Neurofibromatosis type 1 (NF-1) is an autosomal dominant hereditary disease characterized by an abnormal proliferation of cells from the neural crest. Neurofibromatosis type 1 is often associated with orthopedic disorders, especially scoliosis, which is the most common skeletal manifestation of NF-1. The effects of treatment of scoliosis in NF-1 are less satisfactory than other scoliotic types due to the particular pathogenesis and clinical characteristics. Early diagnosis and treatment may be the best way to improve outcomes. This article summarizes the recent genetic and clinical developments of scoliosis in NF-1.

Neurofibromatosis is an autosomal dominant hereditary disease characterized by an abnormal proliferation of cells from the neural crest, which can occur in both the peripheral nervous system and the central nervous system. Both children and adults can suffer from this disease. Neurofibromatosis is usually divided into 2 clinical types: neurofibromatosis type 1 (NF-1) (or von Recklinghausen’s disease or peripheral neurofibromatosis) and neurofibromatosis type 2 (NF-2).

Neurofibromatosis type 2 is caused by inactivating mutations of the NF-2 tumor suppressor gene in chromosome 22q12.1,2 with an incidence of 1 in 25,000 to 40,000 individuals.3,4 Table 1 lists the diagnostic criteria of NF-2. Clinical features of NF-2 typically include nervous system tumors (eg, vestibular schwannomas, intracranial meningiomas, spinal tumors, and peripheral nervous system tumors) and ocular abnormalities.6,8 Bilateral vestibular schwannomas are pathognomonic for NF-2 and occur in >90% of adult patients (Table 1).7

Without special predilection for race or sex, and with an incidence of 1 in 3000, neurofibromatosis type 1 (NF-1) is the most common form of autosomal dominant phakomatoses.10 Neurofibromatosis type 1 is often associated with various orthopedic disorders, especially scoliosis. Spinal deformities in patients with NF-1 were first reported by Gould11 in 1918. Scoliosis is the most common skeletal manifestation of NF-1, with an incidence ranging between 10%12 and 64%.13 However, NF-1 accounts for approximately 3% of all scoliosis cases.14

Scoliosis in NF-1 is classified into 2 basic types based on the natural history and curve characteristics: nondystrophic and dystrophic scoliosis. The manifestations of nondystrophic curvature and methods of management are similar to those of idiopathic scoliosis. Dystrophic curves often occur earlier than nondystrophic curves. Dystrophic curves also have a worse prognosis.

The phenomenon of modulation was first reported by Durrani et al15 in 2000. They described it as spinal deformities with seemingly few initial dystrophic features that showed a tendency to acquire dystrophic changes during a 7-year follow-up period. In 81% of patients with spinal deformity diagnosed before age 7 years and in 25% of patients diagnosed after age 7 years, evidence of modulation was observed. Deformities presenting with dystrophic changes can acquire further dystrophic features. The research shows that of the deformities that acquired ≥3 penciled ribs, 87% showed significant clinical progression. Durrani et al15 reported that when a curve acquires either 3 penciled ribs or a combination of 3 dystrophic features, clinical progression is almost a certainty. They were concerned that spinal deformities in patients with NF-1 should be thought of as deformities in evolution, and one should resist assigning these evolving deformities to either the dystrophic or the nondystrophic.15

---

Mr Wang and Dr Liu are from the First Hospital of Jilin University, ChangChun, China.
Mr Wang and Dr Liu have no relevant financial relationships to disclose.
Correspondence should be addressed to: Zhenyu Wang, MS, The Second Hospital of Jilin University, ChangChun, Jilin Province, 130041 China (successwzy@sohu.com).
doi: 10.3928/01477447-20100329-20
**IMAGING FEATURES**

Five imaging features of the dystrophic spinal curve are seen. First, the curves most commonly show first in thoracic spine and then involve the thoracolumbar and cervical spine, while lumbar scoliosis is rare. The typical scoliosis has been described as being a short, sharply angulated curve involving 4 to 6 vertebrae in the thoracic spine. Also, the orientation of the curves, whether to the left or right, are equal.

