

ORIGINAL PAPER

Bone abnormalities occurring in the follow-up of the patients with neurofibromatosis type 1

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Abstract

Neurofibromatosis type 1 (NF1), also called von Recklinghausen disease or peripheral neurofibromatosis, is a common autosomal dominant disorder characterized by multiple neurofibromas, "café au lait" spots and Lisch nodules of the iris with a variable clinical expression. Osseous anomalies appeared in the patients with NF1 including dysplasia, scoliosis and pseudoarthrosis. We propose a research of the osseous involvement at 11 patients, seven female and four male with ages from 9 to 60 at which the cutaneous aspect has the complete form, hyperpigmented spots and cutaneous neurofibromas and only more than six "café au lait" spots. All the patients suffered radiological exams, CT- and MRI-scan. The results were different from case to case from the extreme severe deformations, especially at the children, to clinical unapparent osseous involvement, incidental found or with occasion of our investigation. *Conclusions.* The patients with NF1 has osseous abnormalities specific of the disease, like dysplasia, scoliosis, pseudoarthrosis, often gentle but sometimes extremely severe. The most severe osseous involvement are presented in the cases when these development early in the childhood. Other times the osseous abnormalities are clinical asymptomatic, their finding been clinical incidental. We want to have a separate mention for the maxillary and mandible involvement, which according to our information is not a rare form.

Keywords: neurofibromatosis type 1, bony abnormalities.

Introduction

Neurofibromatosis type 1 is an autosomal dominant neurocutaneous disorder with an estimated prevalence of two to three cases per 10 000 population [1].

NF1 is characterized by multiple brown skin macules ("café au lait" spots), intertriginous freckling, iris hamartoma (Lisch nodules), and multiple cutaneous neurofibroma [2]. NF1 can be associated with optic gliomas, spinal and peripheral nerve neurofibromas, neurological or cognitive impairment, scoliosis and other bone abnormalities, malignant tumors of the nerve sheath, pheochromocytoma, and vasculopathy [2–4].

The gene for NF1 is located on the long arm of chromosome 17 [5].

The product of this gene is neurofibromin, which, amongst other functions, regulate cell proliferation and differentiation. Phenotype expression of the gene is extremely variable, so individuals with identical germline NF1 gene mutations may have dramatically different clinical manifestations [6].

Bone involvement is one of the characteristic of the disease, but differs from patient to patient. Sometimes,

the involvement is extremely severe, appear from the birth or become evident early in the childhood or adolescence and will accentuate with the age. We want an evaluation of an osseous manifestation at patients with NF1, which deal with in the last six years.

Material and methods

Our observations refer to 11 patients with NF1 in care in Pediatrics, Dermatology, and Medical Clinics, for the affections correlate with the base disease or for other intercurrent disease. Every patient has examined dermatological, inclusive pathological, ophthalmologic, orthopedic, respectively imagistic, neuropsychiatric.

The diagnostic has been established on the base of the criteria elaborated by the *National Institute of Health Consensus Conference* in 1987 (Table 1), and namely on the presence of at least two criteria.

The majority of the authors agree that, the diagnosis of NF1 remain a clinical diagnosis because the identification of the mutations at the patients with NF1 requires laborious, expensive techniques and often without success.

Dermatological exams search the presence of the skin macules “café au lait” more than six with diameters between 5–15 mm, variable with age, freckling in the axillar or inguinal regions and skin tumors, neurofibromas or plexiform neurofibromas. From the skin tumors, to some patients had been realized pathological examinations.

Table 1 – Criteria of diagnosis of NF1

<ul style="list-style-type: none"> ▪ Six or more “café au lait” macules over 5 mm in greatest diameter in prepubertal individuals and over 15 mm in greatest diameter in postpubertal individuals; ▪ Two or more neurofibromas of any type or one plexiform neurofibroma; ▪ Freckling in axillary or inguinal regions; ▪ Optic pathway glioma; ▪ Two or more Lisch nodules (iris hamartomas); ▪ A distinctive osseous lesion such as sphenoid dysplasia or thinning of long bone cortex with or without pseudoarthrosis; ▪ First-degree relative with NF1. <p>The diagnosis of NF1 is made in an individual who has two or more of these features.</p>

Ophthalmologic, all the patients, including the children has been examined for searching the optical glioma, knowing that this appear early in the childhood, also the Lisch nodules, small melanocytic iris hamartomas.

Osseous abnormalities have been searched through clinical and radiographic exams and CT-scan. We want to find aspects of the specific osseous dysplasia, as well as sphenoid dysplasia or dysplasia or thinning of a long bone with or without pseudoarthrosis, but also other osseous abnormalities frequent associated with NF1 and that of the thoracic cage or the vertebral column.

Though the palate, maxilla and the mandible are rare involvement in NF1, these places examined with the same attention. We realized measurement of the cranium and the height of the patients. The capacity to learn or to concentrate the attention over a subject served as indicator of an eventual intellectual handicap.

