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REVIEW

Spinal Deformities in Neurofibromatosis Type 1

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ABSTRACT

Neurofibromatosis type 1 (NF-1) is the most common human single-gene disorder. Skeletal complications usually present early in life and can be attributed to abnormalities of bone growth, remodeling, and repair in NF-1 or can be secondary to nearby soft-tissue abnormalities associated with NF-1. Scoliosis is the most common osseous manifestation of NF-1. It is important to recognize the dystrophic curve and to distinguish it from the non-dystrophic curve. The management of spinal disorders in young children in NF-1 continues to be problematic. The use of growing rods allows more longitudinal growth than fusion and more life freedom than bracing. The problems we have encountered are mechanical and could be expected when proximal and distal fixation is performed over an otherwise completely mobile spinal column. The multiple surgeries increase the potential for complications including infections. We continue to pursue solutions to our problems. The intent of this article is to present the spinal deformities that are most commonly associated with NF-1 and to identify the current management of spinal disorders based on the most recent literature.

KEY WORDS: neurofibromatosis; scoliosis; kyphosis; dystrophic deformity; NF-1

1. Introduction

Neurofibromatosis is a multisystemic, autosomal dominant genetic disorder defined as a spectrum of multifaceted diseases involving neuroectoderm, mesoderm, and endoderm. The clinical features of neurofibromatosis type 1 (NF-1), the most common form of the disease, were reported in several family members by German pathologist Virchow in 1847 [1], but it was his student von Recklinghausen [2] who 35 years later described the histological features of the syndrome that often bears his eponym.

NF-1 is characterized by extreme variability of expression. The proposed mechanisms for this variability include germline-modifying genes, environmental agents, second hit somatic mutation events in NF - 1 or other genes, epigenetic modification, and post-zygotic mutations [3]. The NF-1 phenotypes vary to a greater degree with increasing dis-

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tance from a proband, thus documenting that the specific familial NF – 1 mutation is not the primary cause of variability [4]. Common clinical manifestations include café-au-lait macules, neurofibromas, and schwannomas. Skeletal complications usually present early in life and can be attributed to abnormalities of bone growth, remodeling, and repair in NF-1 or can be secondary to nearby soft-tissue abnormalities complicating NF-1.

Skeletal complications can be categorized as generalized or focal manifestations [5]. Generalized skeletal abnormalities include osteoporosis/osteopenia, osteomalacia, shortness of stature, and macrocephaly. These features are common in individuals with NF-1, with decreased bone mineral density in both sexes reported in up to 50% of the patients, but usually mild [6–9]. Focal abnormalities of the skeleton are less common than generalized abnormalities, but may cause significant morbidity. Focal manifestations include spinal deformities, dysplasia of the tibia and other long bones, sphenoid wing dysplasia, chest wall deformities (pectus excavatum), dental abnormalities, periapical cemental dysplasia, and cystic osseous lesions. The effect of generalized abnormalities in the occurrence or progression of focal skeletal manifestations remains elusive.

The incidence of spinal deformities in association with NF-1 varies from 2 to 36% with scoliosis being the most common musculoskeletal manifestation of NF-1 [10, 11]. The purpose of this article is to present the spinal deformities that are most commonly associated with NF-1 and to identify the current management of spinal disorders based on the most recent literature.

2. Classification

Five distinct clinical forms of neurofibromatosis are currently accepted by most investigators: NF-1, NF-2, segmental NF, Legius syndrome, and schwannomatosis.

2.1 Neurofibromatosis type 1 (NF-1)

NF-1 or peripheral neurofibromatosis is a common autosomal dominant single-gene disorder with an estimated prevalence of 1:3,000 [12]. It is the most common form of neurofibromatosis and the one most likely to be encountered by the orthopedist. It is predicted to affect over two million people worldwide in all racial and ethnic groups. The NF - 1 gene is large in size, in the range of 350,000 base pairs with 59 exons, and its locus was discovered on chromosome 17q11.2 [12–14]. NF - 1 is a tumor-suppressor gene that encodes neurofibromin, a large cytoplasmic protein with 2,818 amino acids. Exons 21 through 27a encode a 360 amino-acid domain with homology with guanosine triphosphatase (GTP)-activating proteins (GAPs). The relevant domain, known as GAP-related domain (GRD), downregulates p21-Ras oncogene which promotes cell growth, proliferation, and differentiation. GAPs, including neurofibromin, inactivate Ras oncogene through their GTPase activity. Decreased synthesis or complete absence of neurofibromin expression, as in NF-1, results in unopposed activation of p21-Ras oncogene through GTP binding. This, in turns, leads to aberrant growth-promoting signals and the development of NF-1 associated neoplasms, including benign neurofibromas, malignant peripheral nerve sheath tumors, pheochromocytomas, and optic nerve gliomas, as well as to other clinical manifestations [15 ,16].