Second, the dystrophic curves are rigid. The corrective rate in side-bending radiographic examination is often <30%.

Third, abnormal changes in vertebrae include vertebral scalloping, spindling of the transverse processes, rib penciling, a short curve with severe apical rotation, foraminal enlargement, and defective pedicles (usually becoming longer and thinner). The literature contains 1 report of paraparesis due to spinal cord compression by a rib penetrating through the intervertebral foramina into the spinal cord.17

Fourth, another distinctive osseous appearance is thinning of the long bone cortex, with or without pseudoarthrosis. While some disagree with this conclusion, they maintain that the characteristic radiographic presentation is anterolateral bowing of the lower leg.18

Fifth, myelography shows dural ectasia.19,20 Because the 2 types of scoliosis differ dramatically in management and prognosis, especially for those with dystrophic changes, making a clear distinction between them is important.

**PATHOGENESIS**

In 1987, the von Recklinghausen’s disease neurofibromatosis 1 locus was assigned to the proximal long 17q11.2.21,22 The gene was successfully cloned in 1990.23-27 The full length of NF-1 gene is 350 kb containing 60 exons on chromosome 17q11.2.28-30 The NF-1 gene encodes a protein called neurofibromin, which is a tumor-suppressor gene expressed in several tissues and organs. Exons 21-27a of NF-1 encode the main functional domain (guanosine triphosphate activated protein [GTP]-related domain [GRD]) of neurofibromin, showing a homology with a family of protein that, when stimulated by GTPase, can result in hydrolysis of GTP in a bound state and deactivation of Ras through activating the Ras-GTPase.31 Accordingly, GRD is a negative regulator of signal conduction of Ras. It is believed that the activated Ras can promote a variety of downstream signal pathways at the cell membrane, such as mitogen-activated protein kinase (MAPK), which can affect cell proliferation and differentiation.

Functional analysis has shown that neurofibromin plays a role in adenylyl cyclase and Akt-mTOR mediated pathways. It also appears to affect Ras-GTPase-activating protein activity through the phosphorylation of protein kinase C, which impacts on cell motility by binding with actin in the cytoskeleton.32 The Figure illustrates the cellular pathomechanisms of NF-1.32

Recent research shows that neurofibromin not only regulates the activity of Ras in the cell but also up-regulates the level of cAMP,33 which regulates the growth and differentiation of brain cells.

---

<table>
<thead>
<tr>
<th>Diagnostic Criteria of Neurofibromatosis Type 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Bilateral vestibular schwannomas (VS) OR family history of NF-2</td>
</tr>
<tr>
<td>• Any 2: meningioma, glioma, neurofibroma, schwannoma, or posterior subcapsular lenticular opacities</td>
</tr>
<tr>
<td><strong>Additional criteria</strong></td>
</tr>
<tr>
<td>• Unilateral VS 1 any 2: meningioma, glioma, neurofibroma, schwannoma, or posterior subcapsular opacities</td>
</tr>
<tr>
<td>OR</td>
</tr>
<tr>
<td>• Multiple meningioma (&gt;2) 1 unilateral VS OR any 2: glioma, neurofibroma, schwannoma, or cataract</td>
</tr>
</tbody>
</table>

---

*Figure: Cellular pathomechanisms of NF-1.*32
How NF-1 causes the distinctive change of spinal structure, restructuring in scoliosis, remains unclear. It may be related to chondrodysplasia, disorders of internal secretion, defects of idiopathic mesoderm, and direct invasions of the mass of neurofibroma into the skeleton.34

According to the recent literature, the reasons for scoliosis in neurofibromatosis may include: (1) the vertebral neurofibroma eroding spinal vertebrae from inside; (2) the peripheral neurofibromas around the vertebrae corroding from the exterior; (3) dural ectasis in the spinal canal compressing the vertebrae; (4) an unknown reason leading to osteoporosis of vertebrae; (5) endocrine abnormality (Moiton et al35 believe that the skeletal changes may relate to primary hyperparathyroidism); (6) pathological changes of the vascular system and dysfunction of osteoblasts;36 and (7) adolescent sexual precocity.

