Neurofibromatosis Type 1 Accompanied by Craniofacial Pain: Literature Review and Descriptive Case

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Neurofibromatosis type 1 (NF-1) is a genetic disease with characteristic neurofibromas and bony dysplasia that manifest throughout the body, including the craniofacial region. NF-1 patients are known to frequently report chronic pain in areas below the head; however, the matter of pain in the craniofacial region in this patient group has not been handled intensively so far, and studies have mainly focused on headaches. This article comprehensively reviews the related literature and reports a case of an NF-1 patient whose chief complaint was headache and pain in the temporomandibular joint area. Craniofacial pain is probably not an exceptional problem in NF-1, but the current inadequacy of related data is worrisome, considering the impact of pain on NF-1 prognosis and patient quality of life. The presence of craniofacial pain in NF-1 patients should be actively sought out in the diagnostic process and appropriate guidelines for its diagnosis and treatment should be established. *J Oral Facial Pain Headache 2017;31:402–409. doi: 10.11607/ofph.1787*

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Neurofibromatosis (NF) type-1 is an autosomal dominant genetic disease resulting from a chromosome 17 mutation that affects 1 out of around 3,000 to 4,000 people in the world.[1] A tumor suppressor gene is associated, and nearly 50% of NF patients have a family history while the other half represents spontaneous mutations.[2] NF is categorized into distinct subtypes, with at least eight forms described presently. NF type-1 (NF-1), previously called von Recklinghausen disease, is the most common type, accounting for approximately 85% to 97% of all NF cases.[3]

Genetic testing is possible, but clinical diagnosis is mostly based on the presence of characteristic manifestations of NF-1 (ie, at least two of the seven following major symptoms): *(1)* more than six café au lait macules; *(2)* skinfold freckling in inguinal or axillary regions (ie, Crowe sign); *(3)* more than two cutaneous neurofibromas or one plexiform neurofibroma (PN); *(4)* more than two iris hamartomas (ie, Lisch nodules); *(5)* optic pathway tumors; *(6)* bony dysplasia; or *(7)* a first-degree family history of NF-1.[4] Previous studies reporting oral manifestations of NF-1 mostly have focused on neurofibromas and their sequelae, such as facial deformities and malocclusion.[5–8] However, bony dysplasia is most common in the long bones, with only a small number of reports dealing with osseous manifestations located in the sphenoid wing, orbit, maxilla, and mandible.[9] Reports concerning deformities of the temporomandibular joint (TMJ) are rare.[9,10]

Pain is not an aspect of NF-1 that is frequently referred to as an independent disease entity, and exact data concerning its incidence are sparse. Manifestations of NF-1 known to cause chronic pain include PNs, orthopedic problems such as scoliosis and pseudoarthrosis, and gastrointestinal complications.[11] Previous reports of pain in NF-1 patients have mainly concerned areas below the head and neck.[12–19] There is a general lack of studies on pain occurring in the craniofacial region of NF-1 patients, and the few that exist are limited to headaches.[20] The scant literature concerning pain of the orofacial region usually has described

such pain as arising from pressure on cranial nerves, especially the trigeminal nerve, by adjacent PNs in the oral cavity causing different levels of paresthesia and neuralgia.[5,9,10] Craniofacial pain in NF-1 without causative neurofibromas has not been reviewed so far. The present case report describes a male NF-1 patient with headache and pain in the left TMJ area, which was assumed to originate from an etiology unrelated to neuropathy due to neurofibromas.

Case Report

A 26-year-old male patient visited the Orofacial Pain Clinic of the Department of Oral Medicine, Seoul National University Dental Hospital with the chief complaint of continuous pain in the left TMJ area and severe headaches on the right temporalis area. The patient also reported difficulty in opening his mouth, along with neck and shoulder pain on the right side. Facial asymmetry was perceptible, and the patient reported that 10 years ago he had started to notice this problem along with the craniofacial pain. About 7 years ago, he had visited another university hospital with the same pain symptoms. The clinician in charge had suggested an intraoral appliance at that point; however, the symptoms had worsened after the patient used the appliance. One year ago he had acupuncture therapy on the painful area, but symptom relief was minimal. Recently, the pain in the left TMJ area and headaches in the right temporalis area had gotten worse. The patient reported parafunctional habits, including making TMJ noises on purpose by moving the mandible, but joint noises that had once existed in the right TMJ had disappeared at some point. Other habits included clenching, tongue thrusting, unilateral chewing (left), unilateral sleeping (right), biting on something, and an irregular diet. The patient also reported insomnia. The patient did not report any medical history that was noticeable except for a spinal disc herniation at the lower back level that had occurred 13 years ago and an emergency room visit 2 years ago due to right facial swelling accompanied with pain that had been eliminated with intravenous analgesics. The swelling had not recurred afterwards.

