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A Rare Case of Massive NF1 with Invasion of Entire Spinal Axis by Neurofibromas: Case Report

Tüm Spinal Kanalın Nörofibromalar ile Tutulduğu Nadir Görülen Masif NF1 Olgusu: Olgu Sunumu

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ABSTRACT

Neurofibromatosis type-1 (NF1) is a type of phakomatosis inherited in an autosomal dominant fashion. Also called 'von Recklinghausen disease' or 'peripheral neurofibromatosis', it comprises 90% of all neurofibromatosis (NF) cases. It is characterized by multiple peripheral nerve sheath tumors of benign character called neurofibromas. Surgical intervention is indicated when myelopathy and motor losses develop in the case of paraspinal neurofibromas, which are frequently localized to the cervical and lumbar regions. The level of surgical intervention required should be carefully considered and should take into account neurophysiological tests of paraspinal neurofibroma cases that allow estimation of the risk that the neurofibromas will invade the complete spinal axis. The best results are obtained with patients showing minimal neurological deficits during the pre-operative period. Little improvement may be expected from the patients who develop complete transection syndrome during the postoperative period. In the present paper, we discuss an NF1 case in which paraspinal neurofibromas were observed along the complete spinal axis of a 32-year-old male patient who arrived at the clinic reporting increasingly intense pins and needles and weakness. We discuss the patient's diagnosis, treatment, and prognosis, and relate this case to the literature.

KEY WORDS: Dumbbell tumour formation, Massive neurofibromatosis, Multiple neurofibromatosis, Nerve sheath tumor, Neurofibromatosis type-1, Surgical approach

ÖZ

Nörofibromatozis tip-1 (NF1) otozomal dominant geçişli bir fakomatoz tipidir. 'von Recklinghausen hastalığı' veya 'periferal nörofibromatozis' olarak da adlandırılır. Tüm nörofibromatozis (NF) olgularının %90'ını oluşturur. Nörofibroma adı verilen benign karakterli, multipl periferik sinir kılıfı tümörü ile karakterizedir. Sıklıkla servikal ve lomber bölgede lokalize olan paraspinal nörofibroma olgularında; miyelopati ve motor kayıplar geliştiğinde cerrahi tedavi düşünülmektedir. NF1'in penetrasyon derecesine bağlı olarak gelişen ve tüm spinal aksı tutan paraspinal nörofibroma olgularında; hangi düzeyde cerrahi girişim uygulanması gerektiği, ameliyat öncesi yapılacak nörofizyolojik testlerle beraber dikkatle değerlendirilmelidir. En iyi sonuçlar, preoperatif devrede minimal nörolojik defisiti olan hastalarda alınırken, komplet transseksiyon sendromu gelişen hastalarda bile postoperatif devrede bir miktar düzelme beklenebilir. Biz bu bildiride; 1 aydır kol ve bacaklarında giderek artan uyuşma ve güçsüzlük şikayetiyle başvuran 32 yaşında, erkek hastada saptanan, tüm spinal aks boyunca paraspinal nörofibromaların gözlendiği NF1 olgusunu; tanı, tedavi ve prognoz açısından literatür eşliğinde tartıştık..

ANAHTAR SÖZCÜKLER: Cerrahi yaklaşım, Kum saati şeklinde tümör, Masif nörofibromatozis, Multipl neurofibromatozis, Nörofibromatozis tip-1, Periferik sinir kılıfı tümörü

INTRODUCTION

NF1 is the most frequently-observed phakomatosis, with a frequency of occurrence of approximately 1 in 3300. Half of the cases occur via autosomal dominant inheritance, and the rest occur as a result of spontaneous mutations. The NF1 gene is located on chromosome 17 and encodes a protein called neurofibromin, which functions as a tumor suppressor (7,9,15). Tumoral formations observed in NF1 occur due to mutations in this gene (31). Despite advances in molecular genetics, diagnosis of NF1 still depends on clinical criteria. The diagnostic criteria were established at the National Institutes of Health (NIH) Consensus Development Conference in 1987 (17) (Table I). The present paper examines the diagnosis, treatment, and prognosis of paraspinal neurofibromas showing complete spinal axis invasion in a 32-year-old male patient diagnosed with NF1.

CASE REPORT

A 32-year-old male patient, who was diagnosed with NF1 according to the NIH criteria, arrived at our clinic with complaints of progressively increasing weakness developing first in the legs and then in the arms, pins and needles in the hands, and constipation. Systematic examination of the patient, who had no family history of NF1, showed him to be normal. Dermatological examination revealed the following: widespread, hyperpigmented macular lesions (freckling), light brown in color and with dimensions varying between 1 and 7 mm in the axillary and inguinal regions; 15 brown macular lesions with sharp borders (cafe au lait) on the back, abdomen, arms and legs, varying between 1.5 and 4 cm; and 5 subcutaneous nodular lesions of millimeter size in the waist region. Lisch nodules were not detected during examination of the eye with a slit lamp.