**Diagnosis and Clinical Manifestation**

The diagnosis of NF-1 is based on clinical criteria defined by the 1987 Consensus Development Conference of the National Institutes of Health on NF-1. Diagnosis requires at least 2 of the criteria to be present (Table 2).

**Skeletal Problems**

The common osseous changes of NF-1 include scoliosis, scalloping of the vertebrae, penciling of the ribs, broadening of the interpedicular distance, erosion of the vertebral margins, spindling of the transverse processes, thinning of the long bone cortex with or without pseudoarthrosis, demineralizing osteoporosis, and nonossifying fibromas.

**Skin Manifestation of NF-1**

Café au lait spots are well-circumscribed, uniformly light to dark brown macules with an average size of 2 to 5 cm in adults. The frequency of ≥5 café au lait spots in normal individuals is rare, and thus an excess of this number provides a significant diagnostic feature for NF-1.

Diffuse freckling is common in NF-1, but clustering hyperpigmentation on the axilla and inguinal area is unusual, except in NF-1.

Skin neurofibroma, a benign tumor derived from the cutaneous or subcutaneous nerve sheath, is comprised of Schwann cells, fibroblasts, perineural cells, mast cells, axons, and blood vessels. Some arise from a broad base of skin, whereas others form pedunculated lesions. Histologically, plexiform neurofibromas are similar to cutaneous neurofibromas except for an increase in the extracellular matrix and greater vascularization. Tumors may be discrete, homogeneous, and well circumscribed, or diffuse, heterogeneous, and infiltrative. Facial dysmorphisms with visual acuity loss are not uncommon in large facial plexiform neurofibromas.

Martínez-García et al39 reported an elephantiasis neuromatosa in a patient with neurofibromatosis type 1.

**Vascular Lesions**

Neurofibromatosis type 1 patients exhibit vascular complications that include arterial stenosis, aneurysm, and arteriovenous fistulas involving the abdominal aorta and its branches.32,40 Tang et al41 reported an NF-1 family with multifocal stenosis in intracranial arteries with complete occlusion of the left middle cerebral artery causing a fatal brain ischemia. Strokes occur in <1% of patients. The most common cause is the occlusion of the carotid or middle cerebral artery with proliferation of small vessels in the basal ganglia resulting in large cortical infarction. These vascular defects are not confined to the central nervous system; however, Gao et al42 reported the existence of a left renal artery stenosis and aneurysm.

Of all the clinical manifestations of NF-1, bony abnormalities, which are often the reason for surgery, are the most closely related to corrective spinal surgery.

**Neurological Disorders in Neurofibromatosis Type 1**

Neurofibromas originating from the spinal roots may cause pain, weakness, muscle atrophy, and depressed tendon reflexes. Radiculopathy associated with myelopathy can occur in the dumbbell-shaped tumors. Occasionally, images of the multiple root neurofibromas look like a Christmas tree with many hanging gifts. Involvement of the lumbar roots causes back pain that is aggravated by exertion and coughing. There can be massive proliferation of tumors with infiltration of the bladder and compression of the uterus, rectum, and ureters.

Nearly 15% of patients have optic gliomas.43 Although rapid deterioration of visual acuity is not common, these tumors require careful monitoring because they can progress to compromise vision. The brainstem and cerebellum are common sites for tumors. Most tumors identified on magnetic