From the 11 patients in the study six patients between 6 and 28 years had not skin tumors but presents more than six hyperpigmented spots “café au lait”, and freckling in the axillar or/and inguinal regions. They had at least other two diagnostic criteria like optical glioma, Lisch nodules, and a first-degree relative with NF1. This group, named by us like the group without skin tumors included three children, a boy of 6 years old and two girls of 9, and respectively 16 years old, two adult women of 26, and respectively 28 years old, and an adult male of 32 years old.

The second group constituted from five patients, three women of 40, 46 and 50 years old, and two men of 36 and 60 years old, which presented “café au lait” spots and skin tumors. In addition, they had other criteria from the criteria established for diagnosis. This group represented in our study the group of patients with skin neurofibromas.

☐ Results

In the group of the patients with hyperpigmented spots, without skin tumors, two patients, the children of 9 and 16 years old presented severe osseous modifications.

The first case, a boy of 9 years old had from the birth “café au lait” spots, which increased in number and dimensions. In addition, he presents an asymmetry of the thoracic cage with the prominence of the inferior ribs. In the following years, he presented an accentuated kyphosis.

The radiological exam showed a kyphoscoliotic thorax, a thoracic scoliosis plano-convex with maxim point T4–T5 (Figure 1a), and angular kyphosis with maxim point at vertebra T5–T6 (Figure 1b). In addition, it can observe lateral left and anterior compressions of the vertebral centrum with secondary deformation of the costal cage, an accentuated lumbar lordosis and prominent stern (Figure 1, a and b) the MRI scan offered clearer imagines than the radiological ones (Figure 1, c–f).

The second case, a girl of 16 years old had from birth a shorter inferior left limb with the aspect of elephantiasis and curved foot. During the years the difference in the length of the limbs accentuated, in the present are 8–9 cm. In addition, it appeared an asymmetrical pelvis.

The radiographic exam of the tibio-tarsian left articulation, point out dysplasia of the distal epiphysis of tibia and peroneus and an aspect of *varus equin* of the foot (Figure 2, a and b). At the right foot, the radiological exam shows a permanent metatarsal abduction (Figure 2c).

The CT-scan shows a condensation of the temporal bilateral (Figure 2, d and e).

The third case from the same group with NF1 at which the cutaneous aspect was represented only by the hyperpigmented spots, a patient of 26-years-old presented from the birth an asymmetrical thorax with vertebral dextroconcave kyphoscoliosis, which accentuated with the age. At 9 years old, she had a hydrocephaly drained with valve Holter.

The clinical exam shows hypostature with hypotrophic limbs and fragile fingers and macrocephaly with facial asymmetry. Radiologically, at the skull examined pseudocystic imagine at the horizontal mandible right ram, premolar included at the same mandible ram and multiple lesions of apical and marginal parodontitis (Figure 3), and at the CT-scan observed ventricular valve, cortical atrophy predominant temporo-parietal bilateral and a mucoid cyst of 1.5 cm at the right maxillary sinus.

Bilaterally, the femur shows ovalar radiotransparent images, well delimited with cystic aspect with osteosclerosis at the metaphysis and in the thickness mean third cortical of the diaphysis. Hand bilateral radiographs cannot evidentiate any modification of osseous structure of the hand.

Finally, the fourth case with osseous abnormalities from this group is a male of 37 years old with paresthesias all over the right limb. The MRI exam discovers the presence of a tumoral structure at the right conjugated foramen L1–L2 neural foramina, well delimited, which determines the enlargement of the neural foramina. A similar tumoral structure observes at the neural foramina T11–T12. The RMI aspect pleads for neurofibromas in the both places (Figure 4, a–d).