Intraoral and Extraoral Findings

Midline deviation was clearly observed; the midline between the maxillary incisors showed a 3-mm shift to the left, and the midline between the mandibular incisors showed a 1-mm shift to the left with the pronasale (tip of the nose) and philtrum as baseline. The patient showed an Angle Class II, division 1 right molar key and an Angle Class I left molar key. The left maxillary first molar had been extracted and had not been restored. Crossbite of the right posterior teeth was observed. The crowns of several teeth were fractured. Tongue and buccal mucosa ridging were evident. There were no other remarkable intraoral findings. Comprehensive laboratory blood tests, including complete blood cell count with white blood cell differential, red cell indices, blood chemistry, and erythrocyte sedimentation rate, showed normal results except for a slightly increased absolute neutrophil count (8,799/μl; reference value 1,800 to 7,000/μl).

Extraoral examinations were conducted following the Research Diagnostic Criteria/Temporomandibular Disorders (RDC/TMD).[21] The patient reported pain on palpation of the insertion and upper part of the right trapezius muscle. The maximum opening range (50 mm) was not restricted, but the path deviated to the right and returned to midline on maximum opening. Joint noises were absent. The occlusion checked with an 8-μm thick film was sound.

The Symptom Checklist-90-Revised was applied for psychological evaluation, and the Global Severity Index was 50.[22] The T score for somatization was 64, reflecting a slight tendency, but no dimension scores were over 70. RDC/TMD Axis II questionnaire results showed a characteristic pain intensity of 70 (0 to 100 range). The patient was classified as grade II (low disability due to pain, high intensity of pain) on the Graded Chronic Pain Scale.[23] The patient's depressive/vegetative symptom (1.0) and somatization (1.5) scores suggested the possible presence of moderate depression (0.535 to 1.105) and severe somatization (≥ 1.000). His jaw disability score was 0.75 (0 to 1 range) based on the Jaw Functional Limitation Scale, and he expressed difficulty in chewing, exercising, smiling, tooth brushing, yawning, swallowing, talking, and making facial expressions.[24] The presence of diurnal clenching and tinnitus along with morning stiffness of the TMJ area was reported on the questionnaire. Descriptive values are presented in Table 1.

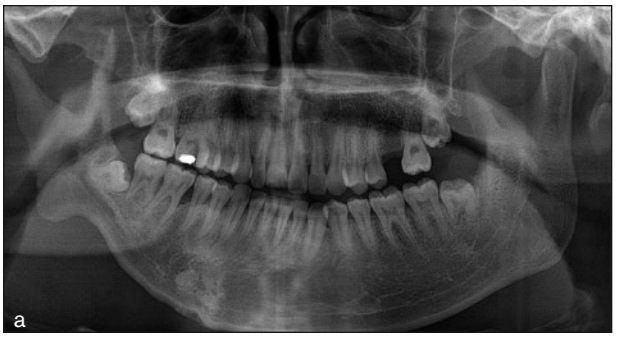
Imaging

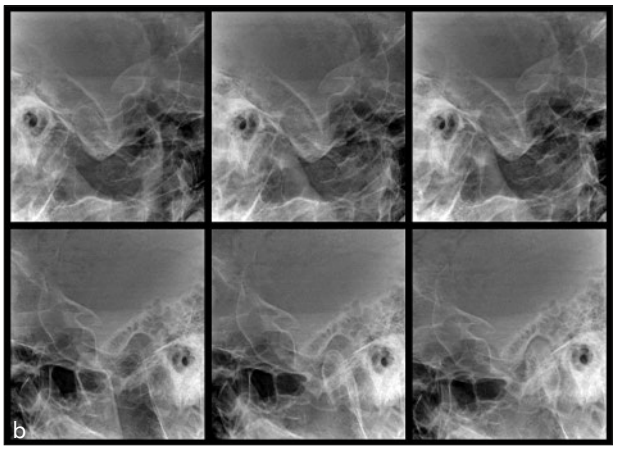
The duration of the patient's pain along with the history of facial swelling warranted further imaging. Plain radiographs including an orthopantomogram, TMJ panoramic, and transcranial view were evaluated. Cone beam computed tomography (CBCT) and magnetic resonance imaging (MRI) were also conducted. Results are shown in Figs 1 to 3. Severe mandibular asymmetry was observed. The right mandibular condyle showed hypoplasia, and the inferior border of the right side of the mandible showed irregularity compared to the left side. The right mandibular canal was enlarged. The right sigmoid notch was very steep, and overgrowth of the right articular eminence was evident. The surface of the right TMJ condyle showed degenerative changes on plain radiographs. Degenerative bone change of both TMJ condyles and