Table I : Neurofibromatosis type-1 diagnosis criteria

1. The presence of six or more cafe au lait macules 5 mm or more in size during prepuberty, or 15 mm or more in size during postpuberty.
2. The presence of two or more neurofibromas of any type, or the presence of one plexiform neurofibroma.
3. The presence of freckling in the axillary and inguinal regions.
4. The presence of optic glioma.
5. The presence of two or more Lisch nodules (iris hamartoma).
6. The presence of bone anomalies, such as long bones with thin cortex without arthrosis, together with sphenoid aplasia or pseudo-arthrosis.
7. The presence of NF1 diagnosis in first-degree relatives according to the diagnosis criteria written above.

- Two or more of the above points should be present in the cases diagnosed with NF1.

Tongue facilitation and distal-weighted spastic quadriparesis were identified during neurological examination of the patient. Atrophy was sporadically present in the upper-extremity muscles. Reflexes were brisk, Hoffmann's reflex was (+/+), and widespread myokymia was detected. Bilateral foot drop was present in the lower extremities, and reflexes were vivid. Babinski's reflex was evaluated as insignificant on the left, and (+) on the right. The patient had an ataxic gait. A lesion of millimeter dimensions displaying no contrast enhancement in the subcortical area in the left frontal region was found to be hypointense on T1-weighted series and hyperintense on T2-weighted and FLAIR series in MRI scans of the brain (Figure 1A, B). Multiple massive lesions, consistent with plexiform neurofibroma located paraspinally, were observed in MRI scans of the spinal axis to have caused neural foraminal extension by filling all cervical, thoracic, lumbar, and sacral neural foramen; the lesions appeared hypointense on T1 sequences and hyperintense on T2 sequences, with heterogenous insignificant contrast enhancement (Figure 2A,B,C,D,E). The mass filling in the epidural space was determined to have caused significant cord compression at the C4-5 level (Figure 3A,B). However, multiple massive lesions located in the paravertebral area at thoracic levels had not caused epidural extension or cord compression (Figure 2B,C). At the lumbar level, massive intradural lesions in multiple numbers had caused scalloping at L3 and L5 vertebral posterior regions and were linked to intraabdominal dumbbell tumor formation (Figure 2D,E). Multiple, massive lesions that had caused scalloping at the posterior parts of the sacral vertebrae were detected (Figure 2D,E). On the EMG, spontaneous muscle fiber activity (myokymia) was

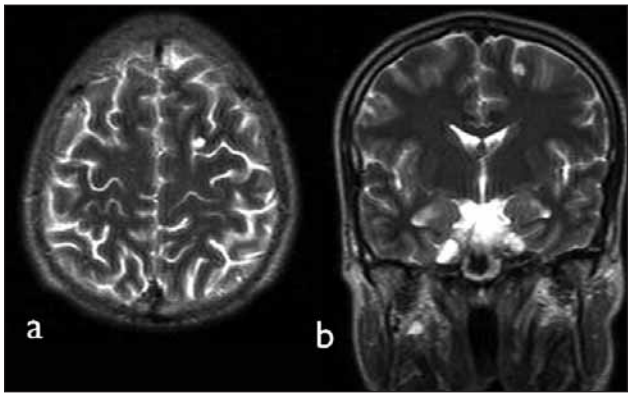

Figure 1: *A hyperintense lesion of millimeter dimensions displaying no contrast enhancement in the subcortical area in the left frontal region was detected in a preoperative, T2-weighted MRI scan of the patient's brain (**A**) in the transverse plane and (**B**) in the coronal plane.*

reported in addition to neurogenetic variations in C5, C7, L3, and L4 innervated muscles.

Patient was operated by posterior cervical approach. Partial resection was performed to C3 level and total resection was performed to C4, C5 and C6 levels. Two tumoral masses through which rootlets passed and caused marked spinal cord compression at C4-5 and C5-6 levels could be excised by partial resection in order to achieve decompression. In partial resection, intradural component of tumor is completely removed while foraminal and extradural components are left (Figure 3C, D). Neurological examination performed at the early postoperative period revealed partial improvement compared to preoperative period.