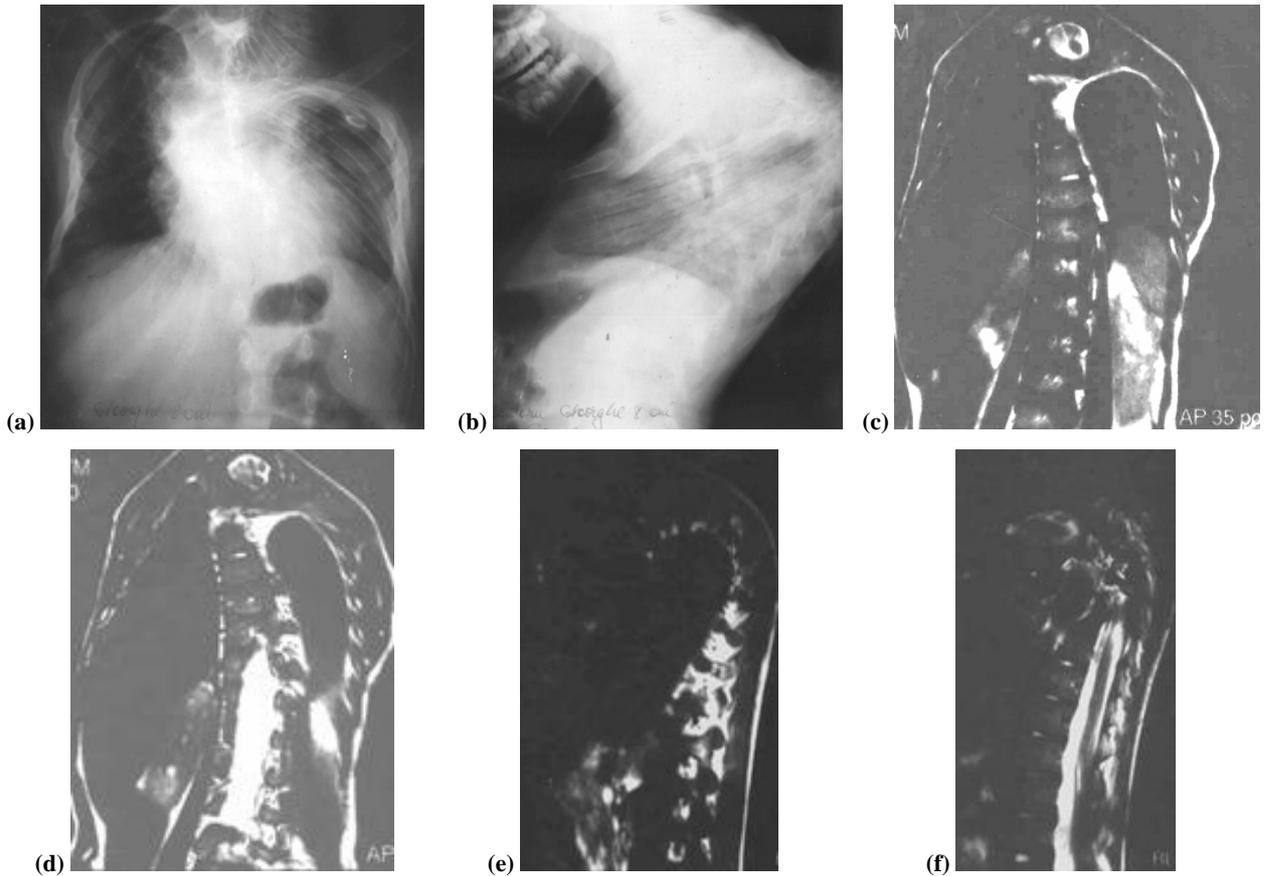


Figure 1 – Vertebral column thoracal radiography: (a) anterior–posterior; (b) profile. Thoracal kyphoscoliosis – thoracal kyphoscoliosis dextroconvex with maxim point at vertebrae T4–T5 (a), and angular kyphosis with maxim point T5–T6 (b), lateral left and anterior compressions of vertebrae with secondary deformation of the costal cage. Accentuated lumbar lordosis. Prominent stern. RMI scan: (c)–(f)

