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REVIEW

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Spinal deformity in neurofibromatosis type-1: diagnosis and treatment

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Abstract Spinal deformity is the commonest orthopaedic manifestation in neurofibromatosis type-1 and is categorized into dystrophic and non-dystrophic types. Management should be based on a meticulous assessment of the spine with plain radiography and magnetic resonance imaging (MRI) to rule out the presence of dysplastic features that will determine prognosis and surgical planning. MRI of the whole spine should also be routinely obtained to reveal undetected intraspinal lesions that could threaten scheduled surgical interventions. Non-dystrophic curvatures can be treated with similar decision-making criteria to those applied in the management of idiopathic scoliosis. However, close observation is necessary due to the possibility of modulation with further growth and due to the increased reported risk of pseudarthrosis after spinal fusion. The relentless progressive nature of dystrophic curves necessitates aggressive operative treatment, which often has a significant toll on the quality of life of affected patients through their early childhood. Bracing of dystrophic curves has been unsuccessful. Combined anterior/posterior spinal arthrodesis including the entire structural component of the deformity is indicated in most cases, particularly in the presence of associated sagittal imbalance. This should be performed using abundant autologous bone graft and segmental posterior instrumentation to minimize the risk of non-union and recurrence of the deformity.

Keywords Neurofibromatosis · Spine deformity · Management · Radiography · MRI

Introduction

Neurofibromatosis is the most frequent single-gene disorder affecting mankind [12]. It is a disorder of neural crest cells defined as a spectrum of multifaceted diseases, probably hamartomatous in origin, involving neuroectoderm, mesoderm and endoderm [16]. Its clinical manifestations have in common the presence of neurofibromas, schwannomas and cafè-au-lait macules, which can potentially appear within any organ system of the body, involving primarily the skeleton, skin and soft tissues.

Individuals with the disorder have attracted in the past significant public interest mainly due to the dramatic cutaneous manifestations, the overgrowth of an extremity as part of a gigantism process and the development of severe spinal deformities causing devastating cosmetic results. ''The Hunchback of Notre Dame'', a novel written by Victor Hugo, portrays Quasimodo as a man with a deformed back who was probably affected by neurofibromatosis [33]. The condition drew public attention when Joseph Carey MacDonald Merrick (John Merrick), who was portrayed in

the book and play "The Elephant Man", was thought to have neurofibromatosis. However, it is now believed that Proteus syndrome was a much more likely diagnosis [4, 61].

Historically, the clinical symptomatology of neurofibromatosis has been described as early as the 14th century [52]. Virchow, a well-known German pathologist, reported more than 150 years ago clinical features of the condition in several members of the same family, while 35 years later his student von Recklinghausen investigated the histological characteristics of the disorder that was later named after him [70, 72].

Classification and diagnosis

Two distinct clinical forms of neurofibromatosis have been described; neurofibromatosis-1 (NF-1) or peripheral neurofibromatosis and neurofibromatosis-2 (NF-2) or central neurofibromatosis. Other investigators also accept two additional clinical types namely segmental and mixed neurofibromatosis [16]. Central neurofibromatosis affects 1:50,000 individuals and is characterized by bilateral acoustic neuromas. It is not associated with primary skeletal disorders and orthopaedic complications [43, 55]. The most common form of neurofibromatosis is NF-1, which affects 1:3000–4000 individuals and 1,000,000 people worldwide, being seen in all racial and ethnic groups [2, 9, 27, 32, 39]. Inheritance of the disorder is autosomal dominant with high penetrance. Nevertheless, approximately 50% of cases arise sporadically due to de novo mutations [7, 67, 54, 71]. Advanced paternal age appears to predispose to new mutations in the NF-1 gene [54].

NF-1 is caused by a defect in the gene responsible forthe production of the protein neurofibromin. This is a tumour suppressor gene linked to the long arm of chromosome 17 [16, 67, 71]. Neurons, oligodendrocytes, non-myelinated Schwann cells, adrenal medulla, testes and leukocytes are the primary sites where neurofibromin demonstrates its highest expressivity [18, 31]. The major function of the gene product appears to be regulation of the ras protein [44, 71]. Absence of neurofibromin expression results in tumourgenic effects and the development of NF-1 associated neoplasms, including malignant peripheral nerve sheath tumours, pheochromocytomas, malignant myeloid dysplasias and benign neurofibromas [46, 71]. The role of ras in the pathogenesis of tumours in NF-1 has suggested an approach to treatment using ras inhibitors, some of which are likely to begin clinical trials in patients with NF-1 in the near future [44]. Moreover, neurofibromin is a large protein with 2,818 amino acids and has many locations probably interacting with other intracellular proteins. Therefore, one could postulate that interruption of this combined activity could be contributory, apart from the formation of neoplastic lesions, to the development of the other numerous clinical manifestations evident in individuals with NF-1 [19, 30].

The NF-1 gene is fairly large, with approximately 300,000 base pairs [16]. It also demonstrates a considerably high mutation rate, lacks hotspots where these mutations arise, has a variable expressivity from patient to patient and does not show a clear genotype-phenotype correlation [71]. These are the reasons why, despite the identification of the neurofibromin gene, prenatal genetic diagnosis still remains clinically impractical [16, 29]. The detection of new cases is, therefore, still based on clinical criteria defined by the 1987 Consensus Development Conference of the National Institutes of Health on NF-1 (Table 1) [53]. Diagnosis requires at least two of the described criteria to be present [53].

Clinical manifestations of NF-1

Patients with NF-1 may present with a wide variety of clinical manifestations that may not all be readily apparent at birth. Café-au-lait spots are present in over 90% of all individuals affected by NF-1, usually in early childhood and classically take on a Coast of California appearance [16, 71]. Axillary or inguinal freckling also bears a high specificity for confirming the diagnosis of NF-1 in children. Lisch nodules of the iris are common in children above the age of 6 years [48] and are evident in most patients older than 30 years [54]. In contrast, optic gliomas constitute an infrequent finding [39]. However, a limited percentage of these tumours may enlarge rapidly and cause exophthalmos and visual compromise [16]. Neurofibromas appear around puberty and can be cutaneous or deep, infiltrating the sur-

Table 1 Diagnostic criteria defined by the 1987 Consensus Development Conference of the National Institutes of Health for the diagnosis of neurofibromatosis [53]. Two or more criteria present confirm the diagnosis of NF-1

Diagnostic criteria for NF-1
Six or more cafe-au-lait macules >5 mm in greatest diameter in pre-pubertal individuals and >15 mm in greatest diameter in post-pubertal individuals
Two or more neurofibromas of any type or more than one plexiform neurofibroma
Freckling in the axillary or inguinal regions
Optic glioma
Two or more Lisch nodules (iris hamartomas) by slit lamp examination
A distinctive osseous lesion, such as sphenoid dysplasia or thinning of a long bone cortex, with or without pseudoarthrosis
A first-degree relative (parent, sibling, or offspring) with NF-1 by the above criteria

rounding tissues and affecting peripheral nerves or the spinal cord. These lesions can potentially increase in size and number due to puberty or pregnancy and are quite frequent in patients over 30 years old [14, 54].

Approximately 50% of patients with NF-1 will develop severe orthopaedic complications during childhood with spinal deformity and congenital pseudarthrosis of the tibia creating the most challenging therapeutic dilemmas [12, 71]. A recent study reported that 70% of affected individuals would require hospitalization to address surgical or medical issues directly related to neurofibromatosis [79]. Familiarity with the various manifestations of NF-1 in different anatomic locations is, therefore, critical in making an early diagnosis and optimizing treatment. The mainstay of care for these patients focuses on the symptomatic management of disease complications. Counselling of patients and their families should provide adequate information on the possible disease complications, which may impede the quality of patients' life at a very early age, while emphasizing that most individuals with NF-1 have normal life expectancy and lead a productive life.

Spinal deformity in NF-1: classification and imaging evaluation

Scoliosis is the most frequent musculoskeletal manifestation in NF-1, usually occurring in the thoracic region [2, 16, 58]. Almost a century ago, both Gould [28] and Weiss [73] called attention to the high incidence of spinal deformity in patients with neurofibromatosis. However, the true prevalence of spinal deformity in NF-1 remains unknown, with figures in the literature ranging from 2 to 69% [2, 12, 16, 21, 26, 35, 38, 45, 50, 57, 58, 63, 64, 66]. Conversely, 2–3% of all scoliotic patients with significant curves have neurofibromatosis [57]. Suggested aetiological theories for the development of spinal imbalance in this condition include erosion or infiltration of bone by localized neurofibromas, primary mesodermal dysplasia, osteomalacia and endocrine disturbances [8, 16, 26, 43].

