele should be approached surgically with removal of the meningocele or with placement of a shunt. Consultation with a neurosurgery colleague is highly recommended.

Dumbbell-Shaped Lesions

A dumbbell-shaped lesion is a solitary neurofibroma that is constricted as it exits the neural foramen. The constriction gives



Fig. 12-A
Photograph showing a dumbbell tumor (neurofibroma) that was removed from the neural foramen at the time of surgery. The term “dumbbell” refers to the constriction that occurs where the lesion exits the neural foramen, thus causing the appearance of a weight lifter’s dumbbell.

the neurofibroma the appearance of a dumbbell that is used by weight lifters (Figs. 12-A and 12-B). With continued growth, erosion and widening of the intervertebral foramen occur. Erosion, however, may also be caused by a meningocele, and magnetic resonance imaging may be helpful to distinguish the two entities. Neurofibromas that arise from the spinal canal may be intradural or extradural and are most commonly seen at the cervical and thoracic level⁶². We recommend early fusion in patients who had a laminectomy for resection of a spinal canal tumor to prevent instability (usually kyphosis) of the spinal column. Other tumors may come from the nerve sheath or from the nerve itself, presenting as interstitial hypertrophy, in which case the nerve is the tumor and the tumor is the nerve. The neurofibroma is usually benign but may cause complications by its local growth. The intraspinal portion of the tumor may cause spinal-cord compression and nerve root failure. The peripheral tumor may compress blood vessels, nerves, lung, and pleura⁶². Resection of the tumor originating from the nerve may result in a neurologic loss. Patients need to be advised of this possible neurologic deficit prior to surgery.

Novel Treatments of NF1

The understanding of the pivotal role of neurofibromin in the regulation of the p21-Ras pathway suggests that in-

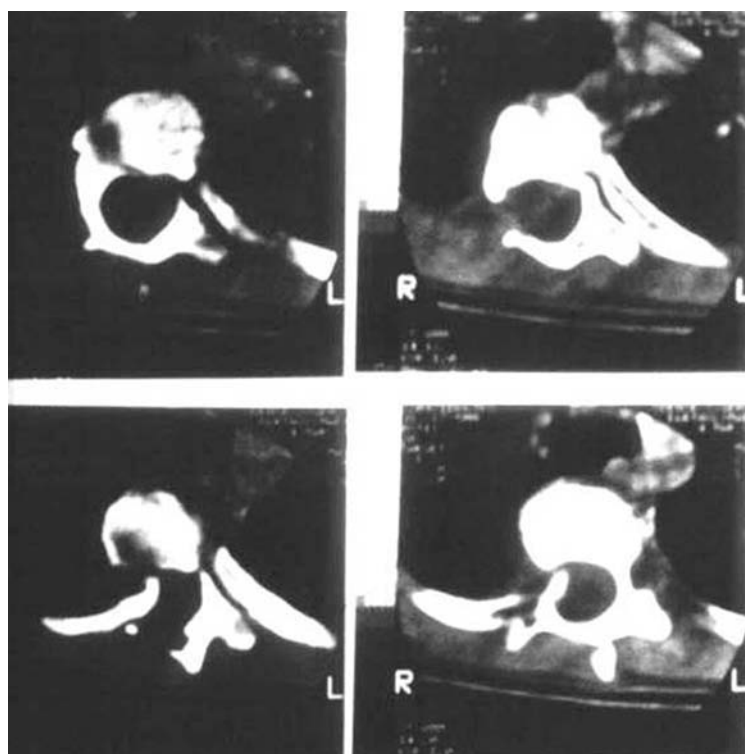


Fig. 12-B
Computed tomographic scans of the vertebra with the neurofibroma in situ. The right image of panel 1 shows the soft-tissue (neurofibroma) shadow exiting the neural canal. The left image of panel 2 shows that an adjacent rib is protruding into the spinal canal. The child was asymptomatic. (Reprinted, with permission, from Crawford AH, Gabriel KR. Dysplastic scoliosis: neurofibromatosis. In: Bridwell KH, DeWald RL. The textbook of spinal surgery. 2nd ed. Philadelphia: Lippincott-Raven; 1997. p 292.)

hibitors of p21-Ras pathway activation may assist in the control of NF1 tumors, including plexiform neurofibromas, especially those which are deep-seated and not amenable to surgical options. Farnesyltransferase inhibitors, specifically tipifarnib (R115777), have been shown to inhibit the post-translational modification and activation of p21-Ras pathway and are currently in phase-II clinical trials⁶³. Pirfenidone, another novel antifibrotic agent that inhibits the overexpression of fibroblast growth factor, epidermal growth factor, and platelet-derived growth factor in plexiform neurofibromas, is undergoing clinical trials. Thus, new efforts to treat various symptoms and tumors associated with neurofibromatosis are under clinical investigation, representing the progress in clinical treatment based on the understanding of cellular and molecular mechanisms of the disease process.

Conclusion

While correction of idiopathic scoliosis is the goal of the spinal surgeon, halting the progression of the deformity

even with only a small correction can be considered a good result in patients with NF1 spinal deformities. We currently use three modalities to assess spinal cord function: transcranial (motor and sensory evoked potential monitoring), electromyography following insertion of the pedicle screw, and, if necessary, the gold-standard wake-up test.

The surgeon's responsibility is to stabilize the spine in the most expedient, safe, and permanent method possible without causing permanent neurologic injury. ■

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