Table 1 RDC/TMD Evaluation and Imaging Results

Tentative diagnosis	RDC/TMD Axis II scores		Imaging results		Final diagnosis
RDC/TMD Axis I: Right ADD with reduction (Group IIa.)	Characteristic pain intensity score (range)	70 (0–100)	Plain radiograph	DJD of right TMJ condyle, condylar hypoplasia, and facial asymmetry	I. Neurofibromatosis II. RDC/TMD Axis I: 1) Myofascial pain (Group Ia.) 2) Right ADD without reduction without limited opening (Group IIc.) 3) Osteoarthritis (Group IIIb.) III. Tension-type headache
	GCPS score (range)	Grade 2 (1–4)	CBCT	DJD of both TMJ condyles, osteodystrophy	
	Depressive and vegetative symptom score (range)	1.0 (0–4)	MRI	ADD without reduction of right TMJ condyle, osteodystrophy associated with vascular lesion or neurofibromatosis	
	Somatization score (range)	1.5 (0–4)			
	Jaw functional limitation score	0.75 (0–1)			

GCPS = Graded Chronic Pain Scale; CBCT = cone beam computed tomography; MRI = magnetic resonance imaging; DJD = degenerative joint disease; TMJ = temporomandibular joint; ADD = anterior disc displacement.





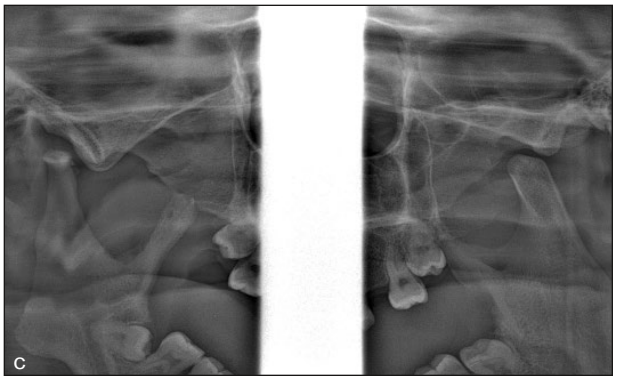


Fig 1 Plain radiography. **(a)** Orthopantomogram showing a hypoplastic right mandible with an acute mandibular angle and enlarged mandibular canal. **(b)** Transcranial view of the TMJ that shows marked restriction of right condylar movement, with the condyle remaining inside the mandibular fossa during maximum mouth opening. **(c)** TMJ panorama showing sclerotic changes of the right mandibular condyle and a deepened sigmoid notch.

generalized osteodystrophy of the right side of the mandible were observed on CBCT. MRI revealed disc displacement without reduction of the right TMJ and atrophic changes in the right masticatory muscles. Also, enlarged blood vessels could be observed medial to the right mandibular ramus. The possible diagnosis of NF or a vascular lesion was explained to the patient. Then the patient revealed his history of being diagnosed with NF and not visiting the Department of Genetic Disorders for the past 3 years.

Treatment

Instructions to control habits that may aggravate the pain were given along with directions to relax the masticatory muscles as an element of cognitive behavioral therapy. Instructions for physical therapy that included moist hot pack application and progressive resistance exercises were given. The patient was also referred to the Department of Oral and Maxillofacial Surgery to discuss treatment of the bony dysplasia and facial asymmetry. However, the patient did not follow through this referral, nor did he return to the clinic for the next appointment. Unfortunately, this limited the opportunity to perform essential investigations, including brain MRI to rule out the possibility of secondary headaches and to gather information concerning patient response to conservative pain treatment.