---

<table>
<thead>
<tr>
<th>Table 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Criteria of Neurofibromatosis Type 1 (NF-1)</strong></td>
</tr>
<tr>
<td>1. ≥6 café au lait macules &gt;5 mm in greatest diameter in prepubertal individuals and &gt;15 mm in greatest diameter in postpubertal individuals</td>
</tr>
<tr>
<td>2. ≥2 neurofibromas of any type or &gt;1 plexiform neurofibroma</td>
</tr>
<tr>
<td>3. Freckling in the axillary or inguinal regions</td>
</tr>
<tr>
<td>4. Optic glioma</td>
</tr>
<tr>
<td>5. ≥2 Lisch nodules (iris hamartomas)</td>
</tr>
<tr>
<td>6. A distinctive osseous lesion, such as sphenoid dysplasia or thinning of the long bone cortex, with or without pseudoarthrosis</td>
</tr>
<tr>
<td>7. A first-degree relative (parent, sibling, or offspring) with NF-1 according to the above criteria</td>
</tr>
</tbody>
</table>
resonance imaging (MRI) are grade I astrocytomas and do not progress.32
Rapidly advancing myelopathy44 and malignant peripheral nerve sheath tumors (which occur in approximately 2% to 5% of NF-1 patients) are also reported.55

Psychiatric Disorders and Cognitive Dysfunction
Psychiatric disorders occur with greater frequency in NF-1 patients (33% of patients56) compared with the general population.32 The most common problem is dysthymia (21% of patients). Patients also display a high prevalence of depressive, anxiety, and personality disorders. Intelligence in NF-1 patients falls within normal limits.

Abdominal Manifestations in Neurofibromatosis
Hartley et al47 reported the most common abdominal presentations: neurofibroma, malignant peripheral nerve sheath tumor, pheochromocytoma, carcinoid, gastrointestinal stromal tumor, and seminoma.

Dental Abnormalities
Dental abnormalities can occur in association with oral neurofibromas but have not otherwise been described in people with NF-1. Questionnaires regarding dental caries were sent to families that included at least 1 individual with NF-1. Siblings with NF-1 reported significantly more dental caries than unaffected siblings or unaffected siblings.

Management
Although the genetic level has been reached in NF-1 research, making gene therapy a possibility, many problems still need to be solved. Regarding scoliosis, most researchers maintain that a full and accurate medical history, physical examination, and complete imaging evaluation are of great importance to distinguish between dystrophic and nondystrophic curves. A careful search for evidence of dystrophic changes should be made in all patients, because prognosis and management depend on the presence or absence of these dystrophic changes.56

Nondystrophic Scoliosis
Nondystrophic scoliosis is managed with the same decision-making process as idiopathic scoliosis.3,13,49-52 If the curvature is <20° to 25°, patients should be observed closely at regular 6-month clinical visits. Brace treatment can be applied for curvature 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.

If the deformity is >40°, it should be surgically corrected by posterior spinal fusion and segmental instrumentation.18 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 nonunion after attempted instrumented spinal fusion in patients with NF-1 in comparison to those with idiopathic scoliosis.13,15,51 For curves of >55° to 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

Close observation of the evolution of deformity is critical due to the possibility of modulation of spinal deformity from nondystrophic 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.13,15 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. It is possible that the dystrophic features in this subgroup of skeletally immature patients with idiopathic-like curves have not yet been developed.16,49

Another explanation, however, could be that at least some patients in the nondystrophic group have occult dystrophic changes that are initially missed on plain radiography.49

Dystrophic Scoliosis
The choice of treatment for dystrophic scoliosis in NF-1 is still under discussion. In general, brace treatment of short, angulated, dystrophic curves has not been successful, and the need for early and aggressive surgical intervention has been well documented, even in young children.13,14,30,31,54,55

Shen et al56 based on their retrospective review of 45 patients, believe that for most patients with dystrophic thoracic scoliosis and kyphosis <95°, single posterior fusion is effective. However, if the kyphosis is >95° or the apical vertebra is lower than T8, combined anterior and posterior fusion is recommended. In addition, if patients have significant neurologic symptoms or signs, and imaging examination shows that the spinal cord is compressed anteriorly or MRI or computed tomography (CT) suggests a neurofibroma is present laterally, the combined operation should chosen. Shen et al56 also strongly recommend that combined anterior and posterior fusion should be done for lumbar or thoracolumbar curves. When subluxation, expansion of the spinal canal, or thinning of pedicles is found, although combined fusion has been well performed, the development of scoliosis may not be completely controlled, and more fusion surgery may be necessary.57 Some authors also maintain that when the curvature is <50°, the single posterior fusion is feasible.13,57

