Orthopaedic aspects of neurofibromatosis: update

Tracey A. DeLucia[a], Kaleb Yohay[b] and Roger F. Widmann[a]

[a]Hospital for Special Surgery and [b]Cornell Medical College, New York Presbyterian Hospital, New York, New York, USA

Correspondence to Roger F. Widmann, MD, Hospital for Special Surgery, 535 East 70th Street, New York, NY 10021, USA
Tel: +1 212 606 1325; e-mail: widmannr@hss.edu

Current Opinion in Pediatrics 2011, 23:46–52

Purpose of review

Neurofibromatosis type I (NF-1), affecting 1 : 3000 people, is one of the most common disorders of the nervous system, and most pediatricians will care for a patient with this condition. It is imperative that careful attention be paid to screening for scoliosis and tibial dysplasia. Prompt referral to an orthopaedist at the time of diagnosis, as well as neurologist, ophthalmologist, and dermatologist, will provide a global spectrum of care for the individual. Patient care between surgical procedures will be inevitable, with 70% of patients with NF-1 undergoing hospitalization or surgery.

Recent findings

This review provides a description of diagnosis, presurgical evaluation, and advances in understanding tibial dysplasia, scoliosis and malignant peripheral nerve sheath tumors. New pharmaceutical treatments such as lovastatin have improved bone healing *in vivo* and induced apoptosis *in vitro*. Multiple pharmaceuticals have shown neurofibroma arrest *in vitro* and are in phase II clinical trials.

Summary

As animal models improve and clinical trials proceed, there is momentum toward eliminating the musculoskeletal morbidity associated with NF-1.

Keywords

neurofibromatosis, pseudarthrosis, scoliosis, skeletal

Curr Opin Pediatr 23:46–52

1040-8703

Introduction

The spectrum of diseases involving nerve sheath tumors includes Neurofibromatosis 1 (NF-1), neurofibromatosis 2 (NF-2) and Schwannomatosis. NF-1 is characterized by the presence of neurofibromas, which are benign nerve sheath tumors containing Schwann cells, fibroblasts, mast cells, and collagen [1,2]. Similarly, NF-2 and Schwannomatosis are characterized by benign Schwann cell tumors of the nerve sheath. The tumors can be superficial or deep, and discrete (involving a single nerve fascicle) or plexiform (involving multiple fascicles) [1]. The differential diagnosis also includes tuberous sclerosis, comprehensively reviewed by Arbuckle and Morelli [3] in 2000, and other conditions with café-au-lait spots as reviewed by Jett and Friedman [4•] in 2010.

Schwannomatosis

Schwannomatosis is a disease of adulthood characterized by painful peripheral nerve sheath tumors without other body systems affected. NF-2 and Schwannomatosis can be diagnostically confusing, but the distinction is made by a lack of vestibular disease in Schwannomatosis [5]. A group out of Massachusetts General Hospital presents whole body MRI as a diagnostic tool to determine total body tumor burden in this and other nerve sheath tumor diseases. The advantage of MRI can be discovery of occult tumors and measurement of response to treatment without ionizing radiation [1].

Neurofibromatosis type 2

NF-2 most commonly presents as unilateral hearing loss proceeded by tinnitus from benign vestibular Schwannomas of the eighth cranial nerve. The tumors are found to be bilateral and can initially present as dizziness [6•]. Late symptoms include nausea, vomiting and vertigo [6•]. Prevalence of NF-2 is 1 : 40 000–60 000, and inheritance is autosomal dominant transmission of the tumor suppressor *NF-2* gene on chromosome 22 [5,6•]. Fifty percent of cases involve a new mutation. In addition to Schwannomas, cranial and spinal meningiomas and low-grade central nervous system ependymomas lead to substantial morbidity and early mortality. These patients rarely present with musculoskeletal problems. Current treatment of peripheral Schwannomas is resection, or radiation for larger tumors [6•]. In a recent study, Bevacizumab, an antivascular endothelial growth factor (VEGF) monoclonal antibody, was found to reduce vestibular schwannoma volume and induce a hearing response [7]. Anti-VEGF medications have been reported in the literature for treatment of NF-1 [8•].