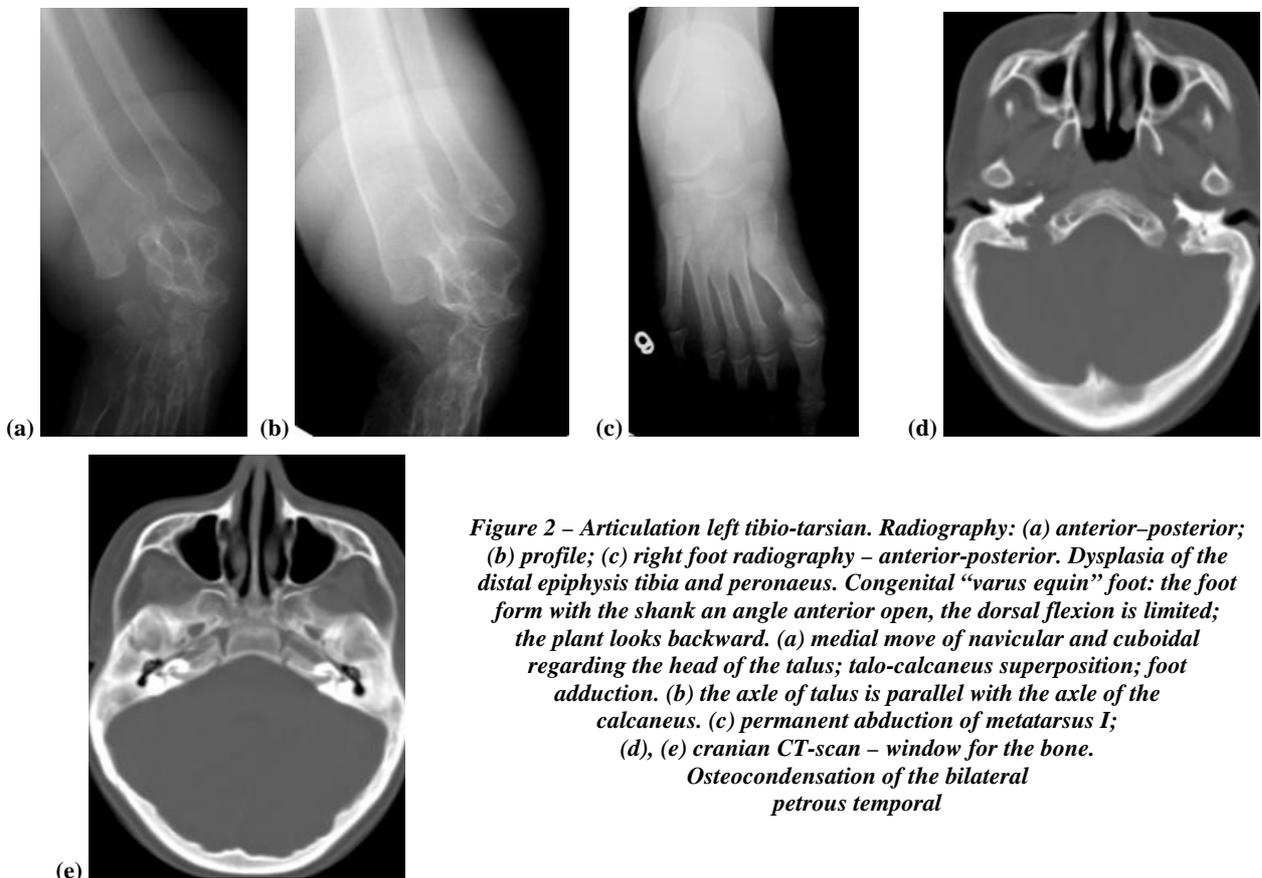


Figure 2 – Articulation left tibio-tarsian. Radiography: (a) anterior–posterior; (b) profile; (c) right foot radiography – anterior-posterior. Dysplasia of the distal epiphysis tibia and peroneus. Congenital “varus equin” foot: the foot form with the shank an angle anterior open, the dorsal flexion is limited; the plant looks backward. (a) medial move of navicular and cuboidal regarding the head of the talus; talo-calcaneus superposition; foot adduction. (b) the axle of talus is parallel with the axle of the calcaneus. (c) permanent abduction of metatarsus I; (d), (e) cranial CT-scan – window for the bone. Osteocondensation of the bilateral petrous temporal



Figure 3 – (a) Mandible radiography defiled for right horizontal ramus. Pseudocystic images the right horizontal mandible ramus; included premolar at the horizontal mandible ramus; multiple lesions of apical and chronic marginal periodontitis; (b) Hands bilateral radiography – comparative. It cannot evidentiate modification of osseous structure in the hands