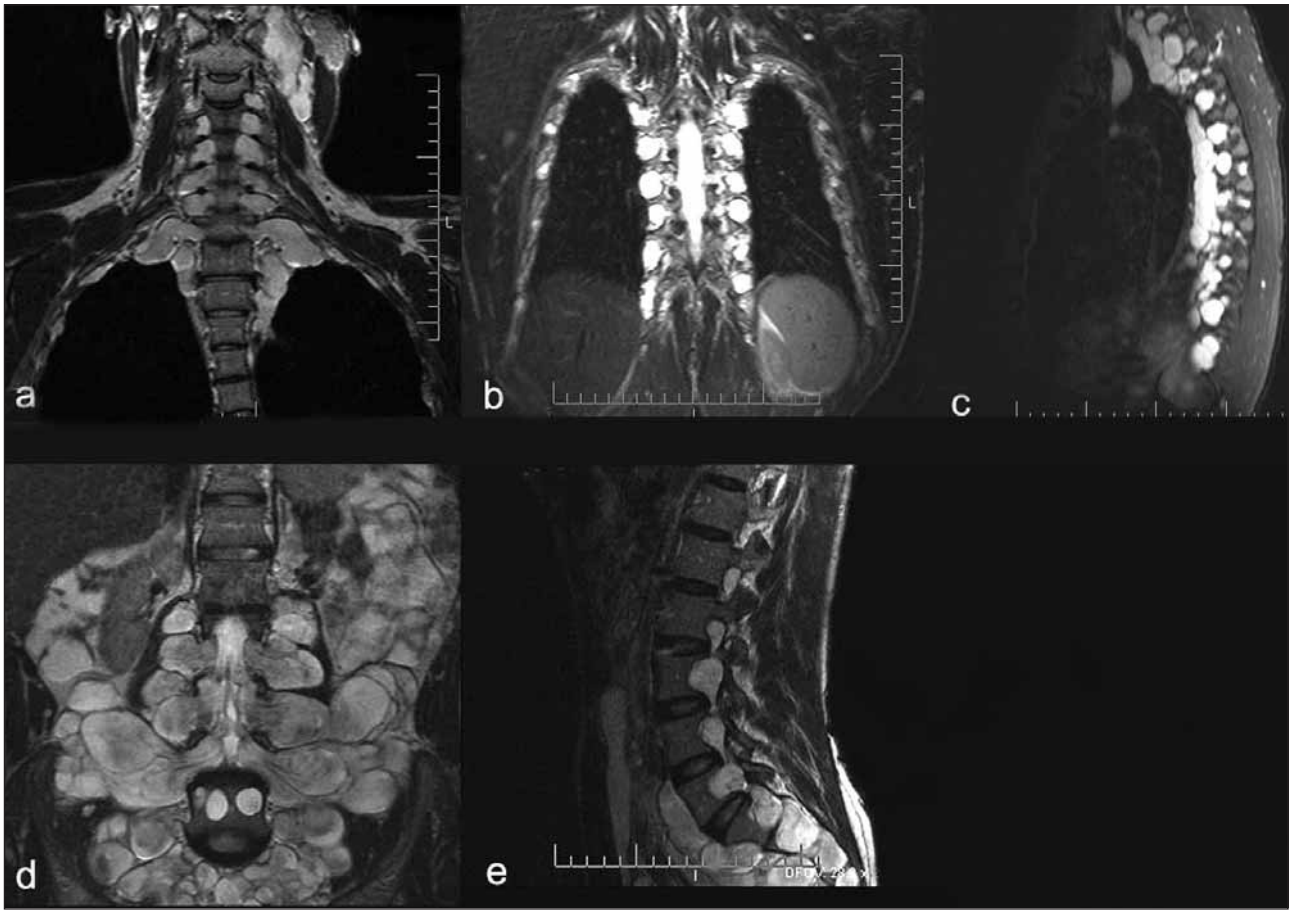

Figure 2: *Preoperative, T2-weighted MRI scan of the patient's spinal axis, revealing mutiple, massive, hyperintense lesions displaying heterogonous insignificant contrast enhancement in the paraspinal region. These lesions caused neural foraminal extension by filling all cervical and thoracic neural foramen; they were detectable (**A**) in the coronal plane in the cervical region, (**B**) in the coronal plane in the thoracic region, and (**C**) in the sagittal plan in the thoracic region. (**D**) View of the coronal plane in the lumbosacral region, showing intra-abdominal dumbbell tumor formation due to multiple, massive, hyperintense lesions causing neural foraminal extension through filling of all neural foramen. The lesions were located paraspinally and showed heterogenous insignificant contrast enhancement. (**E**) Multiple, massive lesions causing scalloping at the posterior parts of the L3 and L4 sacral vertebrae and in the posterior parts of the sacral vertebrae were detected in the lumbo-sacral region of the sagittal plan.*