The NF - 1 gene displays almost complete penetrance. Individuals with NF-1 are constitutionally heterozygous for an NF - 1 gene loss-of-function mutation. Approximately 50% of affected individuals inherited the gene from an affected parent and 50% arise sporadically due to spontaneous mutations [16–19]. De novo mutations in the NF - 1 gene are associated with advanced paternal age [19].

The diagnosis of NF-1 is established when at least two of the most commonly presenting features of the disease as defined by the 1987 Consensus Development Conference of the National Institutes of Health are present (**Table 1**) [20]. In 97% of patients, a diagnosis is made by age 8 [21]. Molecular diagnosis with direct sequencing of the causative mutation is possible in 95% of patients with NF-1 and is indicated in uncertain cases and for prenatal diagnosis [22]. Differential diagnosis includes tuberous sclerosis and other conditions of pigmentation, such as McCune–Albright syndrome and mastocytosis. NF-1 is closely related to a number of other genetic syndromes

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TABLE 1. *Diagnostic criteria of NF-1*

1	Six or more café-au-lait macules more than 5 mm in greatest diameter in prepubertal individuals and more than 15 mm in postpubertal individuals
2	Two or more neurofibromas of any type or more than one plexiform neurofibroma
3	Freckling in the axillary or inguinal regions
4	Two or more Lisch nodules
5	Optic glioma
6	A distinctive osseous lesion, such as sphenoid dysplasia or thinning of long bone cortex, with or without pseudarthrosis
7	A first degree relative (parent, sibling, or offspring) with NF-1 by the above criteria

involving mutations of the Ras pathway, such as Noonan syndrome and LEOPARD syndrome.

2.2 Neurofibromatosis type 2 (NF-2)

NF-2 or central neurofibromatosis has an estimated incidence of 1 in 33,000 individuals and is associated with bilateral vestibular schwannomas and multiple spinal shwannomas [23, 24]. The NF-2 locus is located on the long arm of chromosome 22. Fifty percent of cases involve a new mutation. NF-2 is not associated with primary skeletal disorders; however, multiple paraspinal and intraspinal tumors (schwannomas and ependymomas) are common in this disorder. NF-1 and NF-2 are genetically distinct disorders with different gene loci, despite similarities in names.

2.3 Segmental Neurofibromatosis

Segmental neurofibromatosis is characterized by features of NF-1 involving a single body segment. Typically, only a single segment of the body (such as left upper extremity) is affected with café-au-lait spots and freckling, and lesions usually do not cross the body midline. Other segmental forms may involve deep neurofibromas in a single body segment.

2.4 Legius Syndrome

Early neurofibromatosis literature recognized that a mild form of NF-1 existed, consisting primarily of familial café-au-lait spots. In recent years, multiple families with such mild involvement have now been found to have mutations in the SPRED1 gene. Initially discovered by Legius et al. [25] this condition, now called Legius syndrome, can present with multiple café-au-lait spots, freckling, macrocephaly, and mild learning disabilities, but does not present with any of the benign or malignant tumors associated with NF-1. This condition is quite a bit less common than NF-1, with an estimated prevalence of about 1/50,000. Since patients with Legius syndrome can actually meet the clinical diagnostic criteria for NF-1, it can be appropriate to perform molecular testing if there is any question about diagnosis.

2.5 Schwannomatosis

Schwannomatosis is a distinct form of neurofibromatosis which typically involves multiple schwannomas throughout the body, but without the vestibular schwannomas typical of NF-2. Initially thought to represent a mosaic form of NF-2, it has now been determined that familial schwannomatosis is due to mutations in the INI1 gene, linked to NF - 2 on chromosome 22. It is a disease of adulthood that consists of multiple deep painful peripheral nerve sheath tumors that may occur in a generalized form or in a segmental distribution. Differential diagnosis from NF-2 can be difficult, and genetic testing of NF-2 and INI1 is now available to help in making this distinction.

3. Spinal Abnormalities in NF-1

3.1 Epidemiology

Spinal abnormalities are the most common orthope-

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TABLE 2. *Diagnostic criteria of dystrophic deformities*

1	Rib penciling
2	Posterior vertebral scalloping
3	Vertebral wedging
4	Spindling of transverse processes
5	Anterior vertebral scalloping
6	Widened interpedicular distance
7	Enlarged intervertebral foramina
8	Lateral vertebral foramina
9	Vertebral rotation
10	Paraspinal tumors
11	Dural ectasia

dic manifestation of NF-1. It is quoted as from 2 to 36% in the literature [10, 11]. In a report in 1988, Winter et al. [26] found only 102 patients having NF-1 by clinical criteria in a pool of approximately 10,000 patients with scoliosis. Functional scoliosis resulting from limb hypertrophy or long-bone dysplasia leading to limb length inequality must be ruled out in patients with NF-1. Rarely, unrecognized extrapleural thoracic tumors can present as focal scoliosis. These lesions are usually plexiform neurofibroma and are not visible on plain radiographs [27]. The spinal deformities tend to develop early in the life therefore, all preadolescent children with NF-1 should be evaluated by scoliosis screening or the Adam forward-bend test to rule out the presence of a spinal deformity.