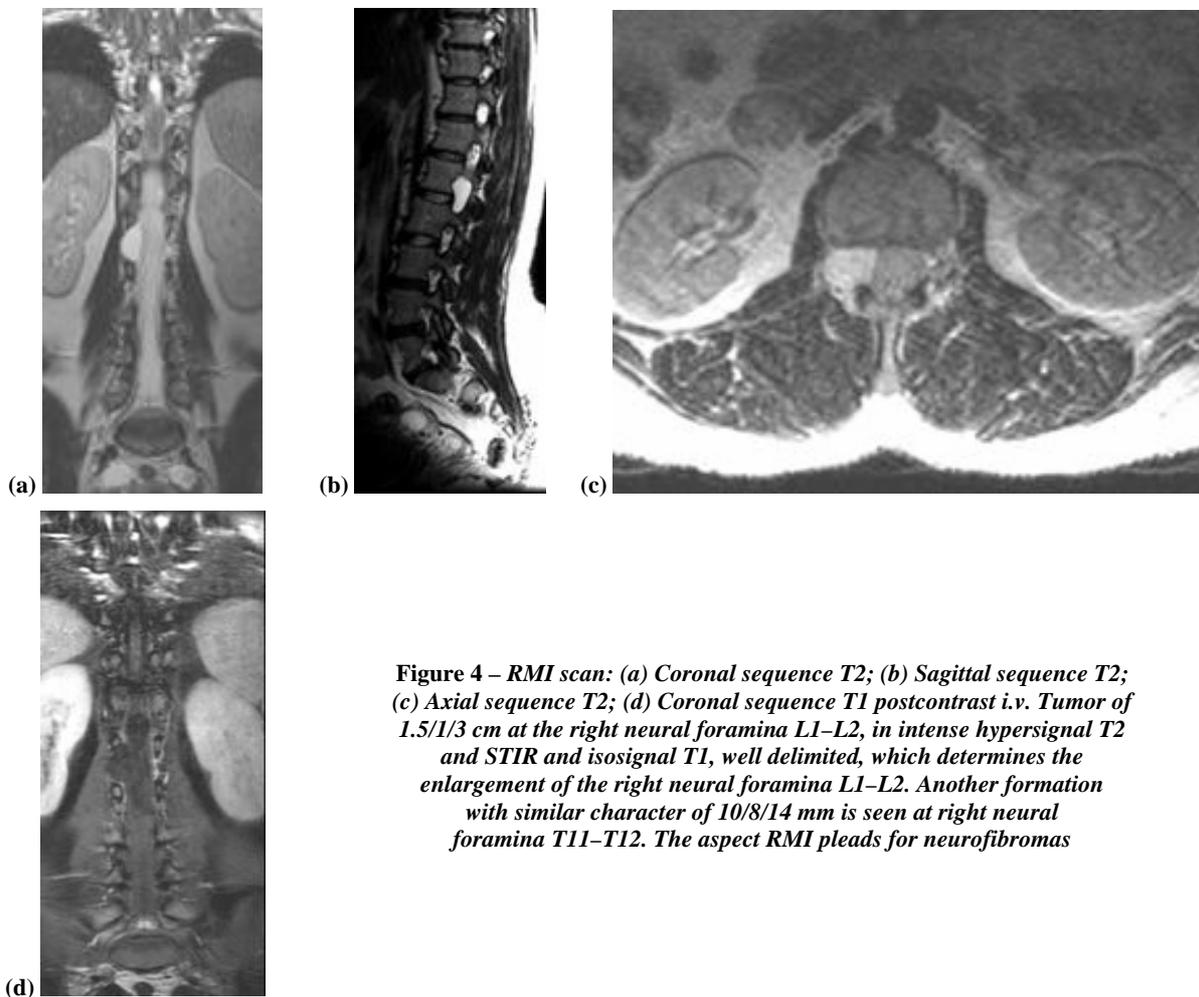


Figure 4 – RMI scan: (a) Coronal sequence T2; (b) Sagittal sequence T2; (c) Axial sequence T2; (d) Coronal sequence T1 postcontrast i.v. Tumor of 1.5/1/3 cm at the right neural foramina L1-L2, in intense hypersignal T2 and STIR and isosignal T1, well delimited, which determines the enlargement of the right neural foramina L1-L2. Another formation with similar character of 10/8/14 mm is seen at right neural foramina T11-T12. The aspect RMI pleads for neurofibromas

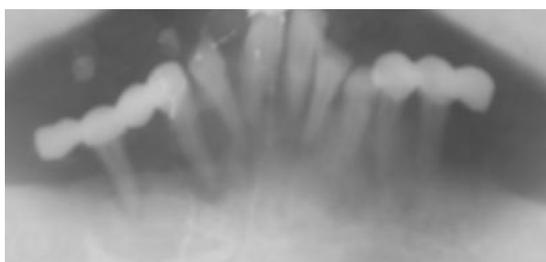


Figure 5 – Mandible panoramic radiography. Chronic marginal periodontitis. Diffuse osteoporosis. Important resorption of the osseous interdental septa. Periodontal pouch 1.3; 2.1; 2.2

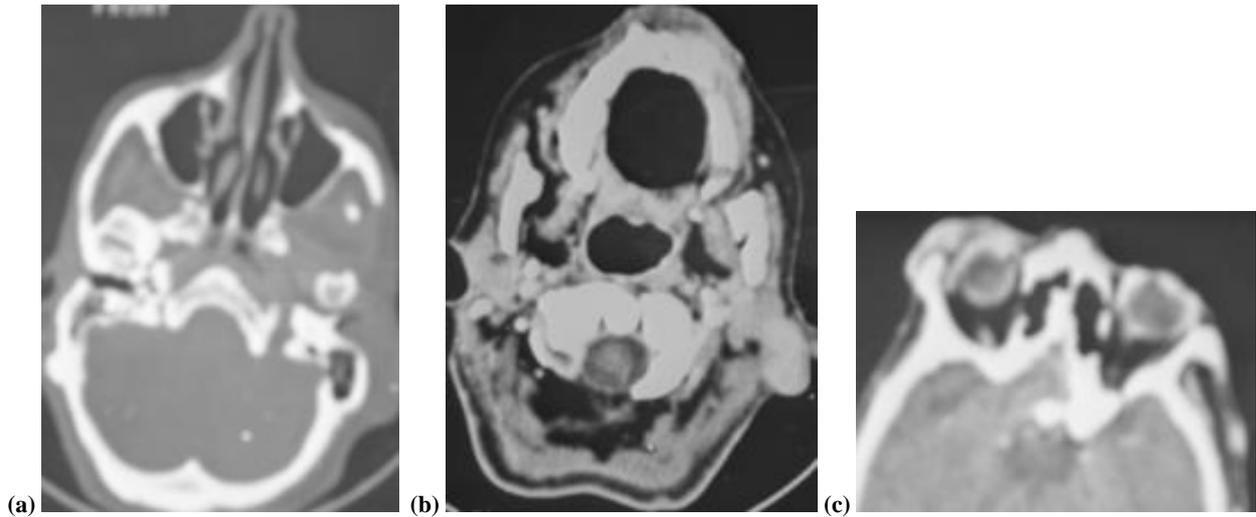


Figure 6 – Cranial CT-scan: (a) Axial section. Window for the bone. Right compact temporal osteoma; (b) Axial section postcontrast. Tissular tumor, iodophile, well delimited with diameter of 1.8 cm on the superficial left parotidian lobe. (c) Axial section postcontrast. Nodular, tissular tumor, intense iodophile with diameter 1 cm on the superior eyelid right eye