Neurofibromatosis type 1

The multiple systemic comorbidities associated with NF-1 are often more troubling than the neurofibromas which characterize this disease. The incidence of NF-1 is 1 : 3000, and NF-1 is an autosomal dominant, single gene mutation of a tumor suppressor found on chromosome 17q11.2 [9]. In order to definitively diagnose NF-1, a patient must have two of the following seven characteristic features: greater than six café-au-lait macules, neurofibromas, axillary or inguinal freckling, optic nerve glioma, Lisch nodules, a distinctive osseous lesion and family history of NF-1 in a first degree relative.

Diagnosis

The most common feature at diagnosis is hyperpigmented macules, or café-au-lait spots. A diagnosis of NF-1 is made in 97% of patients by age 8 [10]. Direct sequencing of the causative mutation is possible in 95% of those with NF-1 [11••]. In addition, prenatal and pre-implantation testing is possible for diagnosis [9]. Once the diagnosis is suspected, regular yearly screening should be initiated, because patients may not manifest all of their diagnostic criteria until young adulthood. The phenotype of NF-1 is extremely variable.

Nonorthopaedic manifestations

A thorough review of the features of NF-1 is presented by Williams *et al.* [11••] in 2009 and the authors highly recommend reference to this manuscript for comprehensive management of the patient with NF-1.

Plexiform neurofibromas

Neurofibromas can be cutaneous, subcutaneous, paraspinal, or more integrated into nerve tissue in the form of plexiform neurofibromas. At least 30–60% of people with NF-1 have plexiform neurofibromas [4•,12]. These benign tumors can become problematic when they expand and impinge on structures or undergo malignant transformation [8•,12]. The lesions appear to grow more quickly at younger ages, and patients may benefit from early removal prior to invasion of contiguous structures; however, this still remains controversial [13,14]. Neurofibroma resection does carry the risk of neurologic injury from surgery, as well as risk of recurrence, since the tumors are often diffusely infiltrative and difficult to remove entirely [9].

Spinal deformities

The most common orthopaedic manifestation of NF-1 is scoliosis, with 21–49% of patients having some abnormality [15,16,17••]. Because of the high prevalence of scoliosis associated with NF-1, routine screening for scoliosis is recommended with a low threshold for obtaining radiographs and orthopaedic referral. Scoliosis falls into two categories: nondystrophic and dystrophic [17••]. Dystrophic curves are characterized by radiographic abnormalities such as rib penciling (the rib diameter is smaller than the midportion of the second rib), vertebral rotation, vertebral scalloping, vertebral wedging, wide interpedicular distance, and enlarged intervertebral foramen [16]. The dystrophic scoliotic deformity is a short, sharp, angular curve involving four to six vertebrae (Fig. 1). Although nondystrophic curves appear radiographically similar to adolescent idiopathic scoliotic curves, nondystrophic curves may be rapidly progressive. Nondystrophic curves can change or modulate over time to become dystrophic curves. This phenomenon of modulation occurs more frequently when three or more ribs have penciling or the curve is present before the age of 7 [16,18]. Treatment recommendations for nondystrophic curves include brace management for curves between 20° and 35° [19]. Surgical fusion is recommended for nondystrophic curves progressing past 35°. Dystrophic curves rarely respond to brace management, and surgical fusion is recommended for curves over 20° (Fig. 2). Anterior and posterior spinal fusion is recommended for curves with kyphosis over 50° [15].

One of the serious complications of surgical management of dystrophic scoliosis is pseudarthrosis, or lack of fusion, which occurs in 63% of patients with NF-1 receiving posterior spinal fusion [20]. With current surgical techniques and modern implants, the pseudarthrosis rate in more recent studies is 20% with anterior and posterior fusion [21]. Kyphosis in NF-1 is particularly concerning because the high risk of spinal cord injury. As the kyphosis progresses, the spinal cord is draped over the gibbus deformity, or sharply angled hump, resulting in progressive stretch injury and possibly paraplegia if untreated. Another rare cause of spinal cord injury is atraumatic subluxation of the ribs into the neural foramen. This is best diagnosed on axial imaging with computed tomography or MRI.

Key points

- A summary of the diagnosis and most recent treatments for congenital tibial dysplasia, spinal disorders and peripheral nerve sheath tumors with neurofibromatosis.
- Multiple clinical trials are ongoing for therapeutic solutions to bone healing and neurofibroma arrest in neurofibromatosis.
- Be mindful of the heightened potential for malignancy in neurofibromatosis.