It is important to emphasize that there is no standard pattern of spinal deformity in NF-1. All manner of spinal deformities in multiple planes and in any part of the spine may occur with NF-1 [28, 29]. The characteristic deformity tends to be a short-segmented, sharply angulated curvature that usually involves four to six vertebrae in the upper third of the thoracic spine [30]. We have traditionally classified the deformities into dystrophic or non-dystrophic types based on the coronal plane x-rays.

There are nine radiographic criteria most often used to classify the deformity as dystrophic. These include rib penciling (the rib being smaller in diameter than the second rib), vertebral rotation, posterior vertebral scalloping, vertebral wedging, spindling of the transverse process, anterior vertebral scalloping, widened interpedicular distance, enlarged interverteral foramina, and lateral vertebral scalloping. Recently, two more magnetic resonance imaging (MRI) findings have been added to the criteria used to classify the deformity as dystrophic: The presence of dural ectasia and the presence of paraspinal tumors (**Table 2**) [31]. More than three of these dystrophic features are considered diagnostic of dystrophic scoliosis. Nondystrophic curves are considered similar to idiopathic scoliosis.

3.2 Etiology

The cause of spinal deformity remains unknown. Several theories including metabolic bone deficiency, osteomalacia, endocrine disturbance, and mesodermal dysplasia have been proposed and are at best inconclusive [32-36]. The dystrophic changes may be attributed to intrinsic factors or may be associated with anomalies of the spinal canal secondary to abnormalities of the spinal cord dura mater.

Pressure erosive effects of dural ectasia and paravertebral tumors have been frequently found to be adjacent to and approximated to the deformities, initiating instability and subsequent deformity. Dural ectasia, a disorder unique to certain conditions, is an expansion or dilatation of the dural sac. The changes in the spinal canal induced by dural ectasia may increase the difficulty in obtaining adequate purchase for fixation of anchors during spinal deformity correction.

Scalloping was initially thought to represent the result of erosive pressure or direct infiltration of the vertebra by adjacent neurofibroma [37–41]. A neurofibroma-derived locally active biochemical substance or hormone that triggers dystrophic features in the adjacent vertebra has also been proposed [37]. The presence of an altered response of the vertebral bone in NF-1 to a paraspinal tumor has been hypothesized. An interactive pathophysiological mechanism between a genetically compromised bone and a neuroectodermal derivative, such as a contiguous

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neurofibroma or an abnormal meningeal sheath, is suggested by some authors [37, 39].

The etiological theory of vertebral scalloping being a primary developmental defect was supported by the presence of scalloping without adjacent lesions [42]. This was also supported by an MRI study in patients with NF-1, in which posterior vertebral scalloping was highly associated with dural ectasia, lateral scalloping was related to dural ectasia or neurofibromas in 50% of cases, and anterior scalloping was unrelated to dural ectasia or tumors [43]. The authors could not identify any association with dural ectasia or paraspinal tumors in more than one-third of their patients with MRI evidence of vertebral scalloping. Nevertheless, dural ectasia without associated vertebral scalloping was recorded in 10% of the cases.

A recent study in ten monozygotic twins with NF-1 demonstrated mixed concordance and discordance for presence of scoliosis [3]. The affected twin pairs were discordant for presence of dystrophic features, degree of curvature, and need for surgery. This finding suggests that both heritable and nonheritable factors contribute to the pathogenesis of spinal deformities in NF-1 patients. Dystrophic curves most likely require a nonhereditary event, such as an adjacent tumor or dural ectasia, or a second hit event in local bone cells leading to the underlying dysplasia. If occurrence and progression of dystrophic spinal deformity is affected by adjacent neurofi bromas, then therapies targeting to reduction or stabilization of paraspinal tumors could provide a promising approach to spine deformity prevention in patients with NF-1. Apart from its tumor suppressor activities through the Ras signaling, the role of neurofibromin pathways, such as bone morphogenetic protein (BMP) signal transduction [44]. This theory suggests that intrinsic bone pathology due to loss of a functional NF - 1 allele with subsequent Ras deregulation may be responsible for osseous manifestations in NF-1 through altered osteoblastic/osteoprogenitor differentiation, overgrowth of cellular tissue due to preferred fibroblast differentiation of mesenchymal cells, and impaired bony callus formation. Double inactivation of NF-1 by somatic mutation of the NF -1 gene in a population of cells which depends on neurofibromin-regulated Ras signaling to maintain normal bone was suggested to contribute to the occurrence or progression of tibia pseudarthrosis [45]. Although such second hit events have been demonstrated in pathological tissue from NF-1 tibias, it is unknown whether spinal deformities of NF-1 require a second hit event.