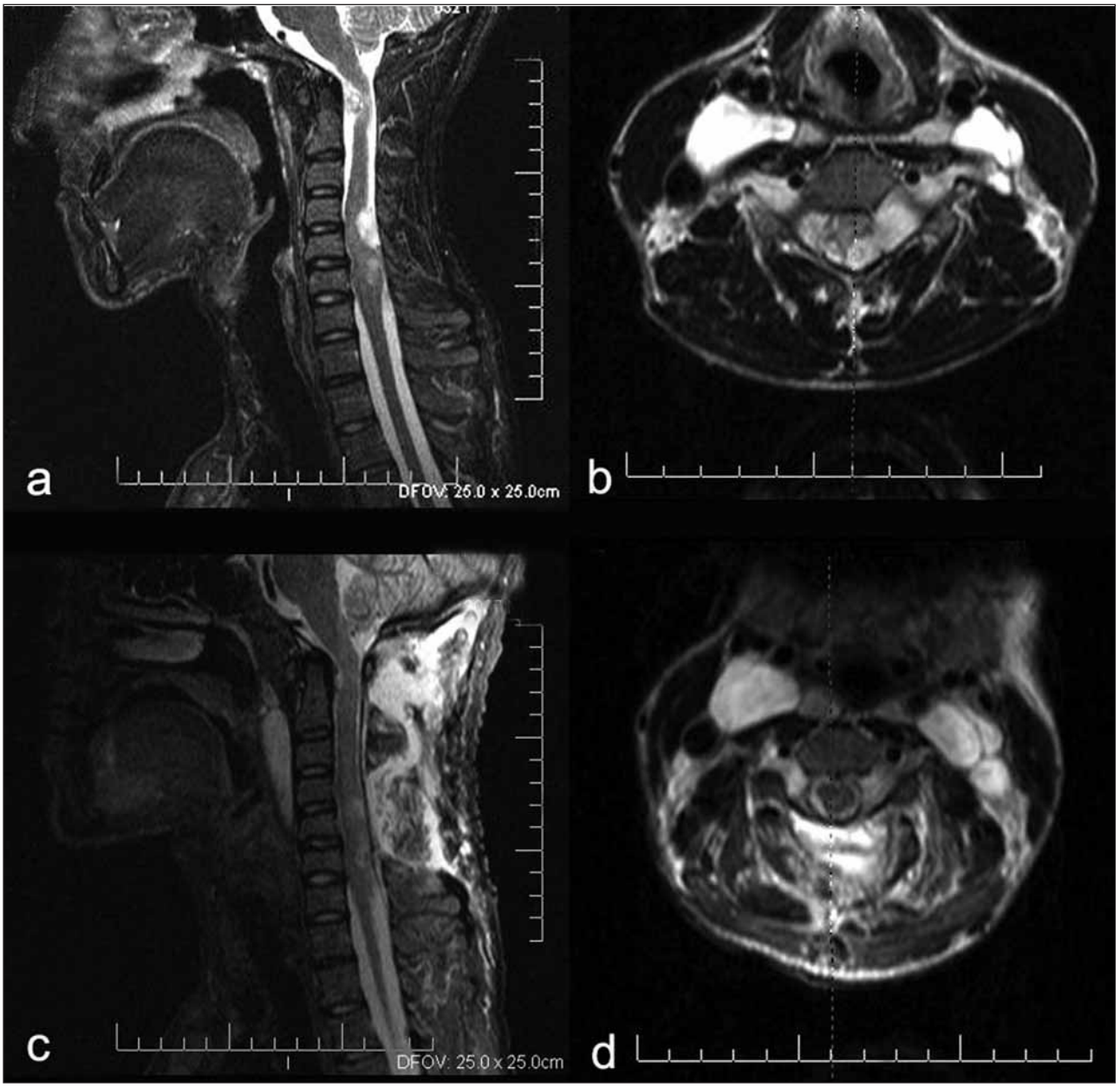

Figure 3: *Detection of a massive, hyperintense lesion, located paraspinally and displaying heterogenous insignificant contrast enhancement, that was causing significant cord compression at the C4-5 level by filling in the epidural distance. The lesion was visible in preoperative MRI scans of the patient's cervicospinal area: (**A**) T2 sagittal sequence, (**B**) T2 axial sequence. After surgical intervention, removal of the lesions was confirmed in (**C**) a T2-weighted sagittal sequence and (d) a T2-weighted axial sequence.*

Muscle strength was 4+/5 at the proximal, and 2/5 at the distal part of the upper extremity and 4+/5 at the proximal and 2/5 at the distal part of the lower extremity.

Physical rehabilitation and myorelaxants were used after surgical intervention. After discharge of the patient, monthly follow-ups were performed by clinical and radiological evaluation. Spinal MRI of the patient performed 1 month after operation proved that mass lesions in the posterior epidural space of C4-5 and C5-6 levels were successfully removed and compression of spinal cord was relieved. Neurological examination at the postoperative 4th month showed marked improvement of the muscle strength of the distal part of the upper and lower extremity (proximal grade: 5/5, distal grade: 4/5). Deep tendon reflexes were hypoactive, Hoffmann reflex was (-/-) and

Babinski reflex was (-/-). Patient was able to better walk after resolution of spasticity and drop-foot.