Figure 1 Dystrophic scoliosis: a radiograph of a characteristic sharp dystrophic scoliosis

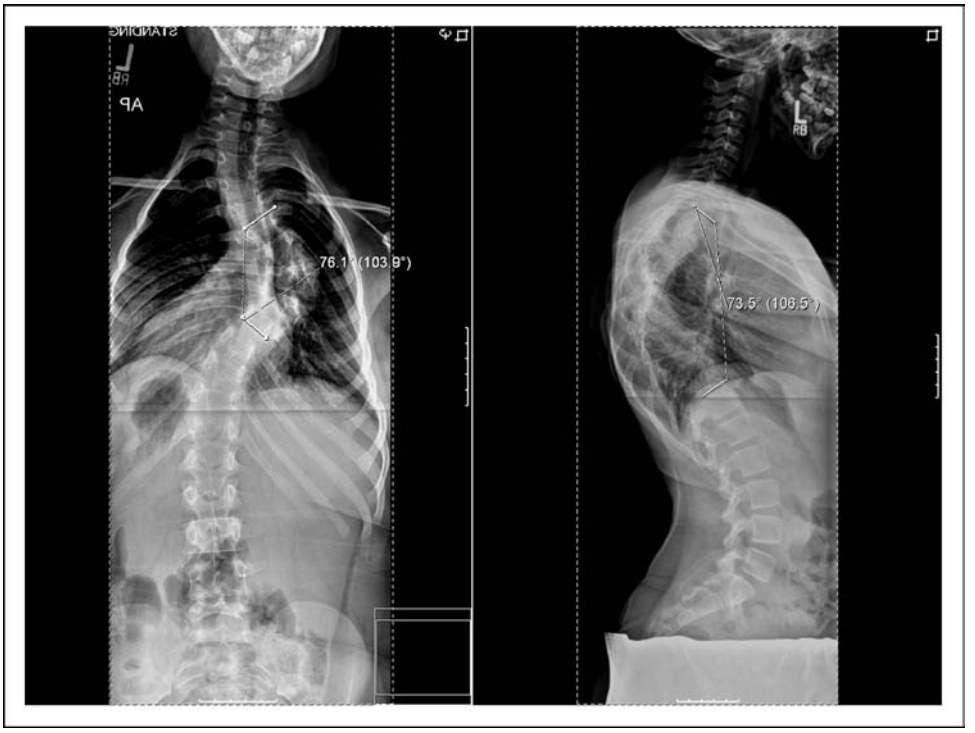
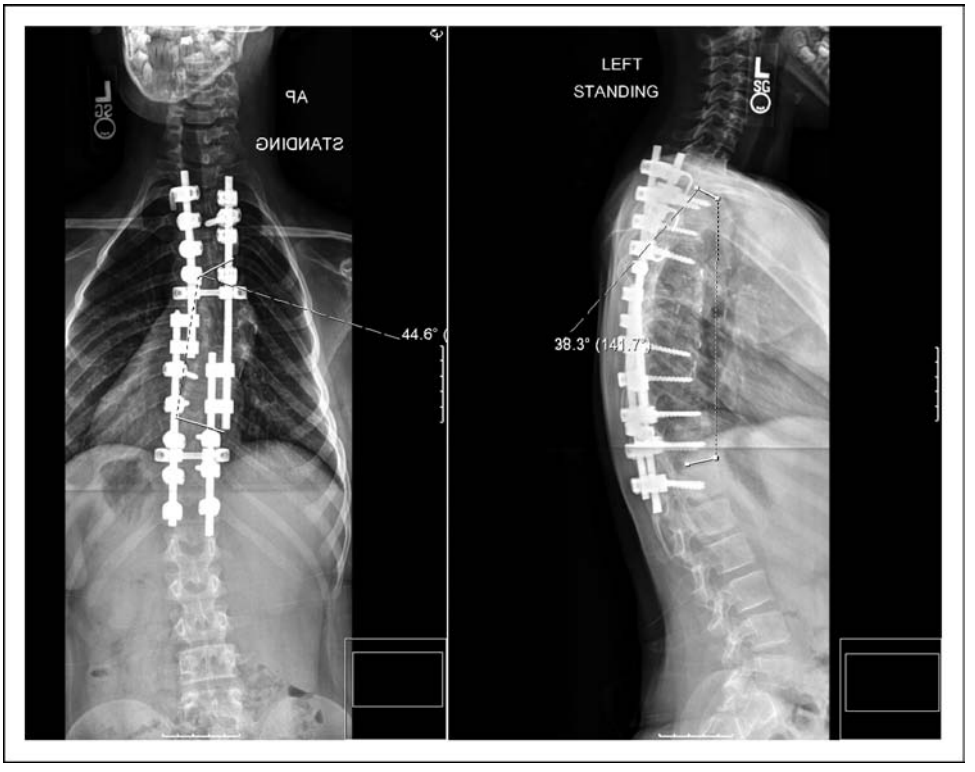