3.3 Imaging

Most often plain standing posterior-anterior and lateral radiographs are sufficient for screening the curvature. An angle of greater than 10° assigns the deformity as structural. When treatment is to be initiated, multiple planar films in supine bending modes and traction are necessary to determine flexibility. If there are adjacent structures requiring further clarification, higher levels of imaging are required, such as computed tomography (CT) for bony deformity or high- resolution contrast CT or MRI for soft tissue delineation.

3.4 Dural Ectasia

Dural ectasia is a circumferential dilatation of the dural sac which is filled with proteinaceous fluid. The slow expansion of the dura results in erosion of the surrounding osseous structures resulting in widening of the spinal canal, thinning of the laminae, and ultimately destabilization of the spine. Dural expansion through the neural foramina can cause meningoceles giving the radiographic dumbbell appearance. However, enlargement of a single neural foramen on an oblique radiograph is usually caused by neurofibroma exiting from the spinal canal rather than from the dural ectasia. Similar lesions are seen in other connective tissue disorders, e.g., Marfan's syndrome and Ehler–Danlos syndrome, although cause of these lesions in NF-1 is not known.

During this process, the neural elements are not affected. As a result of slow nature of this process and enormous widening of the spinal canal the neural elements have adequate room for accommodation, and there may be severe angular deformity and distortion without neurological deficit. The patients remain neurologically intact until later in the course of

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the disease process when destabilization of the vertebral column jeopardizes the neural elements. Dislocation of the vertebral column due to dural ectasia has been reported in the literature [46]. The destabilization at the costovertebral junction can result in penetration of the rib head into the spinal canal with neurological compromise [47, 48]. The presence of rib head or the neurofibroma in the spinal canal can result in intraoperative neurological deficit if instrumentation is used for correction of the curve without adequate decompression.

Dural ectasia can be readily seen on high volume CT myelography or contrast-enhanced MRI and is recommended before surgical intervention is undertaken for dystrophic curves. Higher imaging studies help to demonstrate extremely thin laminae. Surgical spinal stabilization and fusion does not alter the course of dural ectasia. Dural ectasia can result in failure of the primary fusion or the expanding dura ultimately can destroy a solid fusion leaving behind the instrumentation.

4. Cervical Spine Abnormalities

The cervical spine abnormalities in NF-1 have not received enough attention in the literature [49, 50]. Usually, the cervical lesion is asymptomatic. When the lesion is symptomatic, pain is the most common presenting symptom [51]. Cervical abnormalities are likely to be missed in presence of scoliosis or kyphoscoliosis of lower regions of the spine where the examiner's attention is focused on the more obvious deformity. In a study of 56 patients with NF-1, Yong-Hing et al. [52] reported that 17 patients (30%) had cervical spine abnormalities. Out of these, seven patients were asymptomatic, whereas the rest had limited motion or pain in the neck. Four patients had neurological deficits that were attributed to cervical instability. Four of the 17 patients required fusion of the cervical spine. Curtis et al. [53] described eight patients who had paraplegia and NF-1. Four of these patients had cervical spine instability or intraspinal pathology in the cervical spine.

The upper cervical spine should also be examined carefully. Isu et al. [54] described three patients with NF-1 who had C1–C2 dislocation with neurological deficit. All patients improved after decompression and fusion. We recommend that the cervical spine should be evaluated at the initial scoliosis assessment.

A lateral radiograph of the cervical spine is the initial screening tool. The NF-1 can be manifested on a plain radiograph in the form of dystrophic changes or malalignment [55]. If any suspicious area is noted on plain radiographs, right and left oblique views should be obtained to look for widening of the neuroforamina which may represent dumbbell lesions. MRI is the definitive study to evaluate these lesions.

Anteroposterior and lateral radiographs of the cervical spine should be obtained in all NF-1 patients who: (1) are placed in halo traction; (2) undergo surgery; (3) require endotracheal intubation; (4) present with neck tumors; (5) complain of neck pain; and (6) present with symptoms indicating intra- or extraspinal neurofibromas, such as torticollis or dysphagia [56]. If there is any suspicion of instability, CT and/or flexion- extension MRI are indicated. Erosive defects of the skull may be present in some patients with NF-1. Thus, plain radiographs of the skull prior to halo or Gardner–Wells tong traction pins application are strongly recommended.