DISCUSSION

NF1 was defined for the first time by Freidrich von Recklinghausen in 1882. A majority (71%) of the cases have a family history, and the frequency of occurrence is reported to be 1 in 3300. The NF1 gene is found on chromosome 17 and encodes a protein called neurofibromin, which is a tumor suppressor. Mutations in this gene can result in decreases of this protein by different amounts, leading to development of different types of NF and to the various tumoral lesions seen in NF. Watson syndrome, NF-Noonan syndrome and segmental NF1 are accepted as NF1 variants (8,9,25,31).

Despite advancements in molecular genetics, diagnosis in NF1 depends on clinical criteria. 'Cafe au lait' spots are seen in 95% of patients, and axillary and inguinal freckling is observed in 70% of adult patients with NF1. Both types of spots were detected in our patient as well. They may occur either before or after birth (9,21).

The Lisch nodule, or melanocystic hamartoma in the iris, in the most frequently seen ophthalmologic feature in NF and is observed in 95% of cases. Nevertheless, it was not detected in our patient. In the slit lamp examination, these nodules appear as small, yellowish-brown dome-like lesions located superficially on the iris. Another optic feature seen in NF is optic glioma, which is an optic nerve pilocytic astrocytoma located in the prechiasmatic area. Observed in 15% of NF patients, it was not detectable in our patient. Though most gliomas are asymptomatic, they may cause visual field defects, diplopia, and ptosis. These two eye conditions are among the important diagnostic criteria for NF (3,19).

Cognitive disorders can also be observed in NF, including communication disorders (50% of cases), learning disorders (25%), and mental retardation (8.4%). Hyperdense lesions with significant borders on T2-weighted MRI, called 'NF1 bright objects', are thought to be responsible for these disorders. These lesions, most of which disappear during puberty, have been reported in 43%-93% of patient MRI series, including in the cerebellum, pons, internal capsule, basal ganglia, and white matter. In the case of our patient, a bright object was observed in the subcortical area in the left frontal region (23,26).

NF1 is accompanied by bone lesions of various types, such as head asymmetry, parieto-occipital defects, sphenoid wing aplasia, sella distortion, and expansions of the ipsilateral orbita. The short stature of our patient is consistent with the GH deficiency and early puberty related to NF. The macroglossia, macrocephalia, and specific mandibular anomalies detected in our patient were also related to NF (9,15,25).

Vertebral bone anomalies develop independently of spinal and paraspinal neurofibromas. The scoliosis detected in our patient is the most frequently seen skeleton deformity, often observed in the cervicothoracic junction. Its rapid progression may lead to neurological deficits. Moreover, scalloping of the dorsal aspect of the vertebral bones, which was detected in our patient and in 10% of all NF cases, should always evoke the possibility of an NF1 diagnosis (5,10).

Neurofibromas are one of the major characteristics of NF1. They can develop from the Schwann cells or fibroblasts of any peripheral nerve. More rarely, schwannoma, menengioma, and astrocytoma from other spinal tumors are observed. Single or multiple skin neurofibromas are observed in more than 95% of cases. Plexiform neurofibromas, occurring in 30% of cases, are multiple neurofibromas with diffuse neural expansion along the peripheral nerve (10,13,23,30).

Nodular neurofibromas may occur anywhere on the peripheral nerves. They frequently originate in the dorsal roots and invade the sensorial branches. They have a round and flexible structure with a capsule. Of the paraspinal neurofibromas, 72% occur in the intradural extramedullar region, whereas 14% are extradural, 13% show a dumbbell formation, and 1% occur in the intramedullary region (10,13,14).

Neurofibromas in the spinal canal are frequently seen to invade the peripheral segment of the nerve by extending out of the intervertebral foramen and developing a dumbbell tumor. In these dumbbell neurofibromas, the extraspinal part is usually larger than the intraspinal ones. Dumbbell formation is important, especially because the part located in the extramedullary canal attaches to the surrounding tissues. Extremely large tumors have lobular structures and may show cystic degeneration. Tumors extending into the chest cavity,

retroperitoneally, and subcutaneously have been reported. In our patient, dumbbell tumor formation was detected in the abdominal region. Such abdominal tumors can cause serious respiratory problems if they compress the lung parenchyma and airways. As reported in other cases, our patient showed intra-abdominal organ compression and he complained of constipation, which responded to the surgical intervention (4,12,32,34).