Figure 2 A radiograph surgical correction with posterior instrumentation of a dystrophic scoliosis



Cervical spine

The cervical spine deserves special attention because many patients with NF-1 will undergo general anesthesia at some point. Common cervical spine deformities include cervical kyphosis, subaxial subluxation and atlantoaxial instability [22]. Cervical kyphosis is most commonly iatrogenic, resulting from prior laminectomy for decompression of nerve sheath tumors. It is recommended that all patients with NF-1 have routine cervical spine radiographs prior to general anesthesia in order to avoid cervical cord injury. Routine clinical screening should also be used to rule out torticollis and neurofibromas of the neck [22]. Rarely, skull base pathology may be suspected in patients with NF-1 and velopharyngeal insufficiency. This is a speech disorder attributed to abnormal nasal flow during speech secondary to brainstem tumors. Forty-six per cent of patients with this speech abnormality had brain stem tumors in one study [8•].

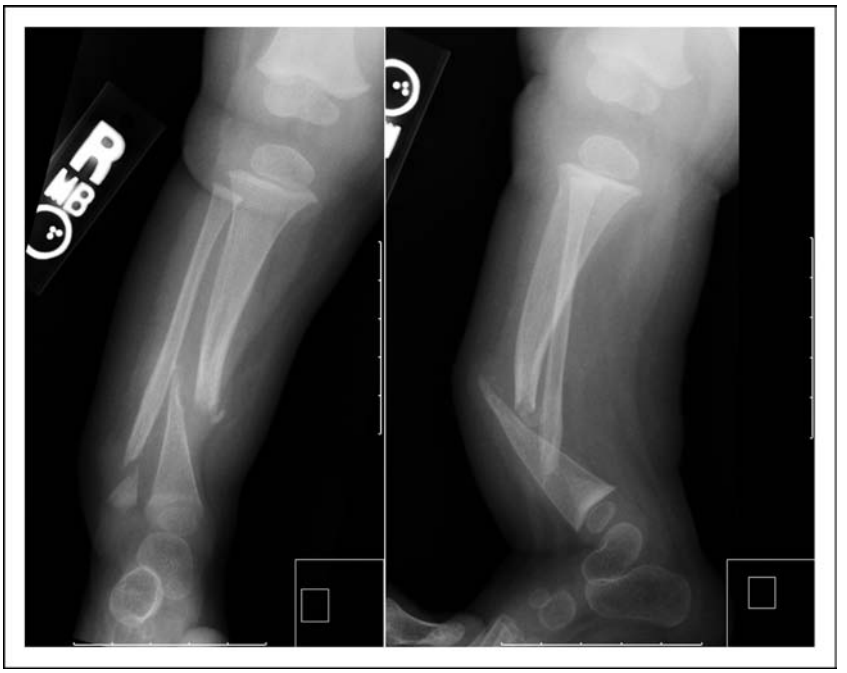
Intraspinal pathology

Intraspinal pathology in NF-1 may include neurofibromas which straddle the neural foramina and which may cause compression injuries of the nerve roots. These are commonly referred to as dumbbell lesions and may be decompressed if causing neural injury. The vertebral spinal canal is often expanded in association with thinning of the bony elements including pedicle and laminae resulting in a condition called dural ectasia. Despite the progressive osseous erosion of the vertebral canal and bodies in dural ectasia, there is a relatively low rate of neurodeficit. Presumably, this canal expansion occurs slowly, resulting in more room for the cord. A current, alternative causative hypothesis of dural ectasia is mesodermal dysplasia rather than a focal expansion of the dura from increased fluid pressure [8•].