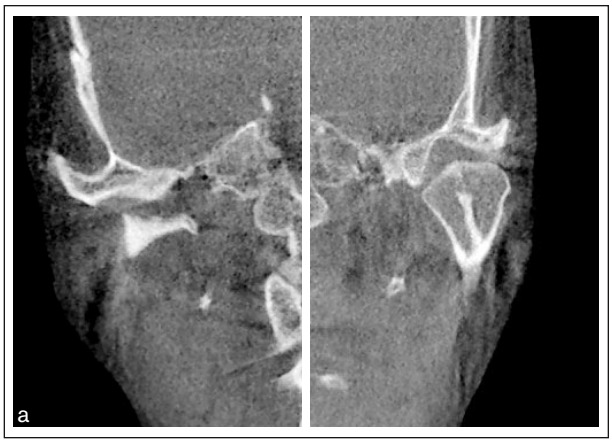
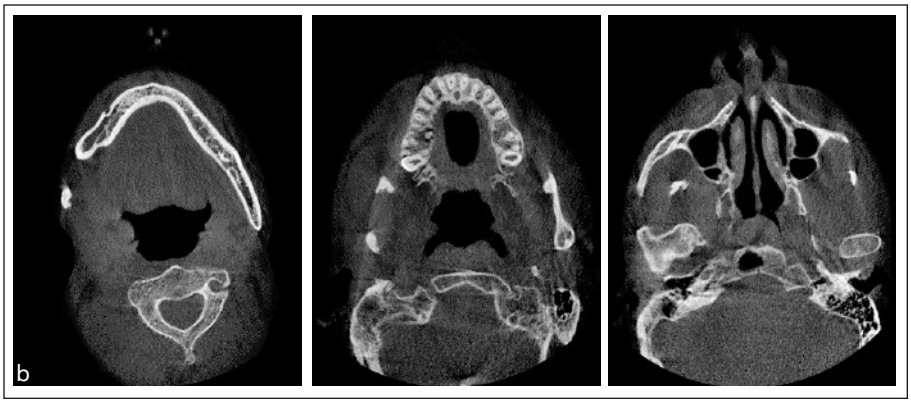
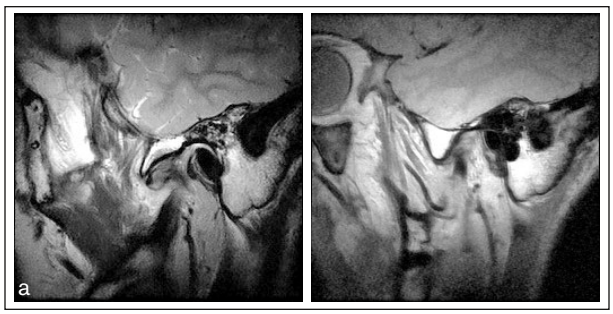


Fig 2 Cone beam computed tomography. **(a)** Coronal view of the TMJs that shows irregular surface of the right mandibular condyle and sclerotic changes with focal erosion of the left mandibular condyle. **(b)** Axial view of the TMJs that shows osteodystrophy of the right mandible and mandibular asymmetry.





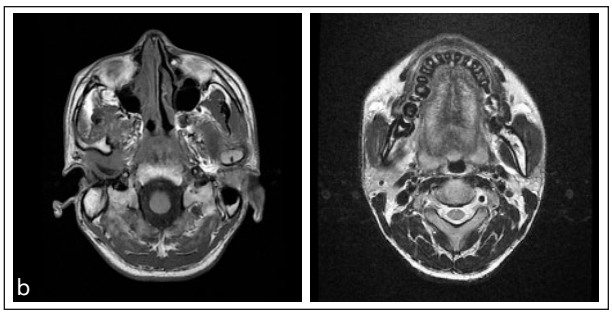


Fig 3 Magnetic resonance imaging (MRI). **(a)** T2-weighted sagittal MRI showing anterior disc displacement of the right TMJ in closed and open mouth positions with signal voids of enlarged blood vessels observed medial to the right mandibular ramus. **(b)** T2-weighted axial MRI showing osteodystrophy of the right mandible and atrophic changes in the right masticatory muscles.

Discussion

Orofacial manifestations including oral/perioral neurofibromas and osseous lesions of the maxilla and mandible can be observed in 4% to 92% of NF-1 patients and are most commonly located in the tongue, lips, mucobuccal fold, gingiva, and floor of the mouth.[5,9] Intraosseous lesions were known to be relatively rare, but owing to technical improvement of radiologic instruments, lesions that once had been missed are more easily recognized today. The present patient showed characteristic mandibular deformities that have been reported in previous studies, such as deviation of the mandible to the affected side, coronoid notch deformity (inferior displacement), pseudo-enlongation of the condylar/coronoid process, and hypoplasia of the ascending ramus, body of the mandible, and the ipsilateral maxilla and zygoma.[9]

Contrary to the abundance of studies on craniofacial skeletal deformities and radiographic features

of NF-1, little attention has been paid to craniofacial pain in this patient group. Nerve and spinal cord compression due to PNs is considered the main cause of pain in areas below the head and neck.[25,26] PNs are benign tumors that can be observed in over 50% of NF-1 patients.[27] Such tumors can show rapid growth and progress to malignant peripheral nerve sheath tumors (MPNST) in 8% to 13% of patients, and such rapid growth is more common in children and young adults.[27] MPNSTs should always be considered in the differential diagnosis of NF-1 patients with chronic pain, novel neurologic deficits, and/or changes in clinical characteristics of a known neurofibroma.[28] Such alertness to persistent pain in NF-1 patients is crucial, since MPNSTs can be an early manifestation of the disease and are known to be the leading cause of mortality in its advanced stages.[15] The possibility of MPNST should also have been considered in the present case, since the patient described worsening headaches and facial pain along with sleep disturbance of a higher-than-moderate level on the RDC/TMD Axis II questionnaire. Pain with duration longer than 1 month and at a level that disturbs sleep is a red flag for the diagnosis of MPNST.[15] Deep surgical biopsy is called on to rule out such possibilities, and evaluations should be carried out more than once a year. Immediate testing is required when associated with pain.[29]

Sleep disturbance is an aspect of NF-1 that should be considered for evaluation from a separate perspective. A study reporting on sleep quality of adult NF-1 patients showed that 21% had poor sleep quality.[30] Sleep problems may be a result of pain and many other factors that accompany NF-1, such as psychological issues (ie, anxiety and depression),[31] medication,[30] and cognitive impairment.[32] Since disturbed sleep itself may worsen pain through various direct and indirect mechanisms,[33,34] the presence and intensity of sleep problems should be evaluated and also actively managed.