Coronal spinal decompensation in neurofibromatosis is generally classified into non-dystrophic and dystrophic types based on the absence or presence of skeletal dysplasia on plain radiographic evaluation, with the clinical and radiological features in the non-dystrophic type being similar to idiopathic scoliosis [26, 75] (Fig. 1). A meticulous search for evidence of dysplastic changes should be performed in all patients since prognosis and management of the scoliotic curve depend largely on the presence of dystrophic features (Table 2). Dystrophic features include vertebral scalloping (posterior, lateral or anterior) (Fig. 2), rib pencilling (Fig. 3) or spindling of the transverse processes, wedging of one or more vertebral bodies (Fig. 4), paraspinal or intraspinal soft tissue masses, a short curve with significant apical rotation, occasionally leading to subluxed or dislocated vertebral bodies, foraminal enlargement and defective pedicles. Dystrophic changes are thought to be either intrinsic in origin or associated with intraspinal anomalies, namely abnormalities of the dura mater such as dural ectasia, or dumbbell neurofibromas extending through the intervertebral foramina and causing foraminal enlargement [16, 43]. As a general rule, the more severe the dystrophic changes identified in the vertebral bodies, the higher the likelihood that the scoliotic curvature will deteriorate. In a previous study investigating the evolution of spinal deformity in NF-1, when a combination of three or more dysplastic features was present, the risk of curve progression was significantly increased in 85% of the patients, while rib pencilling was the only singular

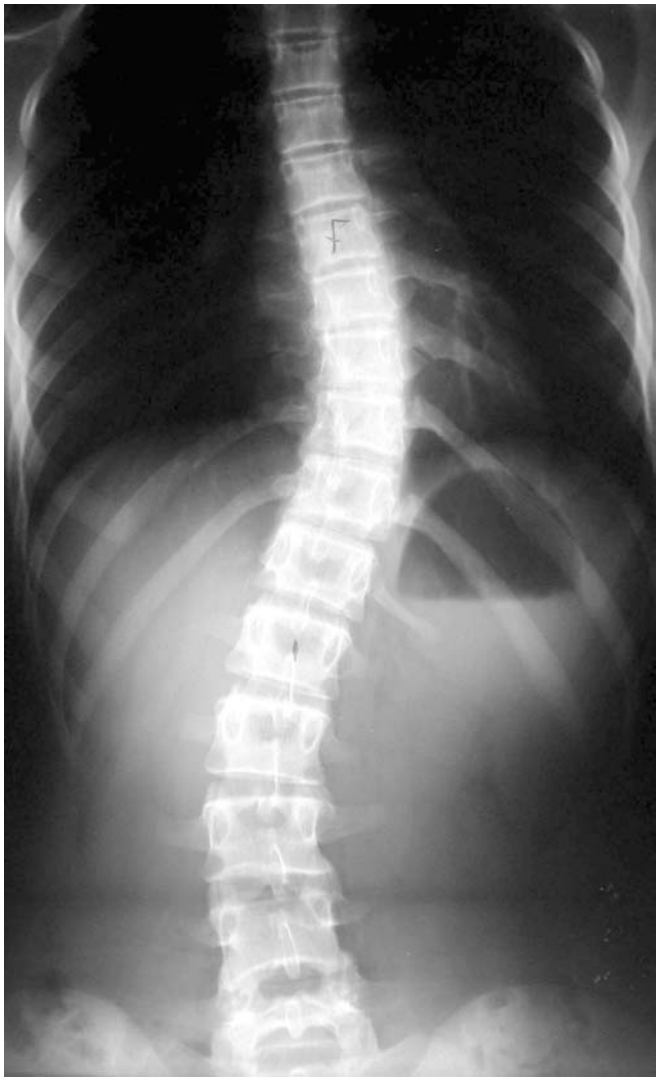

Fig. 1 PA radiograph of the spine demonstrating a non-dystrophic curve pattern in NF-1

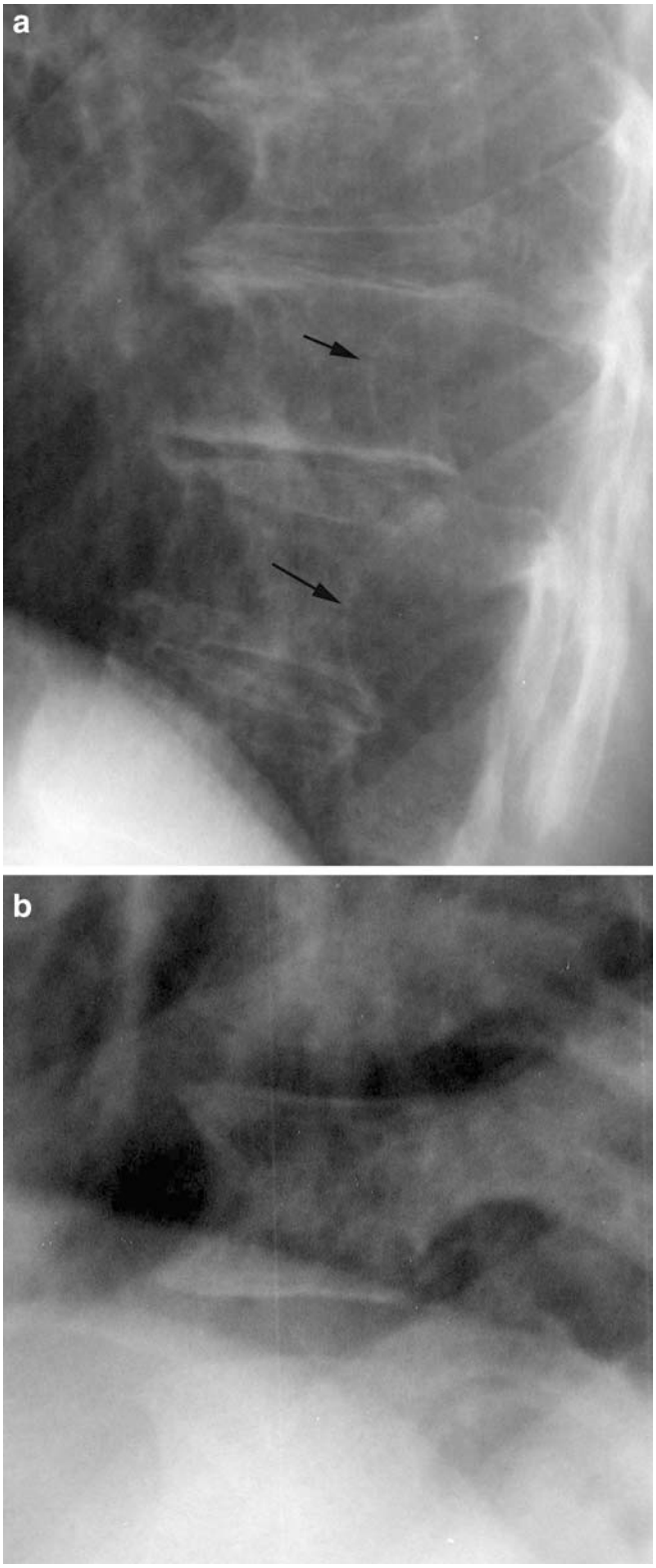

Fig. 2 Vertebral scalloping in NF-1. **a** Lateral coned radiograph of the lower thoracic spine demonstrating posterior vertebral scalloping (*arrows*). **b** Lateral coned radiograph of the lower thoracic spine demonstrating anterior vertebral scalloping

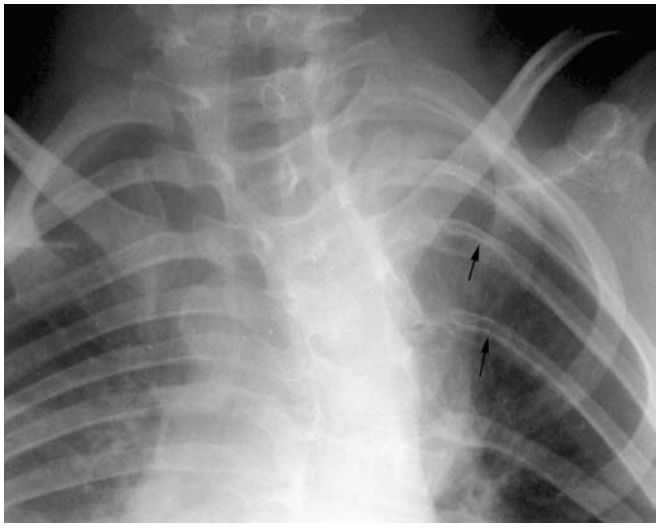

Fig. 3 AP radiograph of the upper chest wall demonstrating rib pencilling (*arrows*)

dystrophic factor statistically influencing risk of scoliosis deterioration [22].