Congenital tibial dysplasia

Characteristic anterolateral tibial bowing (describes the direction of apex of the deformity) and associated tibial dysplasia are found in 5% of patients with NF-1 [15]. In many cases, the diagnosis of NF-1 is first suspected secondary to the initial presentation of a child with anterolateral tibial bow and fracture (Fig. 3). The diagnosis of NF-1 includes 'a distinctive osseous lesion such as a sphenoid wing dysplasia or thinning of lone bone cortices, with or without pseudarthrosis' [23]. The cortices in the tibial dysplasia are thickened with small medullary canals as opposed to previous diagnostic descriptions of cortical thinning in bowing [23]. Individuals with NF-1, but without congenital tibial dysplasia, also have altered tibial anatomy as measured by cross-sections of computed tomography and compared with unaffected controls [24]. Even though congenital pseudarthrosis of the tibia is rare even in NF-1, 75% of individuals who present with this 'false joint formation of the tibia' will have NF-1 [17••]. The pathologic tissue in tibial dysplasia consists of hyperplasia of fibroblasts with formation of dense fibrous tissue. This dysplasia is a

Figure 3 A radiograph of tibial pseudarthrosis with anterolateral tibial bowing



spectrum progressing from failure of long-bone tubulation to fracture to pseudarthrosis. At the more extreme end of the spectrum is tibial nonunion.

Fractures associated with tibial dysplasia and NF-1 rarely heal spontaneously and are associated with progressive angulation, limb length deficiency and ankle instability. Although the tibia is the most common site of long-bone dysplasia and pseudarthrosis in NF-1, other bones may be affected, including the ulna, femur, clavicle, radius and humerus.

The initial treatment for dysplasia is total contact bracing to prevent fracture. Knee–ankle–foot orthoses and later ankle–foot orthoses are used through skeletal maturity in an attempt to prevent fracture. In the setting of pseudarthrosis or fracture of the dysplastic tibia, surgery is currently recommended. There are multiple surgical alternatives, but all surgical procedures include thorough excision of pseudarthrosis and fibrous tissue. After resection is completed, the limb may be reconstructed with intermedullary fixation and iliac crest bone grafting to the pseudarthrosis site using the Williams Rod technique (Fig. 4). Other alternatives include free vascularized fibula transplant to the pseudarthrosis site or limb reconstruction utilizing bone transport and Ilizarov technique with external fixation. Even after surgical stabilization, bracing is recommended until maturity. Clinical treatments on the horizon include lovastatin, for, in an NF-1 mouse model with tibial bowing, the cholesterol-lowering drug led to increased biomechanical properties of fracture callous [8•]. A case report of mesenchymal stromal cell transplant into tibial pseudarthrosis demonstrated new bone formation with increased mineral content [25].

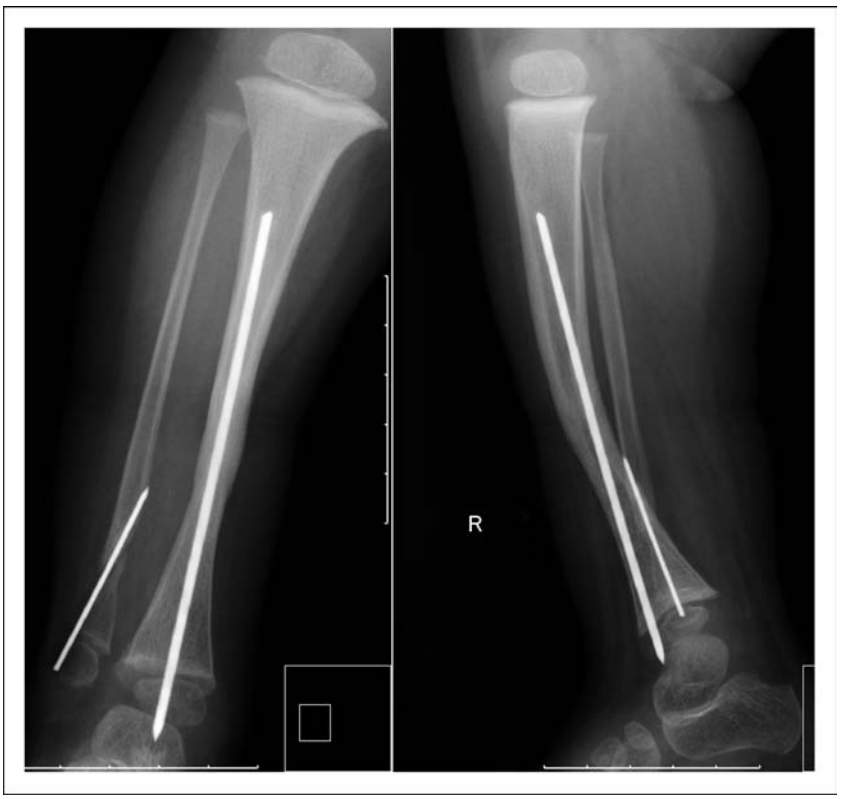
Bone mineral density

Children with NF-1 have decreased bone mineral content compared with age-matched controls in the absence of any orthopaedic issues [26]. In adults with NF-1, osteoporosis occurs earlier than the postmenopausal peak in women [8•]. Unfortunately, there are no clinical trials to support therapeutic use of bisphosphonates in NF-1, and treatment should be directed toward normalizing vitamin levels [27•].