Parisini et al58 maintain that to plan surgery adequately, it is mandatory to classify the curvature into types based on their patterns.16,50,52,57,59,60 Type I curves are characterized by scoliosis of 20° to 40° and normal sagittal curvatures (kyphosis <50°). Type II curves are short, angulated dystrophic curves with angles of kyphosis >50°. Type I curves can be stabilized using posterior spinal fusion alone, whereas management of type II curves requires an early and aggressive combined anteroposterior (AP) fusion.
Savini et al\textsuperscript{51} note the progression of dysplastic scoliosis due to kyphoscoliosis and recommended anterior fusion and complete disk excision in addition to repeat bone grafting for relapse after posterior fusion. Because a single posterior operation cannot prevent deformity from progressing, if a single posterior instrumentation has been performed, deformation of vertebrae may be found 6 months later. A second posterior fusion should be performed to enhance the stability.

In a study by Hsu et al\textsuperscript{60} 13 children with dystrophic scoliosis treated by AP fusion were followed for 7 years. They concluded that the effectiveness of fusion performed on scoliosis without kyphosis or kyphosis with small curvature is improving. Nevertheless, even when AP fusion had been performed, satisfactory results for scoliosis with severe kyphosis may be hard to achieve.

Crawford\textsuperscript{13} believes that patients with a curvature $<20^\circ$ should be observed for progression at 6-month intervals. For patients with $>20^\circ$ to $40^\circ$ of angulation, a posterior spinal fusion of all articular facets and segmental spinal instrumentation should be performed. The fusion should be carried out from the neutral vertebra above to the neutral vertebra below. The patient should be radiographed at 6 months postoperatively. Oblique views should be taken to assess the fusion of the facet joints and to rule out a pseudoarthrosis. If there is any question of failure of consolidation of the fusion mass, reoperation and bone grafting should be performed. Crawford\textsuperscript{13} also suggests that an anterior disk excision and bone graft followed by posterior arthrodesis with instrumentation are indicated if the kyphotic angle is $>50^\circ$ or if scoliosis is $>80^\circ$.

The combined anterior and posterior operation may cause greater impairment and is more time consuming. The question has been raised whether combined AP surgery is necessary for all patients with dysplastic scoliosis in NF-1. Betz et al\textsuperscript{50} deem that single posterior fusion is effective for patients without serious kyphosis. They reviewed 23 patients with scoliosis in NF-1 who had been treated by single posterior fusion. Twenty patients achieved a solid fusion with posterior surgery alone. Thirteen patients required $\geq 1$ posterior augmentation procedures because of progressive deformity.\textsuperscript{50} Recent clinical research shows that many of the posterior segmental fixation systems available have been used successfully. However, dystrophic vertebrae are not always good anchorage points for hardware. Care should be taken when the spine is exposed, because some of the laminae may be extremely thin or eroded from underlying neurofibroma or dural ectasia, and the spinal cord could be injured directly.

If the followed conditions can be fulfilled, most patients can expect a better prognosis: (1) preoperative preparation is adequate; (2) careful auto-bone graft is used to fuse all articular facets; (3) fusion is carried out from the neutral vertebra above to the neutral vertebra below and supported by consolidation through instrumentation; and (4) brace treatment is added in the postoperative period. In addition, regular follow-up examination, especially by spinal radiographs, is vital.