A finding characteristic of NF-1 is dural ectasia, an expansion of the thecal sac at the expense of the bony and ligamentous structures. This may result in posterior vertebral scalloping (Fig. 5) and lateral thoracic meningocele formation (Fig. 6), often causing destabilization of the vertebrae leading to spontaneous subluxation or dislocation, as well as penetration of the spinal canal by protruding ribs separated from their costotransverse attachments [25, 49, 60]. Canal widening, as the result of dural ectasia, is the reason why even tremendous angular deformities may not be accompanied by spinal cord compromise and neurologic deficit. On the contrary, if an intraspinal neurofibroma is the aetiological factor related to the development of canal expansion (Fig. 7), as with any other space-occupying lesion, it can provoke cord compression.

If dystrophic changes are noted on plain radiographs, magnetic resonance imaging (MRI) has been considered absolutely essential to further investigate the intraspinal contents [16], particularly when surgical management of scoliosis is anticipated [16, 43]. MRI of the entire spine is recommended as part of the routine preoperative assessment in all patients with neurofibromatosis to detect intraspinal mass lesions [16, 57, 67]. It is worth noting that the interpretation of MRI can occasionally be difficult in patients with complex deformities including significant vertebral rotation and acute kyphosis.

In our institution, patients with NF-1 who present with spinal curvatures are routinely screened at initial presentation with the use of plain radiographs in order to characterize the deformity in both coronal and sagittal planes and identify associated dystrophic changes. MRI is obtained as part of the regular imaging evaluation,

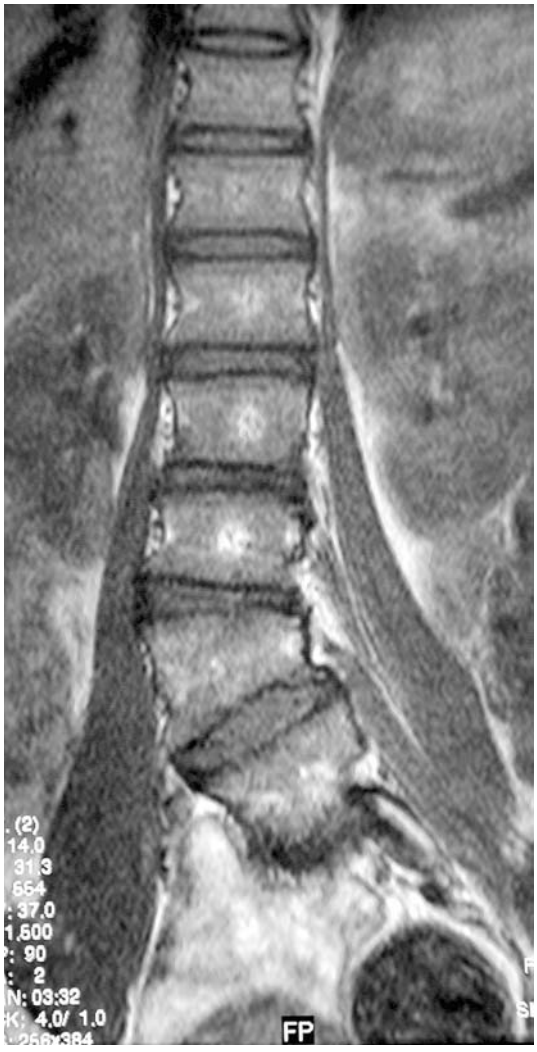

Fig. 4 Coronal T1W MRI showing wedging of the L3 vertebra

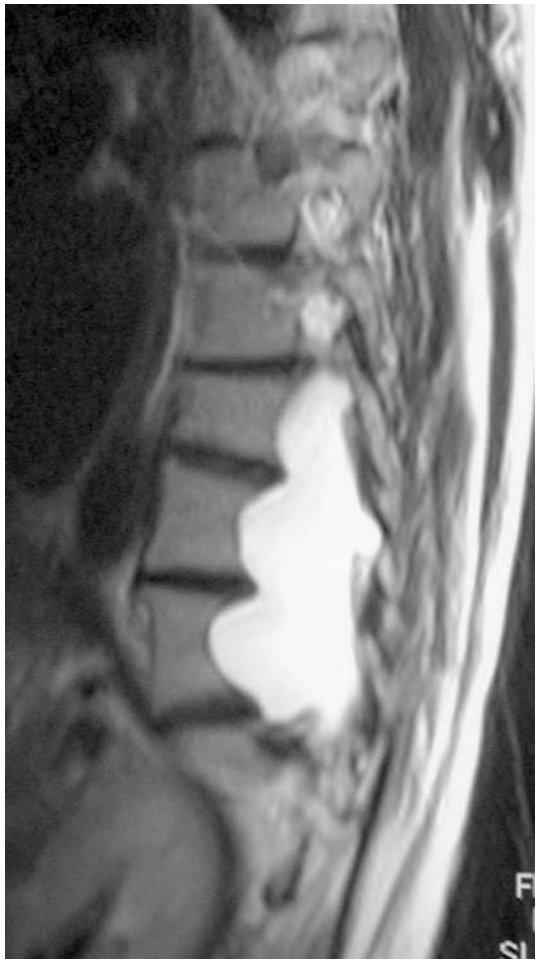

Fig. 5 Sagittal T2W MRI showing dural ectasia in the lower thoracic region associated with posterior vertebral scalloping

Table 2 Typical dysplastic changes evident on plain radiographs in patients with NF-1 [22, 26, 37, 43]

Dysplastic changes
Vertebral scalloping (considered to be present when the depth of scalloping is more than three millimetres in the thoracic spine or more than four millimetres in the lumbar spine)—this is either associated with dural ectasia or neural tumour
Rib pencilling (considered to be present when the width of the rib was smaller than that of the narrowest portion of the second rib)
Transverse process spindling
Vertebral wedging
Paravertebral soft tissue mass
Short curve with severe apical rotation
Intervertebral foraminal enlargement
Widened interpediculate distances
Dysplastic pedicles

regardless of the presence of neurological symptoms, with the aim of delineating intraspinal and paraspinal lesions and better illustrating the components of the deformity. In our experience, MRI of the whole spine identified vertebral dysplasia in 36.3% of cases of NF-1 initially classified on plain radiography as having non-dystrophic curves, while 25% of this subgroup of patients required early surgical correction of the curvature due to rapid progression. This finding indicates the potential value of whole spine MRI at presentation in patients with NF-1 and spinal deformity in clarifying the classification of curve type and assisting management planning.