The most common spinal abnormality in the cervical spine is a severe cervical kyphosis, which is often seen following a decompressive laminectomy without stabilization for an intraspinal lesion and is highly suggestive of the disorder [57]. We recommend stabilization of the spinal column at the same time of surgical removal of tumors from the spinal canal.

Ogilvie reported on the surgical treatment of cervical kyphosis by anterior fusion with iliac- crest or fibular bone graft or both [51]. He considered halo traction to be a useful preoperative step if the kyphosis was greater than 45°. In the presence of progressive cervical kyphosis, we recommend preoperative halo traction only if the deformity is flexible as judged by the radiographs. This should be followed by posterior fusion. If the deformity is rigid, then an anterior soft-tissue release followed by traction is safer.

Internal fixation with pedicle and lateral mass screws is preferred for posterior instrumentation. Sublaminar wire fixation may be difficult second-

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ary to dural ectasia and osseous fragility. For anterior fixation, we currently use bioabsorbable plates. Even with rigid instrumentation, postoperative halo immobilization is recommended until a fusion mass with trabecular pattern is seen on cervical CT.

5. Thoracic/Thoracolumbar Spinal Abnormalities

The two varieties of spinal deformity are well distinguished in these regions of the spine. Also, the natural history of spinal deformities is well studied for thoracic/thoracolumbar region. Patients more likely to develop progressive scoliosis of the thoracolumbar spine are children under 7 years of age who have thoracic lordosis (sagittal plane angle of less than 20° measured from T3 to T12) and paravertebral tumors. There is a strong association between modulation and progression of the spinal deformity. More specifically, curves that acquire either three or more penciled ribs or a combination of any three dystrophic features will almost certainly progress [28]. Other factors that have been associated with substantial curve progression include: 1) high Cobb angle at presentation; 2) early age of onset; 3) abnormal kyphosis; 4) vertebral scalloping; 5) severe apical rotation; 6) location of the apex in the middle-lower thoracic spine [34].

More recent MRI studies have questioned the theory of modulation [43]. Patients with radiographically labeled non-dystrophic curves have been found to have significant dysplastic changes on MRI. Having in mind the higher sensitivity of MRI in identification of dystrophic features than x-rays, we recommend characterization of the curve as dystrophic or not based on a combination of MRI and x-ray findings [31].

5.1 Non-dystrophic Scoliosis

This is the common variety of spinal deformity observed in NF-1. These curves behave similar to idiopathic curves with some differences [7, 9, 58]. This form usually involves 8-10 spinal segments. Most often, the deformity is convex to the right. However, these curves usually present earlier than the idiopathic curves and are more prone to progression. Furthermore, the rate of pseudoarthrosis following a fusion surgery is higher in these patients [49]. These differences can be attributed to the process of modulation and the underlying bone pathology. Compared to dystrophic curves, non-dystrophic curves tend to present in older children with less angulation and rotation of the deformity [59].

5.2 Dystrophic Scoliosis

This is an uncommon but malignant form of spinal deformity. It is characterized by early onset, rapid progression and is more difficult to treat [60, 61]. Typically, the dystrophic curve is a short-segmented, sharply angulated type that includes fewer than six spinal segments. Dystrophic curves may be associated with kyphosis and have a higher incidence of neurological injury [61, 62].

Dystrophic vertebral changes develop over time (**Table 2**).

5.2.1 Natural History

The onset of spinal deformities may occur early in patients with NF-1. Usually early onset scoliosis is associated with kyphosis giving rise to kyphoscoliotic deformities. Calvert et al. [63] presented a series of treated ($n = 34$) and untreated ($n = 32$) patients who had NF-1 and scoliosis. Seventy-five percent of patients in the nontreated group had kyphoscoliosis. The investigators reported that patients, who had severe anterior vertebral scalloping noted on the lateral view, progressed an average of 23° per year for scoliosis and kyphosis.

Some of the non-dystrophic curves exhibit the phenomenon of modulation. Durrani et al. [28] defined modulation as a process by which a nondystrophic curve acquires the features of a dystrophic curve and behaves as a dystrophic curve. They reported that modulation occurred in about 65% of their patients. Modulation occurred in 81% of patients who presented with scoliosis before 7 years of age and in 25% of those diagnosed after 7 years of age. Rib penciling acquired through the modulation period was the only factor that was statistically significant in influencing the progression of the deformity. These authors based their report on plain radiographic findings. Some of the recent reports with the use of MRI of spine have shown the presence of dystrophic findings in the spine before they are apparent on