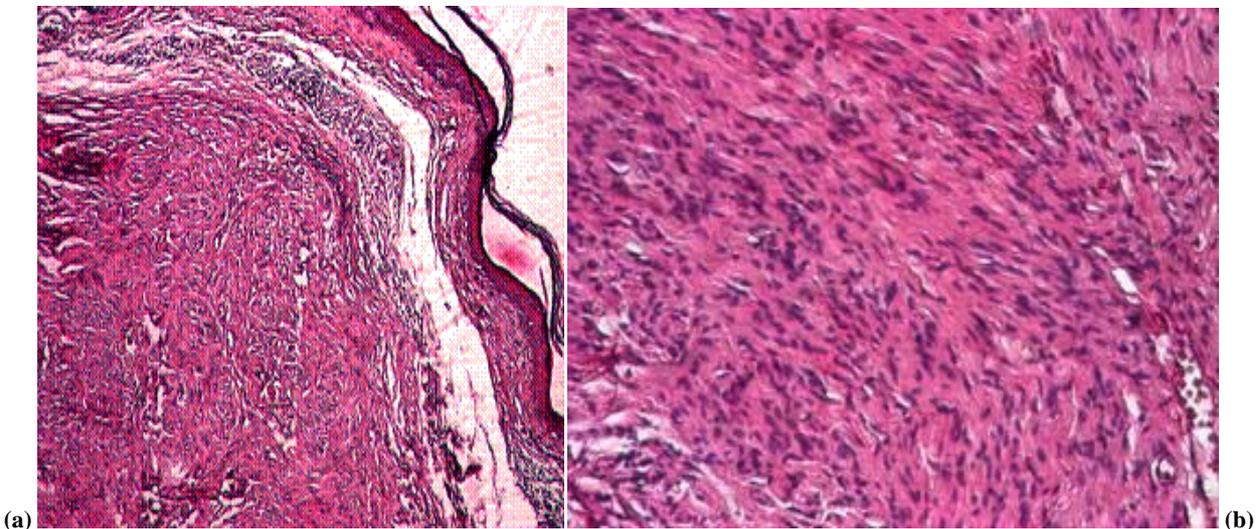


Figure 7 – (a) It observes under epidermis a mass represented by fusiform cells disposed intricate (HE stain, ob. 10×); (b) Dermal neurofibroma. It shows elongate cells with tahychromatic nuclei forming swirling fascicles

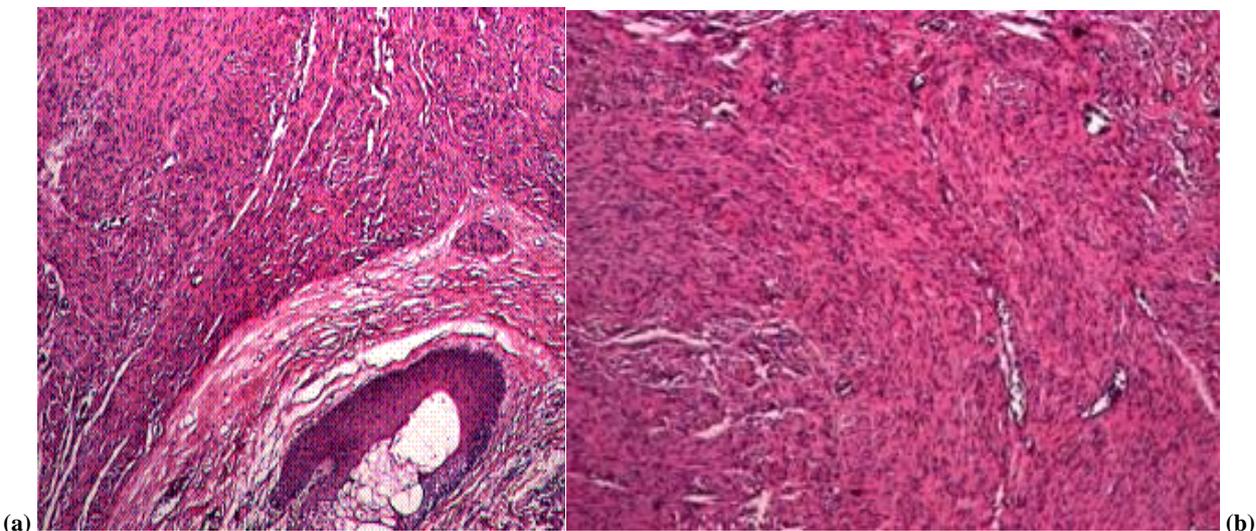


Figure 8 – (a) Dermal neurofibroma. It shows groups of elongate cells disposes in swirling fascicles in a collagenous stroma near a sebaceous gland; (b) Detail – elongate Schwann cell with tahychromatic nuclei forming swirling fascicles

In the group of the patients with skin tumors, the osseous involvement is present at a patient of 40-years-old. She has from the birth a progressive parodontosis, making difficult the nutrition. In addition, she suffered two fractures on tibia at 13 years at the radius at 16 years.