The need for preoperative assessment with whole spine MRI to exclude underlying intraspinal pathology cannot be overemphasized. However, the requirement for radiological surveillance of spinal tumors in patients with NF-1 that are not scheduled for spine surgery is controversial. Previous investigators have used whole spine MRI, in conjunction with plain radiographs, as a

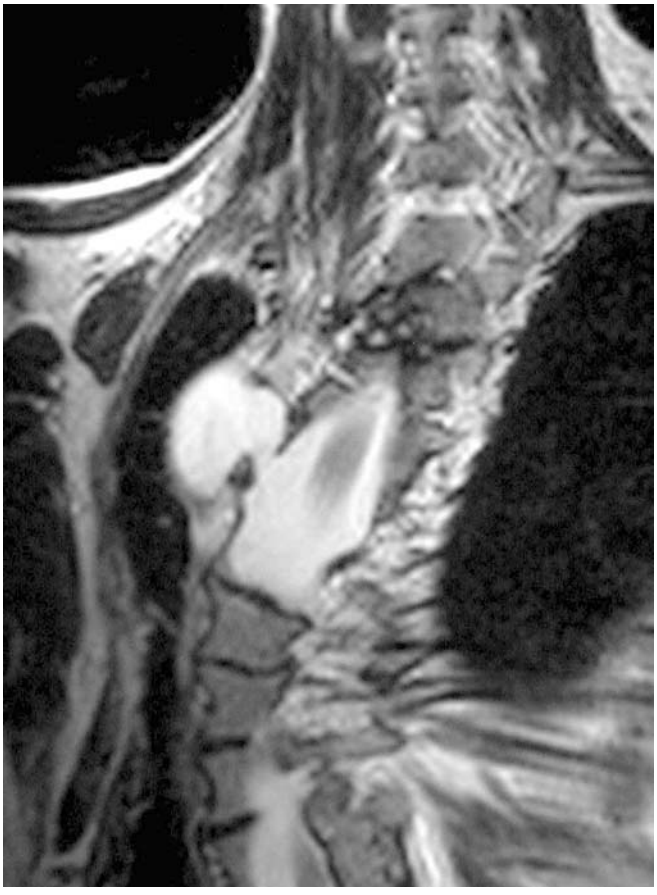

Fig. 6 Coronal T2W MRI showing dural ectasia and a right lateral thoracic meningocele in the upper thoracic region

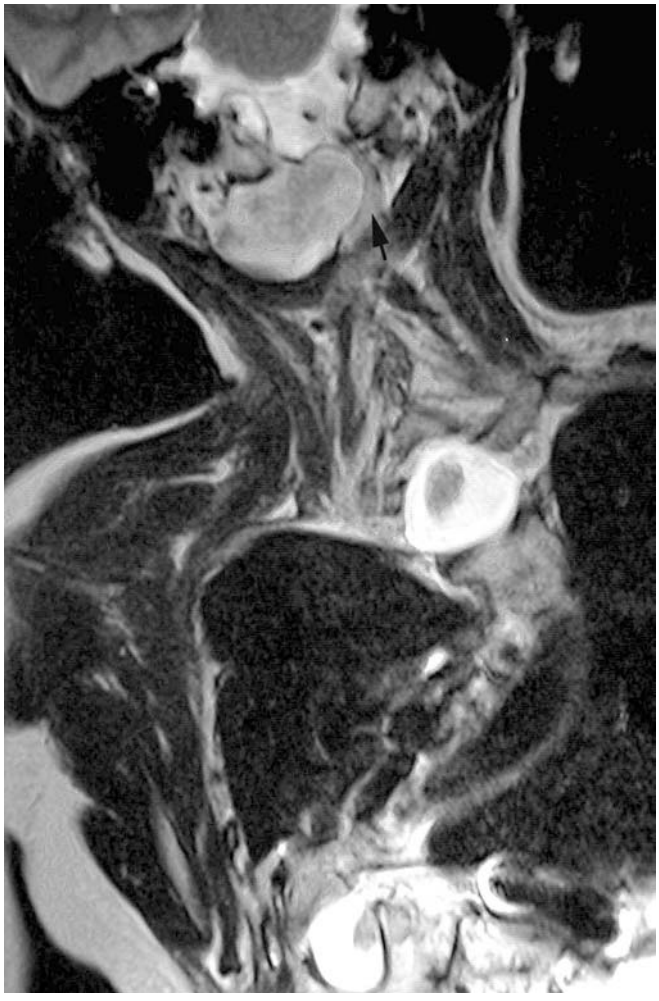

Fig. 7 Coronal T2W MRI in the cervicothoracic region showing a dumb-bell neurofibroma compressing the cervical spinal cord (*arrow*)

diagnostic tool to detect the presence of spinal tumors in patients with NF-1 [23, 42, 69]. Egelhoff et al. [23] identified a high incidence of spinal tumors on MRI (35.7%) in a mixed population of adult and pediatric patients with NF-1 without spinal deformity, and suggested that MRI of the spine should be performed as a routine test in this patient group. In contrast, other investigators do not advocate routine MR imaging and emphasize that MRI should be indicated by clinical necessity [32]. Khong et al. [42] examined 62 children with NF-1 with whole spine MRI and reported an incidence of 13.2% for spinal neurofibromas, closely associated with an increased incidence of scoliosis, localized cutaneous neurofibromas and massive soft-tissue neurofibromas. Thakkar et al. [69] conducted an MRI study including 1,400 children and adults and detected symptomatic spinal tumors in only 23 patients (1.6%).

In our experience, the prevalence of intraspinal and extraspinal neurofibromas was relatively higher compared to that previously documented [23, 42, 69], with a cumulative incidence of 37% in a combined group of patients with dystrophic and non-dystrophic curves. However, none of these tumors was associated with any neurological impairment and all patients were completely asymptomatic on serial clinical examination. Intraspinal or paraspinal neurofibromas were identified in almost half of the patients in the dystrophic group. In this group, there was a tendency for the neurofibromas to develop adjacent to the convexity of the curve (Fig. 8).

Management of spinal deformity in NF-1

Non-dystrophic curves

Non-dystrophic curves can be managed similarly to idiopathic scoliosis and demonstrate comparable response to treatment [3, 13, 15, 43, 55, 62, 75]. If the magnitude of the scoliotic deformity is less than 20–25°,

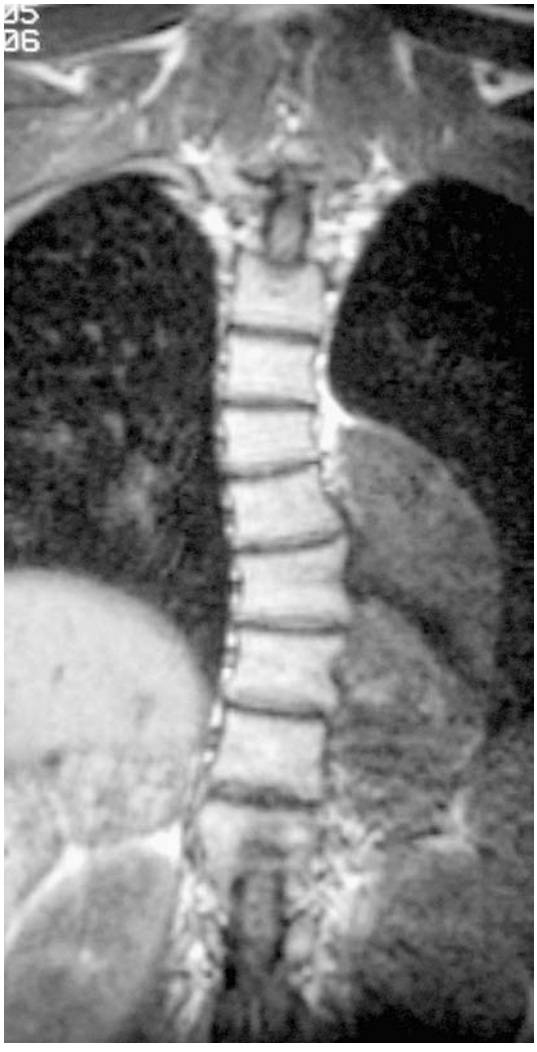

Fig. 8 Coronal T1W MRI in the mid-thoracic region showing a neurofibroma adjacent to the convexity of the curve and associated with minor lateral vertebral scalloping

the patient may be observed closely at regular 6-monthly clinic visits. Brace treatment can be applied for curves between 20° and 40° if the patient still has significant remaining growth. When bracing is selected as the preferred management option, it should be noted that compliance can be particularly challenging, since children with NF-1 may often have cognitive dysfunction, intellectual handicap, attention deficit disorders, seizures and a greater degree of social, emotional and psychological problems compared to their unaffected siblings [24, 41].

If the deformity exceeds 40°, it should be treated surgically by a posterior spinal fusion and segmental instrumentation. The use of autologous iliac crest graft is recommended to enhance a solid bony fusion, especially since there is evidence of a higher incidence of non-union after attempted instrumented spinal fusion in patients with NF-1 in comparison to those with idiopathic scoliosis [1, 13, 15, 16, 43, 55]. For curves of more than 55–60°, where increased rigidity should be anticipated, combined anterior release and bone grafting followed by posterior spine fusion with the use of instrumentation is often necessary to achieve restoration of spinal balance [13, 15, 40, 43, 55].