Muscle force

A recent study found that in addition to decreased muscle cross-sectional area in limbs of individuals with NF-1, muscular force is reduced in patients with NF-1 as

Figure 4 A radiograph of tibial dysplasia treated with intermedullary fixation



compared with age, gender and activity level-matched controls [28].

Malignancy

Malignant transformation of plexiform neurofibromas to malignant peripheral nerve sheath tumors (MPNSTs) occurs in 10% of the population with NF-1 [29]. There is a high risk of mortality, with 5-year survival being 35% in NF-1 patients [29]. Negative outcomes are associated with MPNSTs greater than 10 cm, partial resection and metastasis, but even wide surgical excision with postoperative radiotherapy does not improve survival rates [29]. Case reports of malignant transformation exist when benign plexiform neurofibromas were treated with radiotherapy [8•]. Any neurofibroma with expansion, persistent pain or new neurologic deficit warrants further investigation for malignancy. Fluorodeoxyglucose positron emission tomography may be helpful in differentiating between benign plexiform neurofibromas and MPNSTs [30]. Upon biopsy, immunohistochemistry for KI-67 and S-100 is important to differentiate between benign plexiform neurofibromas and MPNSTs [31]. Neurofibromin, the product of the NF1 gene, most likely functions to decrease Ras, a signaling protein in cell growth. When neurofibromin is absent in NF-1, Ras provides unabated signaling of cell growth. One proposed mechanism is that MPNSTs are formed when a member of the Ras family of proteins, Ral, has overactivation in conjunction with activation of the phosphatase and tensin homolog (PTEN) signaling pathway [32,33].

An increased risk of other malignancies is found in patients with NF-1 [34•]. For example, a group in Birmingham, UK found an eight-fold increase in the presence of bone sarcomas in patients with NF-1 compared with the normal population [35].

Pharmacologic treatment

In vitro, Tranilast, an anti-allergic drug, was found to suppress NF-1 cell culture population, presumably through action on mast cells present in neurofibromas [2]. Also *in vitro*, a combination of farnesyl transferase and lovastatin was found to induce apoptosis and lower malignant cell numbers within an NF-1 culture [36].

Defects in neurofibromin in a mouse model have produced the same congenital tibial dysplasia and neurofibromas as in humans and are being used for various drug treatments [27•,37]. In a mouse NF-1 model with tibial bowing, lovastatin was found to reverse the downregulation of Runx2 and accelerate new bone formation [37,38]. The unique characteristic of loss of tumor suppressor genes in these mice gives insights into the development of tumorigenesis [39].

Multiple phase II clinical trials are ongoing to reduce plexiform neurofibroma tumor volume, including: Rapamycin [an inhibitor of mammalian target of rapamycin (mTOR) in the Ras pathway], tipifarnib (a farnesyl transferase inhibitor in the Ras pathway), thalidomide, pirfenidone (an antifibrotic agent), interferon, Imatinib or sorafenib, a Raf kinase [8•,27•].

Conclusion

NF-1 is one of the most common disorders of the nervous system, and most pediatricians will care for a patient with this condition. It is imperative that careful attention be paid to screening for scoliosis and tibial dysplasia. Prompt referral to an orthopaedist at the time of diagnosis, as well as a neurologist, ophthalmologist, and dermatologist, will provide a global spectrum of care for the individual. Multiple surgical procedures will be inevitable, with 70% of patients with NF-1 undergoing hospitalization or surgery [40]. As animal models improve and the clinical trials proceed, there is momentum toward eliminating the musculoskeletal morbidity associated with NF-1.

Acknowledgement

No funding has been received for this work from National Institutes of Health (NIH); Wellcome Trust; Howard Hughes Medical Institute (HHMI); or others.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 132–133).

1 Cai W, Kassarjian A, Bredella MA, *et al.* Tumor burden in patients with neurofibromatosis types 1 and 2 and schwannomatosis: determination on whole-body MR images. Radiology 2009; 250:665–673.