The panoramic radiographs of mandible and maxilla show marginal chronic parodontosis, diffuse osteoporosis and resorption of the osseous interdental septa (Figure 5).

At the CT-scan appeared a compact temporal right osteoma, and on the postcontrast axial sections two interesting imagines: a iodophile tumor well delimited with 1.8 cm diameter on the superficial left parotidian lobe and another with 1 cm diameter on the superior eyelid of the right eye (Figure 6, a–c).

At the superior and inferior limb, radiographs saw vicious consolidations of the previous fracture, at the tibia and radius.

Histopathological exam at the skin tumor, with the classic method using paraffin and Hematoxylin–Eosin (HE) staining, offered compatible imagines with the diagnosis of the dermal neurofibroma: long cells with hyperchromatic (tahychromatic) nuclei, in shape of fascicles (Figure 7, a and b).

In another case from this group, a male of 35 years old, the radiographs of the spin cord shows modification of the axis of the dorsolumbar region.

The skin biopsy from a tumoral lesion, with the same method like the precedent confirm the diagnosis of dermal neurofibroma (Figure 8, a and b).

In the rest of the cases, the osseous modifications had been less important: deviations in axis of the cervicodorsal and dorsolumbar spin cord in a case, vicious consolidation of the long bone fractures (pseudoarthrosis of the tibia in a case and femur in another).

The histopathological exams has not realized in all the cases because the clinical aspects were insufficient relevant for the diagnosis, hyperpigmented spots more than six without histological specificity or skin intradermic neurofibromas as pediculate tumors (*molluscum pendulum*) or sessile, or subcutaneous, nodular with gelatin consistency, with variable dimensions.

☐ Discussions

Neurofibromatosis type 1, also called von Recklinghausen disease or peripheral neurofibromatosis is a common autosomal dominant disorder characterized by multiple neurofibromas, “café au lait” spots, and Lisch nodules of the iris, with a variable clinical expression [7].

The NF1 gene on chromosome 17q11.2 encompasses over 350 kb of genomic deoxyribonucleic acid and include greater than 60 exons [8, 9]. The NF gene encodes a 220–250 kD (cytoplasmic) protein, termed neurofibromin [10, 11].

Neurofibromin is expressed primarily in neurons, Schwann cells, oligodendrocytes, astrocytes, leukocytes, and the adrenal medulla [6].

Other tissues also express neurofibromin, but at reduced levels [10–12]. The neurofibromin serves as a tumor suppressor. Decreased production of this protein causes varies clinical features.

NF1 is a common genetic disorder, with an incidence of one per 3500 live births and without a preference for sex or race [11].

The manifestations of NF1 are extremely variable from person to person, even within the same family. They also, vary at different times in an individual’s life [3].

The diagnostic criteria for NF1 developed by an *NIH (National Institutes of Health) Consensus Conference* in 1987 (Table 1) are generally accepted for routine clinical use [13].

The clinical diagnosis of NF1 is usually clearly in all but the youngest children [14].

Many of the clinical manifestations of NF1 are dependent upon the patient’s age. In this regard, “café au lait” spots, plexiform neurofibromas, and tibial dysplasias are typically recognized within the first year of life, whereas optic pathway gliomas and axillary freckling may not be apparent until 3–5 years of age. Dermal neurofibromas usually are first observed during adolescence, and often increase in number throughout puberty [6].

Some of the most common and earliest manifestations of NF1 are “café au lait” macules, axillary freckling and Lisch nodules (hyperpigmented iris hamartomas). Often present at birth, “café au lait” macules frequently increase in number during the first two years of life in more than 95% of individuals with NF1 [14].

These macules are characterized by homogeneous pigmentation with a smooth regular border, varying in size from a few millimeters to a few centimeters. These “spots” do not evolve into tumors and often fade during adulthood. They may be found anywhere on the body except on the scalps, eyebrows, palms, or soles. Histological, “café au lait” spots represent increased numbers of melanocytes as well as giant pigmented granules (macromelanosomes).

Freckling in region that are not exposed to the sun, such as axillary and inguinal regions, is also a common manifestation of NF1, occurring in 80% children by 6 years of age [15].