Close observation of the evolution of deformity is critical due to the possibility of modulation of spinal deformity from non-dystrophic to dystrophic curves and the development of spinal canal neurofibromas, giving rise to pressure-induced expansion of the canal and secondary dysplastic changes in the vertebral bodies [16, 22]. Modulation of non-dystrophic to dystrophic scoliotic curvatures is unique to children with neurofibromatosis, with a reported incidence that varies from 81% in patients diagnosed before 7 years of age to 25% in those detected after the age of 7 years [22]. When observing patients with NF-1 initially classified as having non- dystrophic curves over an extended period of time, there is a higher propensity for developing progressive deformity compared to the idiopathic scoliosis population. In these patients dystrophic changes may develop with growth as part of the modulation phenomenon, but do not show a consistent pattern across the neurofibromatosis population [13, 15, 26, 43]. It is possible that the dystrophic features in this subgroup of skeletally immature patients with idiopathic-like curves have not yet been developed. Another explanation, however, could be that at least certain patients in the non- dystrophic group had occult dystrophic changes initially missed on plain radiography. This concept would call into question the theory of modulation as postulated by Durrani et al. [22].

Dystrophic curves

The dystrophic type of scoliosis is less common, but much more resistant to management [6, 67]. This type of deformity is characterized by short segment, sharply angulated, single thoracic curves that involve four to six vertebral levels and present with three or more dystrophic elements [67]. Dysplastic scoliotic curves may be associated with sagittal plane deformities, namely an angular apical thoracic kyphosis (Fig. 9), or less commonly thoracic lordosis. These concomitant deformities should be recognized early, as they play a significant role in surgical planning.

Dystrophic curves should be treated aggressively, as there is a strong tendency for curve progression even following spinal fusion [3, 6, 16, 43, 75, 77]. The natural history of untreated dysplastic curves, particularly between the ages of 6 and 18 years, is that of relentless deterioration [5]. Passive observation of dystrophic

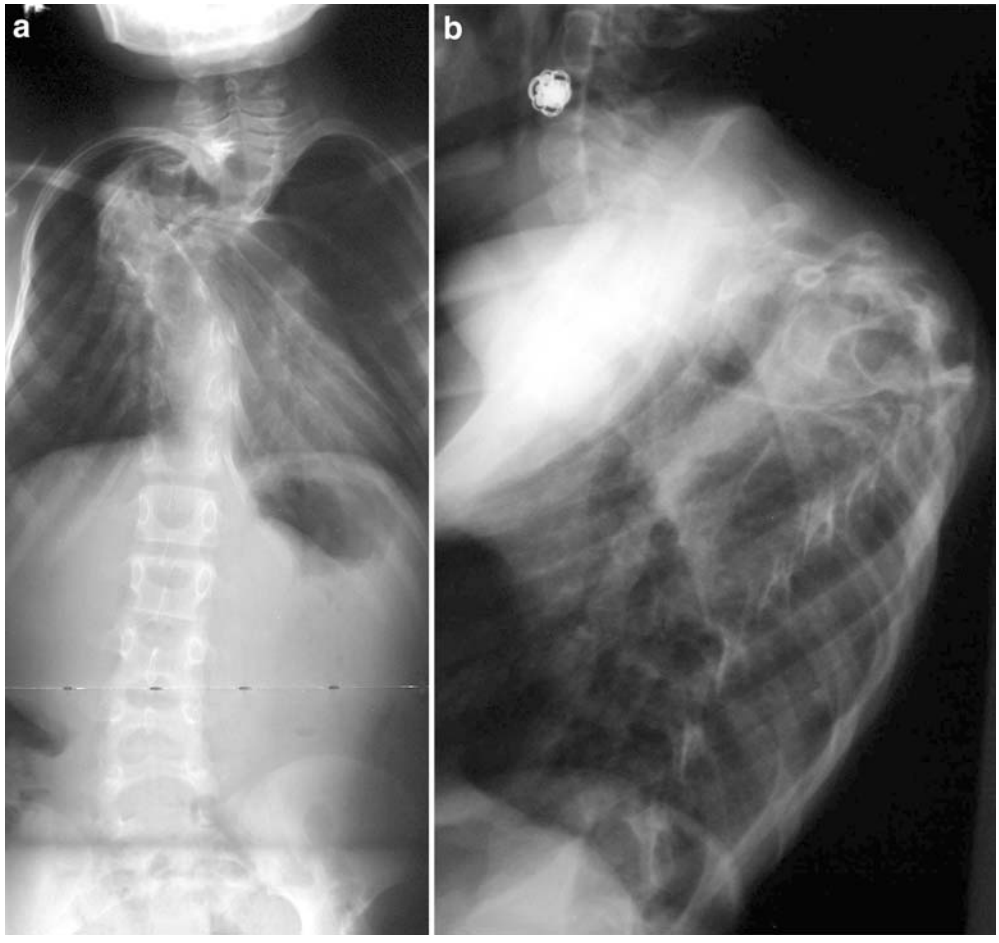

Fig. 9 **a** AP and **b** lateral radiographs of the spine showing the classical acute upper thoracic kyphoscoliosis

curves as they progress throughout childhood is inadequate and unjustifiable [16, 75]. Brace therapy has been ineffective [62, 76] and the need for early aggressive surgical intervention is well documented even in young children [3, 6, 8, 13, 15, 43, 55, 62, 66, 75, 77]. Early spinal fusion does not lead to loss of trunk height since the developing curves are usually short-segment, with limited growth potential. Therefore, loss of height should be anticipated if the deformity is allowed to progress rather than if premature fusion is performed. Apart from the presence of dystrophic changes, other factors that increase substantially the risk of curve deterioration include a young age and a high magnitude of deformity at initial presentation, pathological kyphosis of greater than 50°, location of the apex of the curvature in the mid to caudal thoracic region of the spine, severe apical vertebral rotation of more than 11°, and a severely notched anterior vertebral body [6, 13, 15, 26, 37, 43, 55, 66, 75].

Dystrophic scoliotic curves less than 20° should be closely observed at 6-month intervals to identify any sudden rapid progression and thus prompt surgical management. For patients with scoliotic deformities measuring 20–40° with less than 50° of kyphosis, posterior spinal arthrodesis using segmental fixation with either multiple sublaminar wires or dual rod-multiple hook constructs and the application of autologous iliac crest graft is strongly indicated [16, 43]. Pedicle screws can be occasionally used to provide more stable fixation in the thoracolumbar and lumbar spine in the absence of pedicular dysplasia. Apart from this selective group of patients that can be treated with isolated posterior instrumented fusion, for most types of progressive dystrophic curvatures regardless of the degree of sagittal imbalance, antero-posterior fusion is recommended and provides more reproducible results.

Skeletally immature patients with curves that deteriorate in an uncontrolled fashion require an additional anterior spinal fusion in conjunction to the posterior surgery, with the aim of preventing the development of crankshaft phenomenon. This is produced by continuing unbalanced anterior vertebral growth, which results in increasing rotation of the spine in the presence of a posterior tether caused by the fusion [55]. When the dystrophic scoliotic curve exceeds 40°, combined anterior/posterior spinal fusion including anterior discecto-

my, intervertebral bony fusion with autograft followed by posterior instrumented arthrodesis provides more consistent results in both correcting the deformity and reducing the risk of pseudarthrosis [16]. Both procedures can be performed under the same anesthetic session, unless there is a medical contraindication such as excessive hemorrhage.

Patients with coronal deformity and a dystrophic angular kyphosis also respond poorly to posterior fusion alone. Most authors recommend combined anterior/posterior spinal arthrodesis as the most reliable surgical option in the presence of associated thoracic hyperkyphosis that exceeds 50° [6, 16, 55, 56, 67]. In the latter situation, a structural bone autograft, either rib or fibula, should reinforce the anterior intervertebral fusion followed by posterior instrumentation and arthrodesis using a copious amount of autologous iliac crest bone.