2 Yamamoto M, Yamauchi T, Okano K, *et al.* Tranilast, an antiallergic drug, down-regulates the growth of cultured neurofibroma cells derived from neurofibromatosis type 1. Tohoku J Exp Med 2009; 217:193–201.

3 Arbuckle HA, Morelli JG. Pigmentary disorders: update on neurofibromatosis-1 and tuberous sclerosis. Curr Opin Pediatr 2000; 12:354–358.

4 • Jett K, Friedman JM. Clinical and genetic aspects of neurofibromatosis 1. Genet Med 2010; 12:1–11.
This is a thorough review of the most recent molecular genetics and gives a comprehensive differential diagnosis for disorders that can resemble NF-1.

5 MacCollin M, Chiocca EA, Evans DG, *et al.* Diagnostic criteria for schwannomatosis. Neurology 2005; 64:1838–1845.

6 • Evans DG. Neurofibromatosis type 2 (NF2): a clinical and molecular review. Orphanet J Rare Dis 2009; 4:16.
This article gives a list of features associated with NF-2 and is the most comprehensive review to date.

7 Plotkin SR, Stemmer-Rachamimov AO, Barker FG 2nd, *et al.* Hearing improvement after bevacizumab in patients with neurofibromatosis type 2. N Engl J Med 2009; 361:358–367.

8 • Kissil JL, Blakeley JO, Ferner RE, *et al.* What's new in neurofibromatosis? Proceedings from the 2009 NF Conference: new frontiers. Am J Med Genet A 2010; 152A:269–283.
This is a review of the most recent data on clinical trials, including many that are not even published yet.

9 Ferner RE, Huson SM, Thomas N, *et al.* Guidelines for the diagnosis and management of individuals with neurofibromatosis 1. J Med Genet 2007; 44:81–88.

10 DeBella K, Szudek J, Friedman JM. Use of the national institutes of health criteria for diagnosis of neurofibromatosis 1 in children. Pediatrics 2000; 105:608–614.

11 Williams VC, Lucas J, Babcock MA, *et al.* Neurofibromatosis type 1 revisited. •• Pediatrics 2009; 123:124–133.
This article includes a list of the evaluation and treatment for every feature of NF-1.

12 Mautner VF, Hartmann M, Kluwe L, *et al.* MRI growth patterns of plexiform neurofibromas in patients with neurofibromatosis type 1. Neuroradiology 2006; 48:160–165.

13 Dombi E, Solomon J, Gillespie AJ, *et al.* NF1 plexiform neurofibroma growth rate by volumetric MRI: relationship to age and body weight. Neurology 2007; 68:643–647.

14 Friedrich RE, Schmelzle R, Hartmann M, *et al.* Resection of small plexiform neurofibromas in neurofibromatosis type 1 children. World J Surg Oncol 2005; 3:6.

15 Crawford AH, Schorry EK. Neurofibromatosis update. J Pediatr Orthop 2006; 26:413–423.

16 Durrani AA, Crawford AH, Chouhdry SN, *et al.* Modulation of spinal deformities in patients with neurofibromatosis type 1. Spine (Phila PA 1976) 2000; 25:69–75.

17 Feldman DS, Jordan C, Fonseca L. Orthopaedic manifestations of neurofi-•• bromatosis type 1. J Am Acad Orthop Surg 2010; 18:346–357.
This article highlights the treatments for many of the orthopaedic components of NF-1.

18 Funasaki H, Winter RB, Lonstein JB, *et al.* Pathophysiology of spinal deformities in neurofibromatosis: an analysis of seventy-one patients who had curves associated with dystrophic changes. J Bone Joint Surg Am 1994; 76:692–700.

19 Winter RB, Moe JH, Bradford DS, *et al.* Spine deformity in neurofibromatosis: a review of one hundred and two patients. J Bone Joint Surg Am 1979; 61:677–694.

20 Parisini P, Di Silvestre M, Greggi T, *et al.* Surgical correction of dystrophic spinal curves in neurofibromatosis: a review of 56 patients. Spine (Phila PA 1976) 1999; 24:2247–2253.

21 Koptan W, ElMiligui Y. Surgical correction of severe dystrophic neurofibromatosis scoliosis: an experience of 32 cases. Eur Spine J 2010; 19:1569–1575.

22 Yong-Hing K, Kalamchi A, MacEwen GD. Cervical spine abnormalities in neurofibromatosis. J Bone Joint Surg Am 1979; 61:695–699.