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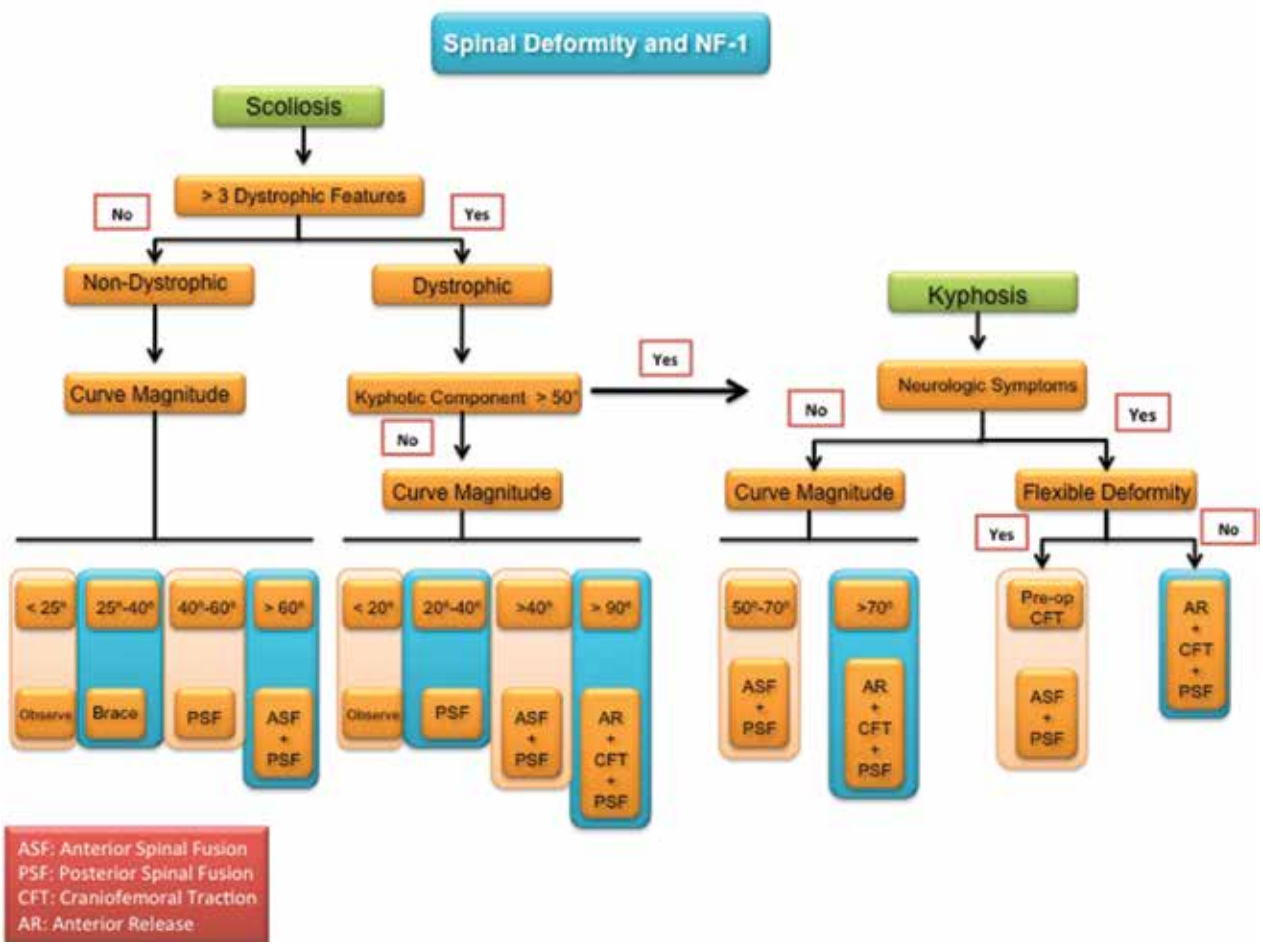

Fig. 1. *Spinal deformity and NF-1*

the plain radiographs. Based on these reports, it can be speculated that true modulation may be rare, and many of the apparent non-dystrophic curves are actually dystrophic curves which subsequently present themselves with radiographical changes of dystrophic curve giving an impression of modulation.

A retrospective review of 694 patients with NF-1 revealing 131 patients (19%) with a scoliosis ranging from 10° to 120° was performed [31]. Mean age at diagnosis of scoliosis was 9.0 years, with 18 patients (15%) having onset before 6 years of age. Forty-six patients (35%) required surgical repair, usually anterior and posterior spinal fusion with instrumentation. Six patients had growing rods successfully placed. Tumors near the spine were found in 65 % of patients requiring surgery.

It is well known that despite apparent solid fusion, some dystrophic curve shows progression. This tendency is more noted in patients with kyphosis (>50°). The vertebral subluxation, disk wedging, and dystrophy of peripheral skeleton are other factors associated with progression of the deformity after fusion [64].