Deformities of the cervical spine have received less attention in the literature. It is known that many patients with these deformities are asymptomatic and that curves in this area occur more frequently in association with dysplastic lesions than in other areas of the spine.\textsuperscript{13,62,63} However, cervical deformities of NF-1 may combine lesions of the spinal cord and nerves, which sometimes lead to paralysis. This situation can complicate the cervical deformity and make treatment more difficult.\textsuperscript{64}

Because not all cervical spine deformities are symptomatic, AP and lateral radiography is recommended at the time of initial evaluation. This is particularly important in patients undergoing instrumentation of the thoracic or lumbar spine who may require halo traction and in those who have neck tumors. If dystrophic changes are noted, oblique radiographs to identify dumbbell lesions and lateral flexion and extension radiographs to rule out instability should be obtained.\textsuperscript{16}

Patients with cervical deformity of NF-1 often present with evident curvature and other complications, such as lesions of the spinal cord and nerves, so surgery is necessary. Surgery should correct the kyphosis to neutral and recover normal locomotion. Meanwhile, decompression of nerves and the spinal cord should be performed.\textsuperscript{63} With respect to patients with severe kyphosis, single decompression laminectomy may aggravate kyphosis. The literature reports that in many patients with cervical deformity, kyphosis was caused by laminectomy\textsuperscript{13} or neurological symptoms, so this condition is considered a contraindication to single decompression laminectomy.\textsuperscript{61}

Yonezawa et al\textsuperscript{65} reported a case of a 15-year-old boy with severe cervical kyphosis due to neurofibromatosis who underwent 1-stage anterior fusion and posterior correction using pedicle screw fixation. The kyphosis was corrected from $72^\circ$ to $35^\circ$. At 16-month follow-up, anterior fusion and posterior stabilization had been obtained without correction loss. Therefore, cervical pedicle screw fixation can be considered as a useful method for the correction of severe cervical kyphosis in patients with NF-1.

Regardless of the approach chosen to treat scoliosis in NF-1—anterior, posterior, or combined anterior and posterior fusion—bone grafting with the intention of acquiring stabilization of the spine is an important part of treatment.\textsuperscript{66} The usual reason for surgery failure is the use of technically inadequate anterior procedures, such as too little bone graft in too limited an area.\textsuperscript{52,59} The entire structural area of the deformity should be fused anteriorly with abundant autogenous bone graft to avoid a subsequent significant deformity from the uninvolved fusion area. When it comes to the source of bone, autogenous bone is most ideal. However, the amount of autogenous bone may be limited due to osteoporosis and low quality of ilium. Thus, prosthesis, xenogenous bone, or ribs from a thoractomy can be used for adequate bone grafting.\textsuperscript{56}
Surgery on spinal deformity is risky, especially for the dystrophic type of NF-1.67 Problems may include intraspinal or extraspinal neurofibromas, severely deformed anatomic structure (thinning of vertebral laminae and pedicles may make instrumentation ineffective), decreased bone mass (low bone density), and the possible abnormality of blood vessels (eg, arteriovenous fistula and proliferation of a venous plexus).16

The most common complications of scoliosis in NF-1 are lesions of the spinal cord and pseudoarthrosis. Lesions of the spinal cord may be caused by: (1) spinal cord compression of the apical vertebral region due to severe kyphosis; (2) spondylolysis at the most serious dystrophic region; (3) a rib penetrating into the spine canal due to rib displacement; or (4) intraspinal tumors. The incidence of postoperative pseudoarthrosis is decreasing. Thus, adequate bone grafting, strong and effective instrumentation, and close observation of the postoperative evolution of the deformity can reduce the incidence of these complications.60

The increased vascularity of neurofibromatous soft tissue can increase intraoperative blood loss and the frequency of postoperative hemorrhage and hematoma formation.60,70

CONCLUSION

The effects of treatment of scoliosis in NF-1 are less satisfactory than other scoliotic types due to the particular pathogenesis and clinical characteristics. However, recent progress resulting from both basic science and clinical studies has generated significant hope for the future. Above all, early diagnosis and treatment may be the best way to improve outcomes.

REFERENCES


42. Tonsgadth JH. Clinical manifestations and manage- ment of neurofibromatosis type 1. Semin Pediatr Neurol. 2006; 13(1):27-.