23 Stevenson DA, Carey JC, Viskochil DH, *et al.* Analysis of radiographic characteristics of anterolateral bowing of the leg before fracture in neurofibromatosis type 1. J Pediatr Orthop 2009; 29:385–392.

24 Stevenson DA, Viskochil DH, Carey JC, *et al.* Tibial geometry in individuals with neurofibromatosis type 1 without anterolateral bowing of the lower leg using peripheral quantitative computed tomography. Bone 2009; 44:585–589.

25 Tikkanen J, Leskela HV, Lehtonen ST, *et al.* Attempt to treat congenital pseudarthrosis of the tibia with mesenchymal stromal cell transplantation. Cytotherapy 2010; 12:593–604.

26 Dulai S, Briody J, Schindeler A, *et al.* Decreased bone mineral density in neurofibromatosis type 1: results from a pediatric cohort. J Pediatr Orthop 2007; 27:472–475.

27 Elefteriou F, Kolanczyk M, Schindeler A, *et al.* Skeletal abnormalities in • neurofibromatosis type 1: approaches to therapeutic options. Am J Med Genet A 2009; 149A:2327–2338.
This article highlights the most recent basic science research in NF-1 and the various mouse models available. The most recent treatments for NF-1 manifestations are also reviewed.

28 Souza JF, Passos RL, Guedes AC, *et al.* Muscular force is reduced in neurofibromatosis type 1. J Musculoskelet Neuronal Interact 2009; 9:15–17.

29 Zou C, Smith KD, Liu J, *et al.* Clinical, pathological, and molecular variables predictive of malignant peripheral nerve sheath tumor outcome. Ann Surg 2009; 249:1014–1022.

30 Ferner RE, Golding JF, Smith M, *et al.* [18F]2-fluoro-2-deoxy-D-glucose positron emission tomography (FDG PET) as a diagnostic tool for neurofibromatosis 1 (NF1) associated malignant peripheral nerve sheath tumours (MPNSTs): a long-term clinical study. Ann Oncol 2008; 19:390–394.

31 Perry A, Roth KA, Banerjee R, *et al.* NF1 deletions in S-100 protein-positive and negative cells of sporadic and neurofibromatosis 1 (NF1)-associated plexiform neurofibromas and malignant peripheral nerve sheath tumors. Am J Pathol 2001; 159:57–61.

32 Bodempudi V, Yamoutpoor F, Pan W, *et al.* Ral overactivation in malignant peripheral nerve sheath tumors. Mol Cell Biol 2009; 29:3964–3974.

33 Gregorian C, Nakashima J, Dry SM, *et al.* PTEN dosage is essential for neurofibroma development and malignant transformation. Proc Natl Acad Sci U S A 2009; 106:19479–19484.

34 Yohay K. Neurofibromatosis type 1 and associated malignancies. Curr Neurol • Neurosci Rep 2009; 9:247–253.
The differential diagnosis of malignancies associated with NF-1, the treatment of optic gliomas and the risk of several tumors in NF-1 are presented.

35 Chowdhry M, Hughes C, Grimer RJ, *et al.* Bone sarcomas arising in patients with neurofibromatosis type 1. J Bone Joint Surg Br 2009; 91:1223–1226.

36 Wojtkowiak JW, Fouad F, LaLonde DT, *et al.* Induction of apoptosis in neurofibromatosis type 1 malignant peripheral nerve sheath tumor cell lines by a combination of novel farnesyl transferase inhibitors and lovastatin. J Pharmacol Exp Ther 2008; 326:1–11.

37 Kolanczyk M, Kuhnisch J, Kossler N, *et al.* Modelling neurofibromatosis type 1 tibial dysplasia and its treatment with lovastatin. BMC Med 2008; 6:21.

38 Wang W, Nyman JS, Moss HE, *et al.* Local low-dose lovastatin delivery improves the bone-healing defect caused by Nf1 loss of function in osteoblasts. J Bone Miner Res 2010; 25:1658–1667.

39 Parrinello S, Lloyd AC. Neurofibroma development in NF1: insights into tumour initiation. Trends Cell Biol 2009; 19:395–403.

40 Wolkenstein P, Durand-Zaleski I, Moreno JC, *et al.* Cost evaluation of the medical management of neurofibromatosis 1: a prospective study on 201 patients. Br J Dermatol 2000; 142:1166–1170.