5.2.2 Treatment

The treatment of non-dystrophic curvatures is very similar to idiopathic scoliosis. The curve of less than 25° should be observed (**Fig. 1**). Curves between 25° and 40° can be treated with brace successfully [35]. Once beyond 40°, surgery by posterior spinal fusion is usually indicated [65]. Curves >55°-60° are treated with anterior release with bone-grafting, followed by an instrumented posterior spinal fusion [49]. This is necessary because the curve is usually more rigid than is a similar-sized curve in idiopathic scoliosis. We recommend postoperative orthotic immobiliza-

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tion, although others have managed these patients without postoperative immobilization, with good early results [29].

Dystrophic curvatures of less than 20° should be treated by observation. Serial spinal radiographs at 6-month intervals should be obtained to check for progression of the deformity [49]. Bracing of progressive dystrophic curvatures is ineffective and surgery is usually recommended [10, 35, 66]. For adolescent patients with dystrophic curvature greater than 20°–40° of angulation, a posterior spinal fusion with segmental spinal instrumentation is recommended [10, 62]. In more severe dystrophic scoliosis, anterior fusion should be performed in addition to posterior fusion, to increase the fusion rate, and to reduce the risk for progression despite solid posterior fusion. Preoperative halo traction may be beneficial for the treatment of severe curves, including those with kyphoscoliosis [10, 58, 67, 68]. It allows gradual and controlled soft tissue relaxation and curve correction before surgery or between staged surgeries; however, it is contraindicated in patients who have cervical kyphosis. Daily neurological evaluations are mandatory to avoid spinal or cranial nerve injuries. Nutrition is also paramount during this time. We use supplemental nasojejunal feeding in between stages to decrease the protein depletion that is seen in staged patients [34, 69]. We recommend anterior release, nasojejunal tube alimentation, and craniofemoral traction for rigid curves of >90°.

The dystrophic curves that are present in late juvenile and early adolescent period pose a challenge to the surgeon. These curves have a high rate of pseudoarthrosis following a posterior spinal fusion [49, 61, 65]. A combined anterior and posterior spinal fusion has been recommended in these patients to decrease the rate of pseudoarthrosis and crank-shaft [70-73]. In our experience, an early fusion of the spine in this age group does not significantly alter the final height and its benefit outweighs the risk of severe progression. It is suggested that the primary reason for fusion failure is an inadequate anterior procedure [74]. However, erosion from enlarging neurofibromas, dural ectasia, and meningoceles may play a role.

Dystrophic curves in infants, toddlers, and early juvenile patients present even more of a challenge. In this age group, a spinal fusion can certainly have a significant effect on overall height as well as the size of the thoracic cage. Smaller size of the vertebrae can pose difficulty in the instrumentation. On the other hand, progression of the curve itself can significantly distort the thoracic cage which can lead to cardio-thoracic decompensation. Most centers recommend observation initially for spinal deformities to determine whether or not it will progress. If the child is very young (under 5–6 years), a corrective cast or bracing may be attempted, most often with little to marginal success. However, it may allow the surgeon to buy some time. Growing rods have been used to obtain correction without definitive fusion and to lengthen or "grow the spine" every 6 months, but with varying success and a high rate of complications.

5.2.3 Growing Rod Instrumentation

The growing rods have been used successfully in the treatment of early onset idiopathic curves.

These devices have been shown to prevent the progression of the curve while preserving the longitudinal growth of the spine [75]. The currently available dual growing rods have been shown to be superior to the previous versions of submuscular single growing rods [76]. We have used dual growing rods on early onset dystrophic curves with a great deal of optimism [62].

The routine lengthening is made at 6-month interval. The use of growing rod instrumentation in NF-1 is also associated with a high incidence of complications. The high rate of complications has also been reported for idiopathic patients (75). The most common complication we have encountered is proximal junctional kyphosis. This is especially common in the patients with high thoracic or cervicothoracic curves. Other complications encountered are infection and rod breakage.

Although the use of growing rod instrumentation is associated with higher complication rate, its benefits outweighs the risk in patients with early onset dystrophic scoliosis. Our early results with the use of growing rods remain encouraging. This is a promising technique made especially useful because most dystrophic curves have early onset.

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6. Other Spinal Deformities

6.1 Kyphosis

Kyphoscoliosis is defined as scoliosis accompanied by a kyphosis of greater than 50°. It may occur by gradual scoliotic rotation and progression or it can be found early in the disease with an abrupt angular kyphotic curve [78]. Vertebral bodies may be deformed so severely that they are confused with congenital deformities. Severe kyphosis is the most common cause of neurological deficits in NF-1 [62]. Use of traction in patients with rigid and severe kyphosis can increase the tension on the spinal cord leading to neurological deficits. Traction following anterior release is safe when monitored appropriately. For curves greater than 50°, anterior surgery (release and fusion) is recommended, followed by posterior segmental instrumentation one or two levels above and below the end vertebrae [32, 49, 58, 64]. Assessment of the fusion mass by CT at 6 months postoperatively is recommended. If pseudarthrosis is noted, augmentation of the fusion mass is indicated.