When a neurological deficit is present in a young patient with neurofibromatosis, it is usually caused by increasing kyphosis. Other contributory factors include penetration of the ribs into the spinal canal, structural instability of the vertebral column, progressive dystrophy or destruction of the vertebrae, fibrofatty tissue reaction, intraspinal tumour or dural ectasia [15, 16, 20, 40, 43, 68, 75, 78]. Kyphosis results considerably more than scoliosis in neurologic impairment by creating a pathological spinal flexion, which produces excessive attenuation and deformation of the spinal cord parenchyma and gives rise to neurological symptoms [17, 47, 51]. If the cord is compressed due to the development of a progressive kyphotic deformity, treatment should consist of anterior decompression through a vertebrectomy in the concavity of the deformity followed by combined circumferential bony fusion. Laminectomy has been shown to be ineffective to release pressure in a sharply angulated spinal cord [77]. In the presence of an angular kyphotic deformity, shown to be flexible on extension radiographs, with associated mild neurologic involvement, preoperative halo-dependent traction may be considered, in order to maximise curve correction during the anterior decompression and facilitate placement of the strut graft [15, 43].

Intraspinal tumours can also contribute to spinal cord encroachment and neurologic compromise, particularly in older patients [16, 43]. Treatment consists of laminectomy in combination with tumour resection. Hemilaminectomy is preferable when feasible with the aim of preserving as much bone stock as possible. Removal of the lesion must be accompanied by prophylactic instrumentation and spinal arthrodesis to stabilize the vertebral segments that have been decompressed and prevent the development of post-laminectomy kyphosis [10, 16, 43, 55].

The development of thoracic lordosis is relatively infrequent in patients with NF-1. However, it is often associated with significant respiratory compromise and mitral valve prolapse [34, 74]. Anterior discectomy and fusion followed by posterior fusion using segmental instrumentation, either sublaminar wires or rod-multiple hook constructs should be performed to restore normal sagittal alignment.

There are several difficulties that a spine surgeon involved in the management of patients with neurofibromatosis should be prepared to encounter. Excessive bleeding can hamper particularly anterior approaches to the vertebral bodies and can occur due to the presence of paraspinal neurofibromas and plexiform venous channels in the soft tissues surrounding the spine (Fig. 10). The disproportionate vascularity of neurofibromatous soft tissue is also responsible for the increased frequency of postoperative haemorrhage and haematoma formation [37, 50]. Meticulous haemostasis and wound drainage are necessary to address this problem. Moreover, patients with NF-1 often suffer from hypertension, occasionally associated with renal artery stenosis or pheochromocytoma [59, 71]. Therefore, thorough investigation is required to identify the aetiology of elevated blood pressure.

In patients with neurofibromatosis the fusion area has to be generous. The usual reason for failure of spine surgery is the implementation of technically inadequate anterior procedures, such as performing a short fusion or using a limited amount of bone graft [16, 43, 75, 77]. The entire structural area of the deformity should be fused anteriorly with complete disc resections, interposition of iliac crest and rib morselized autograft and additional strong strut grafting using fibular or rib autologous graft in the presence of kyphosis. All grafts

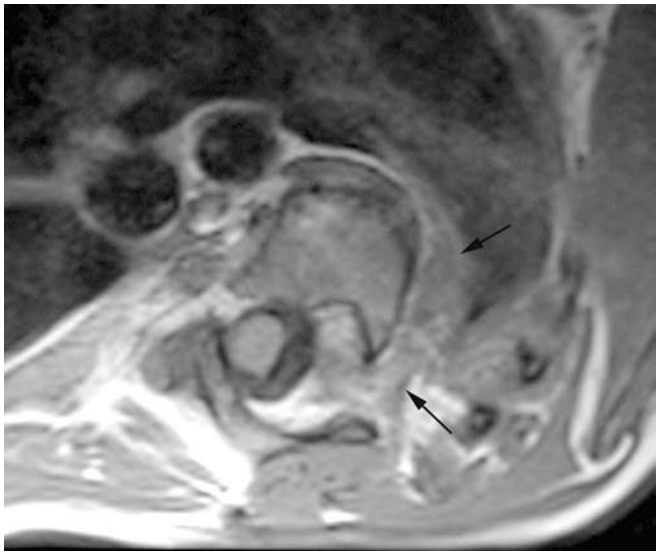

Fig. 10 Axial T1W MRI through the upper thoracic spine demonstrating plexiform neurofibromatous tissue (*arrows*) around the vertebral body, entering the left intervertebral foramen and associated with posterior vertebral scalloping

should have direct contact with the spine and with each other, while any intervening soft tissue should be meticulously excised. Bone grafts surrounded by abnormal neurofibromatous soft tissue demonstrate an increased tendency to resorb in the midportion [75]. Following the anterior stage of the procedure, posterior segmental instrumentation and iliac crest autogenous graft should be used to secure fixation and enhance a solid arthrodesis. The fusion should be extended to include the neutral vertebra above and below the curve [16]. During the posterior exposure of the spine, the surgeon should be particularly careful to avoid invading the spinal canal and injuring the cord in areas where the posterior bony elements are weakened due to the presence of intraspinal tumours or dural ectasia.

Segmental instrumentation can occasionally be challenging, since severely deformed vertebrae constitute poor anchorage points for fixation. If internal fixation is not technically feasible because of poor bone stock, in situ fusion with bone autograft and application of a postoperative cast or brace is necessary [43, 55]. If excessive angular kyphosis is present or if the vertebrae are weak due to the bony dysplasia, postoperative orthotic immobilization is recommended even if instrumentation has been successfully applied, in order to remove excessive strains at the proximal hook sites and prevent dislodgement of the implants [36, 43, 55, 62, 65]. Due to the high incidence of pseudarthrosis, evaluation of the fusion mass should be routinely performed at 6 months. If there is evidence of weakness of the fusion mass, posterior re-exploration and augmentation of the fusion should be undertaken [16, 55, 75, 77].

Scoliosis in the lumbar spine is relatively uncommon in NF-1. However, the principles of treatment do not differ. In the operative management of a lumbar curvature, it is important to rule out the presence of spondylolisthesis, which shows an incidence similar to that in patients without neurofibromatosis. In NF-1, spondylolisthesis can be the result of an increased diameter of the spinal canal, causing pathologic elongation and thinning of the pedicles and giving rise to an abnormal forward displacement of the anterior bony elements of the spine [16]. Distortion of the pedicles precludes reduction maneuvers using pedicle screws, while posterior fusion even after the application of autologous bone graft may be delayed, necessitating further reinforcement of the fusion mass at 6 months, if imaging studies show evidence of poor healing.

Deformities of the cervical spine in NF-1 have received little attention in the literature. They can cause neck pain and occasionally neurological complications, including nerve root compromise and complete or incomplete spinal cord deficits [11, 17, 55, 80]. However, in a large percentage of patients, cervical deformities are asymptomatic, therefore, anteroposterior and lateral radiographs should always be obtained, especially for patients scheduled to undergo instrumented fusion of the thoracic or lumbar spine or halo-dependent traction. If dystrophic features are identified, oblique radiographs can illustrate the presence of dumpbell lesions. Instrumentation and manipulation of the spine in the presence of undetected cervical intraspinal lesions can be extremely dangerous.