Rare cases of huge neurofibromas with unusual localization have been reported in the literature. These include huge neurofibromas at the head and neck region that frequently cause cosmetic problems; presacral huge solitary neurofibromas that cause pelvic compression; huge neurofibromas of the scalp that cause a lambda defect and huge lumbosacral neurofibromas that compress surrounding tissues by extension to the retroperitoneal region. A retroperitoneal huge neurofibroma removed from a 71-year-old female has been reported to weigh 7 kg. The importance of neuroradiological imaging has been emphasized for all of these cases that have tumors with an unusual localization. It is recommended to surgically remove neurofibromas that disturb the appearance of the patient or that cause loss of function due to compression on the surrounding tissues (2,16,20,29,33).

Neurofibromas can arise in any time of life but they are less frequent before puberty. The number of neurofibromas may range from a few to hundreds or even thousands in adults. Although they are observed in any age, the rate of occurrence may change year by year. The largest number of unusual cases of massive NF1 has been reported from Japan in 1992. In these 24 cases of NF1, multiple brain tumors of different histological types (meningioma and neurofibroma) were found to be associated with spinal tumors. All spinal tumors were intradural and extramedullary; and localized on different parts of spinal canal (22). A study on 53 children with NF1 conducted in 2003 showed the incidence of localized cutaneous neurofibroma and massive soft tissue neurofibroma as 71.4% and 28.6% respectively among 7 patients with spinal neurofibroma, whereas these figures were 39.1% and 8.7% respectively in 46 patients without spinal neurofibroma (11). An article published in 1999 has described a neurofibroma originating from the brachial plexus that involved the right hemithorax, base of skull, spinal cord and cervical vertebra and the importance of multidisciplinary approach for surgical treatment was stressed (18). The natural progress of 7 children with NF1 from Canada and their treatment alternatives have been reviewed in 2007. Biopsy was performed in two patients, medical treatment was employed in 2 patients (farnesyl transferase inhibitor, R11577 and cyclophosphamide chemotherapy) and surgical debulking was preferred in 3 patients due to the enormous size of tumor. One patient died due to progressive expansion of tumor causing respiratory distress. As a result, the preferred treatment method for these complex lesions has not been clearly defined, but a conservative approach (neuroradiological and clinical follow-up) is recommended in slowly growing lesions whereas surgical treatment may be needed in selected cases that suffer from loss of function due to compression of an organ (24). Unusual localizations for massive neurofibroma such as hard palate or orbita have been reported. Optimal treatment cannot be defined due to differences in the natural progress and surgical treatment is usually delayed (1,27).

Clinical symptoms develop as a result of local compression of the ventral or motor nerve roots. Root symptoms develop during the early period, while long tract symptoms develop during the late periods. Cervical and lumbar regions are more frequently invaded. Radicular pain and dysesthesia are present in 80% of NF cases. The motor weakness that we observed in our patient is seen in approximately 10% of cases (4,13,14).

Anomalies detected in the direct graphs are suitable for diagnosis in 50% of cases. The most frequently reported findings in direct graphs are pedicule erosion and scalloping in the vertebra body. Regular expansion of the interpedicular distance and the intervertebral foramen may directly indicate the presence of the dumbbell tumor (4,10,30).

The specificity and sensitivity of MRI make it quite valuable for detecting the extent of NF and any accompanying pathologies, and for following the development of complications. Neurofibromas give iso- or hyperintense images of the spinal cord in T1 sequences, while they give hyperintense images in T2 sequences. Dumbbell neurofibromas enhance the contrast regularly as soon as gadolinium is administered. The complete neural axis should be scanned with contrast MRI in order to detect asymptomatic tumors as well (13,26,30).

No treatment is needed for asymptomatic cases of neurofibroma. Symptomatic cases justify surgical treatment. Indication is easily established in simple-localized neurofibroma cases (22,23). The decision for surgery and the surgical approach is quite complex for massive NF1 cases in which neurofibromas occupy the entire spinal axis as in our case. The most important decision in this regard is the site of surgery. The entire spinal axis should be screened by advanced radiological imaging such as MRI to determine the symptomatic region (myelopathy and/or radiculopathy) and supported by neurophysiological studies such as electromyography (EMG) and somatosensorial evoked potentials (SEP). If these examinations reveal one lesion or multiple lesions that are close to each other as in our patient, all may be removed at one session. In cases with multiple neurofibromas apart from each other, sequential surgery may be performed considering the symptomatic region.