We recommend that the anterior procedure should be undertaken from the convex side of the deformity, since the exposure is extremely difficult from the concave side [79]. The anterior fusion should include the entire structural area of the deformity with complete disk excision and local strut grafting. Multiple grafts or cages should be placed into the vertical weight-bearing axis of the torso, with the strong autologous fibula or rib graft placed more anteriorly [62, 66]. Strut grafts should have contact with each other and with the vertebral body to prevent resorption noted when graft material is surrounded by pathological tissue. Anterior release and fusion should be followed by posterior instrumented fusion using a large amount of autologous iliac crest bone graft and BMP in selected cases.

6.2 Lordoscoliosis

Lordoscoliosis has not been so frequently reported in patients with NF-1 compared to kyphoscoliosis. However, lordosis of the thoracic spine predisposes to significant respiratory compromise and mitral valve prolapse [77, 80].

Anterior release and intervertebral fusion followed by posterior instrumented fusion is considered as the most reliable surgical option to achieve correction of dystrophic lordoscoliosis [32].

6.3 Spondylolisthesis

Spondylolisthesis in patients with NF-1 is rare. It is characterized by pathological forward progression of the anterior elements of the spinal column. Spondylolisthesis in patients with NF-1 is most often associated with pathological elongation and thinning of the pedicles or pars interarticularis by lumbosacral foraminal neurofibromas or dural ectasia with meningoceles [32]. The vertebral bodies may also be small and dystrophic.

Fusion may also be delayed because of the forward traction effect of the vertebral bodies and the slow healing and remodeling of bone in NF-1. We recommend a combined anterior and posterior fusion from L4-to-sacrum using intervertebral body grafting and lumbosacral instrumentation. Postoperative immobilization is indicated until the fusion is absolutely solid.

7. Conclusion

NF-1 is the most common human single-gene disorder. Skeletal complications usually present early in life and can be attributed to abnormalities of bone growth, remodeling, and repair in NF-1 or can be secondary to nearby soft-tissue abnormalities associated with NF-1. Scoliosis is the most common osseous manifestation of NF-1. It is important to recognize the dystrophic curve and to distinguish it from the non-dystrophic curve.

The management of spinal disorders in young children in NF-1 continues to be problematic. The use of growing rods allows more longitudinal growth than fusion and more life freedom than bracing. The problems we have encountered are mechanical and could be expected when proximal and distal fixation is performed over an otherwise completely mobile spinal column. The multiple surgeries increase the potential for complications including infections. We continue to pursue solutions to our problems.

Conflict of interest:
The authors declared no conflicts of interest.

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ΠΕΡΙΛΗΨΗ

Η νευροϊνωμάτωση τύπου 1 (NF-1) αποτελεί την πιο συχνή μονογονιδιακή ανωμαλία στον άνθρωπο. Οι σκελετικές επιπλοκές συνήθως παρουσιάζονται νωρίς και μπορούν να αποδοθούν στις ανωμαλίες της οστικής ανάπτυξης, ανακατασκευής και επιδιόρθωσης στην NF-1 ή μπορεί να είναι απότοκες των ανωμαλιών των γειτονικών μαλακών μορίων που σχετίζονται με την NF-1. Η σκολίωση αποτελεί την πιο συχνή σκελετική εκδήλωση της NF-1. Είναι σημαντικό να αναγνωριστούν οι δυστροφικές παραμορφώσεις και να διαχωριστούν από τις μη δυστροφικές. Η διαχείριση των σπονδυλικών παραμορφώσεων στα μικρότερα παιδιά με NF-1 παραμένει προβληματική. Η χρήση των εκπτυσσόμενων ράβδων επιτρέπει την κεφαλουραία ανάπτυξη της σπονδυλικής στήλης και παρέχει μεγαλύτερη ελευθερία συγκριτικά με τον κηδεμόνα. Τα προβλήματα είναι κυρίως μηχανικής φύσεως και παρατηρούνται όταν πραγματοποιείται κεφαλική και ουραία σταθεροποίηση σε μια τελείως ασταθή σπονδυλική στήλη. Οι πολλαπλές επεμβάσεις αυξάνουν την πιθανότητα επιπλοκών όπως οι λοιμώξεις. Σκοπός αυτού του άρθρου είναι να παρουσιάσει τις σπονδυλικές παραμορφώσεις που σχετίζονται με την NF-1 και να αναλύσει την αντιμετώπισή τους έχοντας ως βάση την πιο πρόσφατη βιβλιογραφία.

ΛΕΞΕΙΣ ΚΛΕΙΔΙΑ: νευροϊνωμάτωση, σκολίωση, κύφωση, δυστροφική παραμόρφωση, NF-1