Kyphosis is the most common deformity occurring in the cervical spine in neurofibromatosis (Fig. 11). It is often the result of a previous excision of an intraspinal tumorous mass, which necessitated resection of the laminae and posterior elements creating secondary destabilization of the vertebral column and post-laminectomy kyphosis [13, 16, 43]. Anterior fusion with a combination of iliac crest and fibular autograft supplemented by halo vest or cast can achieve satisfactory results [55]. Alternatively, combined anterior-posterior spinal fusion with segmental fixation can provide adequate stability and avoid postoperative external immobilization. Atlantoaxial instability may also be present and evaluation for this condition is necessary using lat-

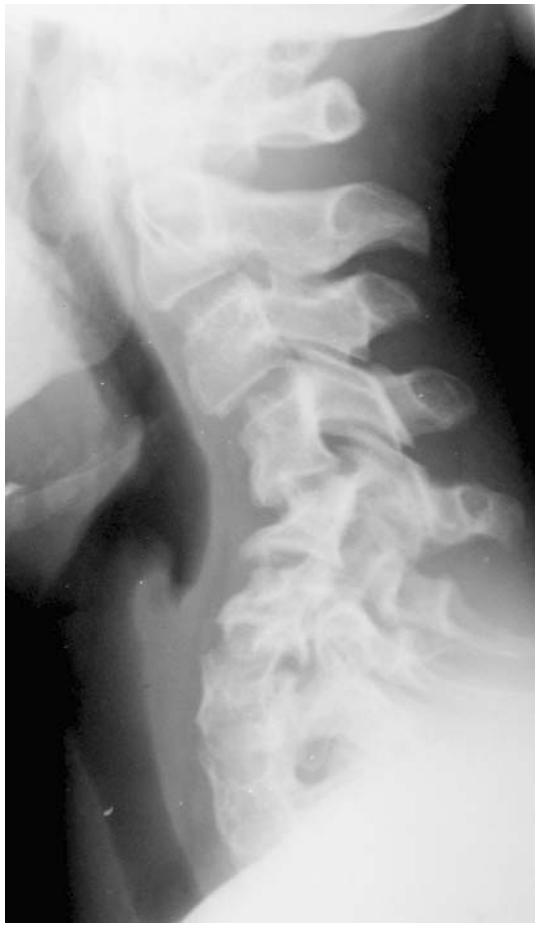

Fig. 11 Lateral radiograph demonstrating the classical cervical kyphosis of NF-1

eral cervical radiographs in flexion and extension, particularly if application of halo traction is anticipated.

In conclusion, spinal deformity in patients with neurofibromatosis type-1 poses a significant diagnostic and therapeutic dilemma. A thorough search for evidence of dysplastic changes on plain radiography and MRI is mandatory and will clarify prognosis and management options. MRI of the entire spine will illustrate the intraspinal contents and unveil the presence of intracanal anomalies that might interfere with any attempt for surgical correction of the deformity. Non-dystrophic curves are treated using the same principles applied in idiopathic scoliosis. On the contrary, dystrophic scoliotic curvatures or multiplanar spinal deformities with significant sagittal decompensation necessitate early aggressive surgical management, which should include an anteroposterior spinal arthrodesis with the use of segmental instrumentation and plentiful bone autograft. The primary goal of surgery in those cases is to stabilize the vertebral column and halt further progression of the deformity rather than perform heroic attempts for correction that could potentially result to permanent neurological injuries.

References

1. Aegeter E (1950) The possible relationship of neurofibromatosis, congenital pseudoarthrosis and fibrous dysplasia. J Bone Joint Surg [Am] 32A:618
2. Akbarnia BA, Gabriel KR, Beckman E, Chalk D (1992) Prevalence of scoliosis in neurofibromatosis. Spine 17:S244–S248
3. Betz RR, Iorio R, Lombardi AV, Clancy M, Steel HH (1989) Scoliosis surgery in neurofibromatosis. Clin Orthop 245:53–56
4. Biesecker LG (2001) The multifaceted challenges of Proteus syndrome. JAMA 285:2240–2243
5. Bunyatov R (1983) Clinical roentgenographic characteristics of scoliosis in neurofibromatosis. Pediatrics (USSR) 5:49–51
6. Calvert PT, Edgar MA, Webb PJ (1989) Scoliosis in neurofibromatosis. Natural history without operation. J Bone Joint Surg [Br] 71B:246–251
7. Cawthon RM, Weiss R, Xu GF, Viskochil D, Culver M, Stevens J et al. (1990) A major segment of the neurofibromatosis type 1 gene: cDNA sequence, genomic structure, and point mutations. Cell 62:193–201
8. Chaglassian JH, Riseborough EJ, Hall JE (1976) Neurofibromatous scoliosis. J Bone Joint Surg [Am] 58A:695–702
9. Cnossen MH, de Goede-Bolder A, van den Broek KM, Waasdorp CM, Oranje AP, Stroink H et al (1998) A prospective 10 year follow up study of patients with neurofibromatosis type 1. Arch Dis Child 78:408–412
10. Cobb J (1950) Discussion of McCarroll H: clinical manifestations of congenital neurofibromatosis. J Bone Joint Surg [Am] 32A:617
11. Craig JB, Govender S (1992) Neurofibromatosis of the cervical spine. J Bone Joint Surg [Br] 74B:575–578
12. Crawford AH, Bagamery N (1986) Osseous manifestations of neurofibromatosis in childhood. J Pediatr Orthop 6:72–88
13. Crawford AH (1989) Pitfalls of spinal deformities associated with neurofibromatosis in children. Clin Orthop 245:29–42
14. Crawford AH (1990) NF-1. In: Morrissy RT (ed) Lovell and winters pediatric orthopaedics, 3rd edn. JB Lippincott, Philadelphia, pp 175–201
15. Crawford AH (1994) Neurofibromatosis. In: Weinstein SL (ed) The pediatric spine. Raven Press, New York, pp 619–649
16. Crawford AH (2001) Neurofibromatosis. In: Weinstein SL (ed) The pediatric spine: principles and practice, 2nd edn. Lippincott Williams & Wilkins, Philadelphia, pp 471–490
17. Curtis BH, Fisher RL, Butterfield WL, Saunders FP (1969) Neurofibromatosis with paraplegia: report of 8 cases. J Bone Joint Surg [Am] 51A:843–861
18. Daston MM, Scrable H, Nordlund M, Sturbaum AK, Nissen LM, Ratner N (1992) The protein product of the neurofibromatosis type-1 gene is expressed as highest abundance in neurons, Schwann cells and oligodendrocytes. Neuron 8:415–428
19. DeClue JE, Cohen BD, Lowy DR (1991) Identification and characterization of the neurofibromatosis type 1 protein product. Proc Natl Acad Sci USA 88:9914–9918
20. Deguchi M, Kawakami N, Saito H, Arao K, Mimatsu K, Iwata H (1995) Paraparesis after rib penetration of the spinal canal in neurofibromatous scoliosis. J Spinal Disord 8:363–367
21. DiSimone RE, Berman AT, Schwentker EP (1988) The orthopedic manifestation of neurofibromatosis. Clin Orthop 230:277–283
22. Durrani A, Crawford AH, Choudhry SN, Saifuddin A, Morley TR (2000) Modulation of spinal deformities in patients with neurofibromatosis type 1. Spine 25:69–75
23. Egelhoff JC, Bates DJ, Ross JS, Rothner AD, Cohen BH (1992) Spinal MR findings in neurofibromatosis types 1 and 2. Am J Neuroradiol 13:1071–1077
24. Es SV, North KN, McHugh K, Silva MD (1996) MRI findings in children with neurofibromatosis type-1: a prospective study. Pediatr Radiol 26:478–487
25. Flood BM, Butt WP, Dickson RA (1986) Rib penetration of the intervertebral foraminae in neurofibromatosis. Spine 11:172–174
26. Funasaki H, Winter RB, Lonstein JB, Denis F (1994) Pathophysiology of spinal deformities in neurofibromatosis. J Bone Joint Surg [Am] 76A:692–700
27. Goldberg M (1987) The dysmorphic child: an orthopaedic perspective. Raven Press, New York
28. Gould EP (1918) The bone changes occurring in Von Recklinghausen's disease. Q J Med 11:221–228