In cases with dumbbell neurofibromas, majority of the nerve fibers are entrapped within tumoral tissue as we have observed during the surgery of our case. It is impossible to remove the tumor without sacrificing the nerve root and aggressive surgery may lead to severe neurologic deficits. Thus partial resection should be preferred in cases of multiple dumbbell neurofibromas that cause compression. (22,23) As aim of partial resection is to resolve the symptoms, extent of surgical treatment is shaped according to clinical picture of the patient. Our patient had myelopathic findings, thus decompressive excision of tumor was planned. In decompression surgery; intradural component of the tumor that compress spinal cord is excised but foraminal and extradural component is retained. Decompression surgery is particularly required for dumbbell neurofibroma cases that suffer from spinal cord compression at multiple levels. Decompression surgery is a partial resection that comprises the risk of recurrence and repeated surgery may be needed.

The best results are obtained in patients with minimal neurological deficit at the preoperative period, but a certain amount of postoperative improvement can be expected even in patients with complete transection syndrome. The distal dominant quadriparesia showed significant improvement in our patient. The patient managed to walk after resolution of spasticity and drop-foot. Patients must be supported by physical rehabilitation and myorelaxant agents should be administered during the postoperative period. Indications for postoperative radiotherapy are limited. (22,23)

The prognosis is excellent after surgical resection in simple-localized neurofibroma cases. Pain diminishes in 80% where complete remission is achieved in 60% of the cases. Symptoms of the patient should be addressed by stepwise decompressive surgery in massive NF1 cases characterized by multiple spinal neurofibromas. Virtually no recurrence is observed after total resection of simple-localized neurofibroma cases. Levy et al. observed recurrence in only one of 66 patients with paraspinal neurofibroma 3 years after treatment. Massive NF1 cases characterized by dumbbell neurofibromas as in our case are treated by partial resection, and therefore have a risk of recurrence. It is crucial to screen all the spinal axis in these patients by advanced imaging modalities such as MRI to detect recurrence and also the development of new neurofibromas (21,24).

CONCLUSION

The surgical treatment of neurofibromas involves their total removal. Since neurofibromas are commonly of root origin, this root must be found, dissected, or resected if necessary (10,14,30). The level of surgical intervention required should be carefully evaluated together with the neurophysiological tests in all paraspinal neurofibroma cases developing due to the degree of penetration of NF1 and invasion of the complete spinal axis. The best results are obtained with patients showing minimal neurological deficits during the preoperative period. Little improvement may be expected from patients who develop complete transection syndrome during the postoperative period.

REFERENCES

1. Baden E, Fischer RJ: Multiple neurofibromatosis and neurofibroma of the palate: report of a case. Oral Surg Oral Med Oral Pathol 16: 1356-1364, 1963
2. Bhatia S, Khosla A, Dhir R, Bhatia R, Banerji AK: Giant lumbosacral nerve sheath tumors. Surg Neurol 37: 118-122, 1992
3. Broniscer A, Gajjar A, Bhargava R, Langston JW, Heideman R, Joner D, Kun LE, Taylor J: Brain stem involvement in children with neurofibromatosis type 1: Role of magnetic resonance imaging and spectroscopy in the distinction from pontine diffuse glioma; Neurosurgery 40: 331-338, 1997
4. Canbaz B, Tanriverdi T: Norofibromatozis. Aksoy K, Palaoglu S, Pamir N and Tuncer R (eds), Temel Norosirurji, Ankara; 2005: 823-829