Psychological problems are another matter that are interrelated with the problem of pain and sleep in NF-1. Psychiatric disorders, including depression and anxiety, are known to be more prevalent in NF-1 patients.[31,35] The present patient also showed a higher-than-moderate level of depression and somatization from the RDC/TMD Axis II. Disturbed sleep may worsen depression and vice versa.[36] Furthermore, there is a significant positive relationship between depression and pain intensity[37]; thus, the psychological status of an NF-1 patient must be assessed in relation to his/her pain and sleep disturbance level.

The meager efforts that have been made to understand craniofacial pain of NF-1 patients have been centered on headache. Although severe craniofacial pain in NF-1 is infrequent, primary migraine is known to be common.[38] Some authors have asserted that headache is not a specific aspect of NF-1 and is thus not an indication for neuroradiologic examination in itself,[39] while others have argued that patients with NF-1 have a higher risk of both migraine and nonmigraine headaches compared to the general population.[20,40] The prevalence of headaches in NF-1 has been reported to range from 2% to 78%.[20,39–42] Abnormalities of brain structures related to migraine,[43] mitochondrial dysfunction,[44] and sleep disturbance[30] are a few of the assumed causes of headaches in NF-1; however, the exact mechanism is yet to be revealed. The portion of headaches due to increased intracranial pressure secondary to tumors is relatively small, with the majority of cases being primary in origin. Tension-type headache[39,40] or migraine with and without aura[20] have been the most common headache types in NF-1, depending on the study. Chiari malformation is also one of the known causes of headaches in NF-1.[45] Patients may consider their headaches irrelevant to NF-1 and may not offer information spontaneously. Therefore, the clinician must actively investigate the presence of headache through history taking, since headache is known to have a significant impact on the quality of life (QoL) of NF-1 patients.[20] Neuroimaging is not compulsory, even in NF-1 patients with headaches, but may be necessary when they are accompanied by neurologic abnormalities.[40] Neurologic abnormalities were not evident in the present case; however, the lack of brain MRI limits the possibility of definitively ruling out the presence of a secondary headache.

The clinical headache diagnosis of the present patient fulfilled the criteria for frequent episodic tension-type headache.[46] The origin of the pain in the left TMJ area was unclear. Unilateral chewing and facial asymmetry may have caused masticatory muscle pain, but the patient did not show a positive response on palpation of the muscles. This may have been due to the severity of the pain caused by headaches masking the masticatory muscle tenderness or a misunderstanding of the patient because of the constant nature of his pain. The chronic TMJ area pain may have been of a multifactorial origin quite similar to masticatory myofascial pain since contributing factors such as insomnia (self-reported) and unilateral chewing were present. The correlation between craniofacial osseous deformity and pain has not been established, and further studies on this topic are needed to investigate the exact cause of pain in this case. Considering the lack of a causative lesion on the TMJ MRI, facial pain secondary to primary headaches in NF-1 is also a possibility and actually may be more common than craniofacial pain due to anatomical causes.

TMD is not a diagnosis commonly linked to NF-1, with only two case reports in existence.[47,48] Another study indicated TMJ dysfunction as a headache phenotype in NF-1, but without further speculation.[20] More studies based on validated diagnostic criteria are necessary to define the relationship between NF-1 and TMD. Mixed connective tissue disease associated with NF-1 has been reported and can be considered a cause of craniofacial pain.[49]

Treatment of pain in NF-1 patients frequently involves pain medications such as nonsteroidal anti-inflammatory drugs, anticonvulsants, and narcotics.[50] However, side effects are common,[51,52] and pain relief is incomplete in some cases.[53] Studies analyzing the analgesic efficacy of pain management in NF-1 are limited. Previous studies have reported that 12% of children with PNs take narcotics,[11] and more than 70% of NF-1 patients use prescription analgesics.[42] Specific data concerning craniofacial pain and its management do not exist. Considering the low efficacy and high prevalence of side effects resulting from pain medications in NF-1, alternative and supplementary methods should be taken into account. Previous reports have described successful headache and cervical pain management using physical therapy, including posture training, stretching, and ultrasound.[45,54] Occipital peripheral nerve stimulation[55] and ultrasound-guided peripheral nerve block[56] are methods that could be conducted in patients with intractable neuralgic pain of NF-1. Surgical debulking of PNs accompanied by severe pain is inevitable when surgery is not limited by adjacent structures.[57,58] Some clinicians are taking a different position and achieving high patient satisfaction by attempting psychological treatment to lessen daily interference from pain.[50] Based on previous literature, it is suggested that the management of craniofacial pain should include patient education, rigorous physical therapy, appropriate exercises, and cognitive behavioral therapy in addition to analgesics. Treatment should aim to reduce pain-related symptoms and interference with daily activities while increasing QoL.