29. Guha A, Lau N, Huvar I, Gutmann P, Provias J, Pawson T et al (1996) Ras-GTP levels are elevated in human NF1 peripheral nerve tumors. Oncogene 12:507–513
30. Gutmann DH, Wood DL, Collins FS (1991) Identification of the neurofibromatosis type 1 gene product. Proc Natl Acad Sci USA 88:9658–9662
31. Gutmann DH, Geist RT, Wright DE, Snider WD (1995) Expression of the neurofibromatosis 1 (NF1) isoforms in developing and adult rat tissues. Cell Growth Differ 6:315–323
32. Gutmann DH, Aylsworth A, Carey JC, Korf B, Marks J, Pyeritz RE et al (1997) The diagnostic evaluation and multidisciplinary management of neurofibromatosis 1 and neurofibromatosis 2. JAMA 278:51–57
33. Hecht F (1989) Recognition of neurofibromatosis before von Recklinghausen. Neurofibromatosis 2:180–184
34. Hirschfeld SS, Rudner C, Nash CL Jr, Nussbaum E, Brower EM (1982) Incidence of mitral valve prolapse in adolescent scoliosis and thoracic hypokyphosis. Pediatrics 70:451–454
35. Holt JF (1978) Neurofibromatosis in children. Edward BD Neuhauser lecture. Am J Roentgenol 130:615–639
36. Holt RT, Johnson JR (1989) Cotrel-Dubousset instrumentation in neurofibromatosis spine curves. Clin Orthop 245:19–23
37. Hsu LCS, Lee PC, Leong JCY (1984) Dystrophic spinal deformities in neurofibromatosis. Treatment by anterior and posterior fusion. J Bone Joint Surg [Br] 66B:495–499
38. Hunt JC, Pugh DG (1961) Skeletal lesions in neurofibromatosis. Radiology 76:1–19
39. Huson SM, Harper PS, Compston DA (1988) Von Recklinghausen neurofibromatosis. A clinical and population study in south-east Wales. Brain 111:1355–1381
40. Jacobsen FS, Crawford AH (1995) Complications in neurofibromatosis. In: Epps CH, Bowen JR (eds) Complications in pediatric orthopaedic surgery. JB Lippincott, Philadelpia, pp 649–683
41. Johnson NS, Saal HM, Lovell AM, Schorry EK (1999) Social and emotional problems in neurofibromatosis type 1: evidence and proposed interventions. J Pediatr 134:767–772
42. Khong P-L, Goh WHS, Wong VCN, Fung CW, Ooi GC (2003) MR imaging of spinal tumours in children with neurofibromatosis 1. Am J Roentgenol 180:413–417
43. Kim HW, Weinstein SL (1997) Spine update: the management of scoliosis in neurofibromatosis. Spine 22:2770–2776
44. Korf BR (2001) Diagnosis and management of neurofibromatosis type 1. Curr Neurol Neurosci Rep 1:162–167
45. Laws JW, Pallis C (1963) Spinal deformities in neurofibromatosis. J Bone Joint Surg [Br] 45B:674–682
46. Legius E, Marchuk DA, Collins FS, Glover TW (1993) Somatic deletion of the neurofibromatosis type 1 gene in a neurofibrosarcoma supports a tumour suppressor gene hypothesis. Nat Genet 3:122–126
47. Lonstein JE, Winter RB, Moe JH, Bradford DS, Chou SN, Pinto WC (1980) Neurologic deficits secondary to spinal deformity. A review of the literature and report of 43 cases. Spine 5:331–355
48. Lubs ML, Bauer MS, Formas ME, Djokic B (1991) Lisch nodules in neurofibromatosis type 1. N Engl J Med 324:1264–1266
49. Major MR, Huizenga BA (1988) Spinal cord compression by displaced ribs in neurofibromatosis. A report of three cases. J Bone Joint Surg [Am] 70A:1101–1102
50. McCarroll HR (1950) Clinical manifestations of congenital neurofibromatosis. J Bone Joint Surg [Am] 32A:601–617
51. Miller A (1936) NF-1 with reference to skeletal changes, compression myolitis and malignant degeneration. Arch Surg 32:109
52. Mulvihill JJ (1988) Neurofibromatosis: history, nomenclature and natural history. Neurofibromatosis 1:124–131
53. Neurofibromatosis (1987) Conference statement. National Institute of Health Consensus Develpment Conference. Arch Neurol 45:575–578
54. North K (1993) Neurofibromatosis type 1: review of the first 200 patients in an Australian clinic. J Child Neurol 8:395–402
55. Ogilvie JW (1995) Neurofibromatosis. In: Bradford DS (ed) Moe's textbook of scoliosis and other spinal deformities, 3rd edn. Saunders, Philadelphia, pp 337–347
56. Parisini P, DiSilvestre M, Greggi T, Paderni S, Cervellati S, Savini R (1999) Surgical correction of dystrophic spinal curves in neurofibromatosis: a review of 56 patients. Spine 24:2247–2253
57. Pediatric scoliosis. In: Garfin SR, Vaccaro AR (eds) Orthopaedic knowledge update spine. American Academy of Orthopaedic Surgeons, Rosemont, pp 183–194
58. Rezaian SM (1976) The incidence of scoliosis due to neurofibromatosis. Acta Orthop Scand 147:534–539
59. Riccardi VM (1992) Type 1 neurofibromatosis and the pediatric patient. Curr Probl Pediatr 22:66–107
60. Rockower S, McKay D, Nason S (1982) Dislocation of the spine in NF-1. A report of two cases. J Bone Joint Surg [Am] 64A:1240–1242
61. Roos KL, Dunn DW (1992) Neurofibrmatosis. CA Cancer J Clin 42:241–254
62. Savini R, Parisini P, Cervellati S, Gualdrini G (1983) Surgical treatment of vertebral deformities in neurofibromatosis. Ital J Orthop Traumatol 9:13–24
63. Schorry EK, Stowens DW, Crawford AH, Stowens PA, Schwartz WR, Dignan PS (1989) Summary of patient data from a multidisciplinary neurofibromatosis clinic. Neurofibromatosis 2:129–134
64. Scott JC (1965) Scoliosis and neurofibromatosis. J Bone Joint Surg [Br] 47B:240–246
65. Shufflebarger HL (1989) Cotrel-Dubousset instrumentation in neurofibromatosis spinal problems. Clin Orthop 245:24–28
66. Sirois JL, Drennan JC (1990) Dystrophic spinal deformity in neurofibromatosis. J Pediatr Orthop 10:522–526
67. Sponseller P (2003) The spine in skeletal syndromes and dysplasias. In: DeWald RL (ed) Spinal deformities. The comprehensive text. Thieme, New York, pp 701–717
68. Stone JW, Bridwell KH, Shackelford GD, Abramson CL (1987) Dural ectasia associated with spontaneous dislocation of the upper part of the thoracic spine in neurofibromatosis. J Bone Joint Surg [Am] 69A:1079–1083
69. Thakkar SD, Feigen U, Mautner V-F (1999) Spinal tumours in neurofibromatosis type 1: an MRI study of frequency, multiplicity and variety. Neuroradiology 41:625–629
70. Virchow R (1847) Ueber die reform der pathologischen und therpeutischen anschaungen durch die mikrokopischen untersuchungen. Arch Pathol Anat Physiol Klin Med 1:207–255
71. Vitale MG, Guha A, Skaggs DL (2002) Orthopaedic manifestations of neurofibromatosis in children: an update. Clin Orthop 401:107–118

72. Von Recklinghausen FD (1882) Ueber die multiplen fibrome der haut und ihre besiehung zu den multiplen neuromen. Hirchwald, Berlin
73. Weiss RS (1921) (A) Von Recklinghausen's disease in the Negro; (B) curvature of the spine in von Recklinghausen's disease. Arch Dermatol Syphilol 3:144–151
74. Winter RB, Lovell WW, Moe JH (1975) Excessive thoracic lordosis and loss of pulmonary function in patients with idiopathic scoliosis. J Bone Joint Surg [Am] 57A:972–977
75. Winter RB, Moe JH, Bradford DS, Lonstein JE, Pedras CV, Weber AH (1979) Spine deformity in neurofibromatosis. A review of one hundred and two patients. J Bone Joint Surg [Am] 61A:677–694
76. Winter RB (1984) Thoracic lordoscoliosis in neurofibromatosis-treatment by a Harrington rod with sublaminar wiring. J Bone Joint Surg [Am] 66A:1102–1106
77. Winter RB, Lonstein JE, Anderson M (1988) Neurofibromatosis hyperkyphosis. A review of 33 patients with kyphosis of 80 degrees or greater. J Spinal Disord 1:39–49
78. Winter RB (1991) Spontaneous dislocation of a vertebra in a patient who had neurofibromatosis. J Bone Joint Surg [Am] 73A:1402–1404
79. Wolkestein P, Durand-Zaleski I, Moreno JC, Zeller J, Hemery F, Revuz J (2000) Cost evaluation of the medical management of neurofibromatosis 1: a prospective study on 201 patients. Br J Dermatol 142:1166–1170
80. Yong-Hing K, Kalamchi A, MacEwen GD (1979) Cervical spine abnormalities in neurofibrmatosis. J Bone Joint Surg [Am] 61A:695–699