5. Chapparo MJ, Young RF, Moyra S, Shen V, Choi BH: Multiple spinal meningiomas: A case of 47 distinct lesions in the absence of neurofibromatosis or identified chromosomal abnormality ; Neurosurgery 32: 298-302, 1993
6. Guillamoj S, Creange A, Kalifa C, Gril J, Rodriquez D, Doz F, Barbarot S, Zerah M, Sanson M, Bastuji-Garin S, Wolkenstein P: Prognostic factors of CNS tumours in neurofibromatosis 1 (NF 1): A retrospective study of 104 patients; Brain 126: 152-160, 2003
7. Gutmann DH, Aylsworth A, Carey JC, Korf B, Marks J, Pyeritz RE, Rubinstein A, Viskochil D: The diagnostic evaluation and multidisciplinary management of nerofibromatosis 1 and neurofibromatosis 2. JAMA 278: 51-57, 1997
8. Gutmann DH: The neurofibromatoses : when less is more; Human Molecular Genetics 10(7): 152-160, 2001
9. Hirsch NP, Murphy A, Radcliffe JJ. Neurofibromatosis: Clinical presentations and anaesthetic implications. Br J Anaesth 86: 555-564, 2001
10. Keles E, Ozer AF: Intrameduller ve ekstrameduller omurilik tumorleri. Zileli M, Ozer AF (eds), Omurilik ve Omurga Cerrahisi, Izmir: 2002: 1113-1119
11. Khong PL, Goh WH, Wong VC, Fung CW, Ooi GC: MR imaging of spinal tumors in children with neurofibromatosis 1. AJR Am J Roentgenol 180: 413-417, 2003
12. Kloos RT, Rufini V, Gross MD, Shapiro B. Bone scans in Neurofibromatosis: Neurofibroma, plexiform neurofibroma and neurofibrosarcoma. J Nucl Med 37: 1778-1783, 1996
13. Lee M, Rezai AR, Freed D, Epstein FJ: Intramedullary spinal cord tumours in neurofibromatosis: Neurosurgery 38: 32-37, 1996
14. Levy WJ Jr, Latchaw J, Hahn JF: Spinal neurofibromas: a report of 66 cases and a comparison with meningiomas. Neurosurgery 18: 331-334, 1986
15. Levy P, Vidaud D, Leroy K, et al: Molecular profiling of malignant peripheral nerve sheath tumors associated with neurofibromatosis type 1, based on large-scale real-time PT-PCR. Mol Cancer 3: 20-33, 2004
16. Nakasu S, Nakasu Y, Matsuda I, Handa J: Giant neurofibroma of the scalp associated with lambda defect: case report. No To Shinkei 33: 181-185, 1981
17. National Institute of Health Concensus Development Conference: Neurofibromatosis Conference Statement. Arch Neurol 45: 579-588, 1988
18. Oliver DW, Wells FC, Lamberty BG, Waters A: Massive plexiform neurofibroma of the sympathetic trunk. Eur J Cardiothorac Surg 16: 569-572, 1999
19. Petronio J, Edwards MS, Prados M, Freyberger S, Rabbitt J, Silver P, Levin VA: Management of chiasmal and hypothalamic gliomas of infancy and childhood with chemotherapy; J Neurosurg 74: 701-708, 1991
20. Pratap A, Negal P, Agrawal A, Singh MP, Pandey SR: Giant malignant nerve sheath tumor of lumbosacral plexus with intraspinal extension in child neurofibromatosis type 1. Pediatr Neurosurg 43: 410-413, 2007
21. Riccardi VM: Neurofibromatosis: Phenotype, Natural History,and pathogenesis, 2nd ed. Baltimore: John Hopkins University Pres, 1992
22. Sakaida H, Hanakita J, Suwa H, Nagayasu S, Nishi S, Ohta F: Two cases of von Recklinghausen's disease with multiple brain and spinal tumors. No Shinkei Geka 20: 51-56, 1992
23. Saltik S, Donmezer B, Yuksel E, Cakı S, Erguven M: Norofibromatozis tip 1 hastalarında klinik ve kraniyal manyetik rezonans goruntuleme ozellikleri. Turk Pediatri Arsivi 40: 94-101, 2005
24. Serletis D, Parkin P, Bouffet E, Shroff M, Drake JM, Rutka JT: Massive plexiform neurofibromas in childhood: natural history and management issues. J Neurosurg 106: 363-367, 2007
25. Sampson JH, Martuza RL: Neurofibromatosis and other phakomatoses, in Wilkins RH and Rengachary SS (eds), Neurosurgery, volume IB, second edition, Mc-Graw-Hill, 1996: 673-685
26. Shu HH, Mirowitz SA, Wippold II FJ. Neurofibromatosis: MR imaging findings involving the head and spine. AJR Am J Roentgenol 160: 159-164, 1993
27. Tada M, Sawamura Y, Ishii N, Chin S, Abe H: Massive plexiform neurofibroma in the orbit in a child with von Recklinghausen's disease. Childs Nerv Syst 14: 210-212, 1998
28. Takayima Y, Friedlander RM, Brem H, Malick A, Martuza RL: Inhibition of angiogenesis and growth of human nevre-seath tumors by AGM-1470. J Neurosurg 78: 470-476, 1993
29. Topsakal C, Erol FS, Ozercan I, Murat A, Gurates B: Presacral solitary giant neurofibroma without neurofibromatosis type 1 presenting as pelvic mass: case report. Neurol Med Chir 41: 620-625, 2001
30. Unal F: Spinal intradural ekstrameduller tumorler. Aksoy K, Palaoglu S, Pamir N and Tuncer R (eds), Temel Norosirurji, Ankara: 2005; 1121-1128
31. Van Es S, North KN, McHuah K, De Silva M: MRI findings in children with neurofibromatosis type 1: a prospective study. Pediatr Radiol 26: 478-487, 1996
32. Webb WR, Goodman PC: Fibrosing alveolitis in patients with neurofibromatosis. Radiology 122: 289-293, 1977
33. Wise JB, Cryer JE, Belasco JB, Jacobs I, Elden L: Management of head and neck plexiform neurofibromas in pediatric patients with neurofibromatosis type 1. Arch Otolaryngol Head Neck Surg 131: 712-718, 2005
34. Woodruff JM. Pathology of tumors of the peripheral nerve sheath in type 1 neurofibromatosis. Am J Med Genet 89: 23-30, 1999