Pain is a clinical aspect of NF-1 that must be actively evaluated and managed since previous reports have shown that pain in NF-1 patients acts as a major factor that lowers QoL,[59,60] which is intimately linked to functional interferences such as cognitive deficits and social problems.[61–63] Pain may also negatively affect disease severity itself.[64] Although there is a great likelihood of craniofacial pain in NF-1 patients, data concerning prevalence and clinical characteristics are lacking, and guidelines for its diagnosis and treatment are nonexistent.

Conclusions

This report presents a case of an NF-1 patient with a chief complaint of headache and TMJ area pain, which was not directly associated with the presence of neurofibromas. The possibility of other forms of pain in addition to headaches should be routinely considered since craniofacial pain is probably not an exceptional problem in NF-1. In spite of its impact on disease prognosis and the patient's QoL, little attention has been paid to craniofacial pain in NF-1 so far, and the current inadequacy of related data and lack of attention are worrisome. The presence of craniofacial pain in NF-1 should be actively sought in the diagnostic process, and further studies are necessary to elucidate its pathophysiology and to establish appropriate guidelines for its diagnosis and treatment. Since the disease has manifestations throughout the body, the dentist specializing in craniofacial pain should cooperate with other specialties in a multidisciplinary approach to diagnose and treat craniofacial pain in NF-1 patients.

Acknowledgments

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References

1. Metheny LJ, Cappione AJ, Skuse GR. Genetic and epigenetic mechanisms in the pathogenesis of neurofibromatosis type I. J Neuropathol Exp Neurol 1995;54:753–760.
2. Cunha KS, Barboza EP, Dias EP, Oliveira FM. Neurofibromatosis type I with periodontal manifestation. A case report and literature review. Br Dent J 2004;196:457–460.
3. Gutmman DH, Aylsworth A, Carey JC, et al. The diagnostic evaluation and multidisciplinary management of neurofibromatosis 1 and neurofibomatosis 2. JAMA 1997;278:51–57.
4. Summers MA, Quinlan KG, Payne JM, Little DG, North KN, Schindeler A. Skeletal muscle and motor deficits in neurofibromatosis type 1. J Musculoskelet Neuronal Interact 2015;15: 161–170.
5. Sigillo R, Rivera H, Nikitakis NG, Sauk JJ. Neurofibromatosis type 1: A clinicopathological study of the orofacial manifestations in 6 pediatric patients. Pediatr Dent 2002;24:575–580.
6. Shapiro SD, Abramovitch K, Van Dis ML, et al. Neurofibromatosis: Oral and radiographic manifestations. Oral Surg Oral Med Oral Pathol 1984;58:493–498.
7. D'Ambrosio JA, Langlais RP, Young RS. Jaw and skull changes in neurofibromatosis. Oral Surg Oral Med Oral Pathol 1988; 66:391–396.
8. Cunha KS, Rozza-de-Menezes RE, Andrade RM, Almeida L, Janini M, Geller M. Oral manifestations of neurofibromatosis type 1 in children with facial plexiform neurofibroma: Report of three cases. J Clin Pediatr Dent 2015;39:168–171.
9. Javed F, Ramalingam S, Ahmed HB, et al. Oral manifestations in patients with neurofibromatosis type-1: A comprehensive literature review. Crit Rev Oncol Hematol 2014;91:123–129.

10. Lorson EL, DeLong PE, Osbon DB, Dolan KD. Neurofibromatosis with central neurofibroma of the mandible: Review of the literature and report of case. J Oral Surg 1997;35:733–738.
11. Wolters PL, Burns KM, Martin S, et al. Pain interference in youth with neurofibromatosis type 1 and plexiform neurofibromas and relation to disease severity, social-emotional functioning, and quality of life. Am J Med Genet A 2015;167:2103–2113.
12. Leung VK, Lee SW, Yuen NW, Kung NN, Loke TK. Epigastric pain in a patient with neurofibromatosis type 1. Hong Kong Med J 2005;11:213–215.
13. Okunoghae E, Starrett E, Gray B. Neurofibromatosis in a toddler with back pain. J Pediatr Health Care 2014;28:88–91.
14. Edmiston J. Leg pain in a teenager with a history of neurofibromatosis. JAAPA 2013;26:63–64.
15. Stavrinides V, Nasra S. A case of persistent foot pain in a neurofibromatosis type I patient. Case Rep Med 2012;2012:479632.
16. Protopapas A, Sotiropoulou M, Haidopoulos D, Athanasiou S, Loutradis D, Antsaklis A. Ovarian neurofibroma: A rare visceral occurrence of type 1 neurofibromatosis and an unusual cause of chronic pelvic pain. J Minim Invasive Gynecol 2011;18:520–524.
17. Leonard M, Harrington P. Painful glomus tumour of the thumb in an 11-year-old child with neurofibromatosis 1. J Hand Surg Eur Vol 2010;35:319–320.
18. Buckley M, Kuan S, Barton D. An unusual cause of collapse and neck pain. Emerg Med J 2008;25:857–858.
19. Batta AG, Gundian JC, Myers RP. Neurofibromatosis presenting as perineal pain and urethral burning. Urology 1989; 33:138–140.
20. Afridi SK, Leschziner GD, Ferner RE. Prevalence and clinical presentation of headache in a National Neurofibromatosis 1 Service and impact on quality of life. Am J Med Genet A 2015; 167:2282–2285.
21. Dworkin SF, LeResche L. Research diagnostic criteria for temporomandibular disorders: Review, criteria, examinations and specifications, critique. J Craniomandib Disord 1992;6: 301–355.
22. Derogatis LR. SCL-90-R: Symptom Checklist-90-R: Administration, Scoring, and Procedures Manual. Minneapolis, MN: NCS Pearson, 1975.
23. Von Korff M, Ormel J, Keefe FJ, Dworkin SF. Grading the severity of chronic pain. Pain 1992;50:133–149.
24. Ohrbach R, Granger C, List T, Dworkin S. Preliminary development and validation of the Jaw Functional Limitation Scale. Community Dent Oral Epidemiol 2008;36:228–236.
25. Citak EC, Oguz A, Karadeniz C, Okur A, Memis L, Boyunaga O. Management of plexiform neurofibroma with interferon alpha. Pediatr Hematol Oncol 2008:25:673–678.
26. Kim A, Gillespie A, Dombi E, et al. Characteristics of children enrolled in treatment trials for NF1-related plexiform neurofibromas. Neurology 2009;73:1273–1279.
27. Tucker T, Friedman JM, Friedrich RE, Wenzel R, F Fünsterer C, Mautner VF. Longitudinal study of neurofibromatosis 1 associated plexiform neurofibromas. J Med Genet 2009;46:81–85.
28. 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.
29. Valeyrie-Allanore L, Ismaïli N, Bastuji-Garin S, et al. Symptoms associated with malignancy of peripheral nerve sheath tumours: A retrospective study of 69 patients with neurofibromatosis 1. Br J Dermatol 2005;153:79–82.
30. Leschziner GD, Golding JF, Ferner RE. Sleep disturbance as part of the neurofibromatosis type 1 phenotype in adults. Am J Med Genet A 2013;161:1319–1322.
31. Mouridsen SE, Sørensen SA. Psychological aspects of von Recklinghausen neurofibromatosis (NF1). J Med Genet 1995; 32:921–924.
32. North KN, Riccardi V, Samango-Sprouse C, et al. Cognitive function and academic performance in neurofibromatosis. 1: Consensus statement from the NF1 Cognitive Disorders Task Force. Neurology 1997;48:1121–1127.
33. Del Gallo F, Opp MR, Imeri L. The reciprocal link between sleep and immune responses. Arch Ital Biol 2014;152:93–102.
34. Patel SR, Zhu X, Storfer-Isser A, et al. Sleep duration and biomarkers of inflammation. Sleep 2009;32:200–204.
35. Zöller ME, Rembeck B. A psychiatric 12-year follow-up of adult patients with neurofibromatosis type 1. J Psychiatr Res 1999; 33:63–68.
36. Rumble ME, White KH, Benca RM. Sleep disturbances in mood disorders. Psychiatr Clin North Am 2015;38:743–759.
37. de Souza JB, Potvin S, Goffaux P, Charest J, Marchand S. The deficit of pain inhibition in fibromyalgia is more pronounced in patients with comorbid depressive symptoms. Clin J Pain 2009; 25:123–127.
38. Tonsgard JH. Clinical manifestations and management of neurofibromatosis type 1. Semin Pediatr Neurol 2006;13:2–7.
39. Clementi M, Battistella PA, Rizzi L, Boni S, Tenconi R. Headache in patients with neurofibromatosis type 1. Headache 1996; 36:10.
40. DiMario FJ Jr, Langshur S. Headaches in patients with neurofibromatosis-1. J Child Neurol 2000;15:235–238.
41. Ferner RE, Hughes RA, Weinman J. Intellectual impairment in neurofibromatosis 1. J Neurol Sci 1996;138:125–133.
42. Créange A, Zeller J, Rostaing-Rigattieri S, et al. Neurological complications of neurofibromatosis type1 in adulthood. Brain 1999;122:473–481.
43. Akerman S, Holland PR, Goadsby PJ. Diencephalic and brainstem mechanisms in migraine. Nat Rev Neurosci 2011;12: 570–584.
44. Sparaco M, Feleppa M, Lipton RB, Rapoport AM, Bigal ME. Mitochondrial dysfunction and migraine: Evidence and hypotheses. Cephalalgia 2006;26:361–372.
45. Herrero Valverde A, Moiron Simões R, Mera Campillo J, Palma T. Headache in patient with neurofibromatosis type 1 [in Spanish]. Neurologia 2007;22:911–914.
46. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia 2013;33:629–808.
47. Van Damme PA, Freihofer HP, De Wilde PC. Neurofibroma in the articular disc of the temporomandibular joint: A case report. J Craniomaxillofac Surg 1996;24:310–313.
48. Pasturel A, Bellavoir A, Cantaloube D, Dandrau JP, Perichaud P, Payement G. Temporomandibular joint dysfunction and neurofibromatosis. Apropos of a case [in French]. Rev Stomatol Chir Maxillofac 1989;90:17–19.
49. Migita K, Kawabe Y, Mori M, et al. Mixed connective tissue disease associated with von Recklinghausen's neurofibromatosis. Intern Med 2001;40:363–364.
50. Martin S, Wolters PL, Toledo-Tamula MA, et al. Acceptance and commitment therapy in youth with neurofibromatosis type 1 (NF1) and chronic pain and their parents: A pilot study of feasibility and preliminary efficacy. Am J Med Genet A 2016; 170:1462–1470.
51. Swann AC. Major system toxicities and side effects of anticonvulsants. J Clin Psychiatry 2001;62(suppl):s16–s21.
52. Rodriguez RF, Castillo JM, Castillo MP, et al. Hydrocodone/acetaminophen and tramadol chlorhydrate combination tablets for the management of chronic cancer pain: A double-blind comparative trial. Clin J Pain 2008;24:1–4.
53. Kim A, Gillespie A, Dombi E, et al. Characteristics of children enrolled in treatment trials for NF1-related plexiform neurofibromas. Neurology 2009;73:1273–1279.

54. Helmers KM, Irwin KE. Physical therapy as conservative management for cervical pain and headaches in an adolescent with neurofibromatosis type 1: A case study. J Neurol Phys Ther 2009; 33:212–223.
55. Skaribas I, Calvillo O, Delikanaki-Skaribas E. Occipital peripheral nerve stimulation in the management of chronic intractable occipital neuralgia in a patient with neurofibromatosis type 1: A case report. J Med Case Rep 2011;5:174.
56. Rocco ML, Rosenblatt MA. Ultrasound-guided peripheral nerve block in a patient with neurofibromatosis. Reg Anesth Pain Med 2011;36:88–89.
57. Baujat B, Krastinova-Lolov D, Blumen M, Baglin AC, Coquille F, Chabolle F. Radiofrequency in the treatment of craniofacial plexiform neurofibromatosis: A pilot study. Plast Reconstr Surg 2006;117:1261–1268.
58. 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 2005;131:712–718.
59. Merker VL, Bredella MA, Cai W, et al. Relationship between whole-body tumor burden, clinical phenotype, and quality of life in patients with neurofibromatosis. Am J Med Genet A 2014;164:1431–1437.
60. Wolkenstein P, Zeller J, Revuz J, Ecosse E, Leplège A. Quality-of-life impairment in neurofibromatosis type 1: A cross-sectional study of 128 cases. Arch Dermatol 2001;137:1421–1425.
61. Hofman KJ, Harris EL, Bryan RN, Denckla MB. Neurofibromatosis type 1: The cognitive phenotype. J Pediatr 1994;124:s1–s8.
62. Dilts CV, Carey JC, Kircher JC, et al. Children and adolescents with neurofibromatosis 1: A behavioral phenotype. J Dev Behav Pediatr 1996;17:229–239.
63. Garwood MM, Bernacki JM, Fine KM, Hainsworth KR, Davies WH, Klein-Tasman BP. Physical, cognitive, and psychosocial predictors of functional disability and health-related quality of life in adolescents with neurofibromatosis-1. Pain Res Treat 2012; 2012:975364.
64. Page PZ, Page GP, Ecosse E, Korf BR, Leplege A, Wolkenstein P. Impact of neurofibromatosis 1 on quality of life: A cross-sectional study of 176 American cases. Am J Med Genet A 2006; 140:1893–1898.