In addition, freckling can be observed under the neck and breast in areas where skin folds exist. Lisch nodules are iris hamartomas that do not have any effect on visual function. They are uncommon in young children, and are found in approximately 30% of individuals with NF1 by the age of 6 years [16]. They are highly characteristic of NF1 and are best detected by split lamp examination.

Optic Pathway Ganglion is the most common central nervous system tumor in patients with NF1 affecting 15–20% of patients [17].

The mean age of presentation of NF1 – associated optic pathway gliomas is 4.2 years [18, 19]. The most common presenting symptom is asymmetric uncorrectable visual loss.

Approximately one half of all optic pathway gliomas are asymptomatic at diagnosis. When symptomatic, the manifestations will be related to the tumor's location along the optic pathway. Optic nerve gliomas occasionally become symptomatic in older children or even adults [20], and can undergo spontaneous regression [21].

The optic pathway tumors can be divided into intraorbital and chiasmatic/hypothalamic tumors. Precocious puberty may also occur in children with optic pathway gliomas, usually because of hypothalamic infiltration [18].

Neurofibromas may affect virtually any organ in the body. The most common tumor in adults with NF1 is the dermal neurofibroma, a benign peripheral nerve sheath tumor composed of Schwann cells, fibroblast, and mast cells [6, 22].

These tumors rarely occur in young children but appear over time in older children, adolescents, and adults. They increase in frequency with age and are present in nearly all adults with NF1. Deep lesions may be detected only by palpation, whereas cutaneous lesions may appear initially as small papules on the trunk, extremities, scalp, or face. Puberty and pregnancy may be associated with increased numbers of neurofibromas and more rapid growth of preexisting lesions. About one third of individuals with NF1 have a more diffuse neurofibroma involving multiple nerve fascicles, termed a plexiform neurofibroma [6, 22].

Plexiform neurofibromas are more diffuse growth that can be locally invasive and quite deep [23]. They may involve multiple tissues, including skin, fascia, muscle, bone and internal organs. Plexiform neurofibromas are believed to be congenital lesions, although they may arise from deep structures and remain clinically silent until later in life [6, 24]. They may stimulate underlying bone growth, causing leg length discrepancies, scoliosis, or sphenoid wing dysplasia [25].

Neurofibromas rarely grow rapidly; such growth can suggest malignant transformation that is highly aggressive. Individuals are 18 times more likely to suffer malignant transformation than patients without internal plexiform neurofibroma.

Distinctive bony abnormalities, including skeletal dysplasia (particularly sphenoid wing dysplasia), scoliosis and tibial pseudoarthrosis are occurred in patients with NF1 [6].

Sphenoid dysplasia usually is asymptomatic but occasionally can be associated with herniation through the bony defect. Patient with plexiform neurofibroma of the eyelid or temporal region often have ipsilateral sphenoid dysplasia. Cortical thinning of the long bones or dysplastic bony changes can lead to repeated pathologic fractures with incomplete healing, and may result in the appearance of a false joint, or pseudoarthrosis [26].

Congenital pseudoarthrosis may be evident at birth. Bowing of the tibia is the most typical presentation. Thinning and angulations of long bones progressive deformity can occur throughout early childhood, and it is imperative that clinicians monitor for this

development in order to prevent limb amputation [16]. Bowing of the forearm is less common.

Thoracic cage asymmetry with flaring or prominence of the inferior ribs is seen in some children with NF1 but rarely requires surgical intervention.

Scoliosis affects 10–20% of children with NF1 and may occur at earlier age than in the general population [16, 26]. Scoliosis with or without kyphosis, may become evident in childhood or adolescence. In a child younger than 10 years, scoliosis is associated with a poorer prognosis and is likely to progress rapidly.

When associated with paravertebral neurofibromas, scoliosis may present with an abrupt angle curvature (dystrophic scoliosis). This type of scoliosis is difficult to correct surgically. Scoliosis detected in adolescence should be followed clinically but is less likely to require orthopedic intervention.

Patient with NF1 are often short in stature, with 13% of patients falling more than two standard deviations (SD) below the mean [6].

Children and adults with NF1 often demonstrated relative macrocephaly, with more than 24% of patients having a head circumference greater than two SD above the mean [6, 13, 16]. There is no association between this macrocephaly and learning disabilities or underlying structural brain abnormalities [13].

Our observation regarding the osseous involvement in NF1 corresponds with the data from the literature. First, it is very different from case to case in aspect and gravity. Also the disease can be evident from the birth, evolving progressively to forms much more severe like in the first three cases described by us, or to evolve much time asymptomatic been discovered tardily in much complex exploration.

This is the case of our patient of age of 37 years old, which presents a suggestive symptomatology of disc hernia. The MRI scan shows tumor, possibly neurofibromas at the L1–L2 and T11–T12 neural foramina with their enlargement which explain the symptoms accused by the patient.

The maxillary and mandible involvement considerable rare [27] has been discovered at two patients from 11, both patients present marginal chronic parodontosis and one of them pseudocystic mandible imagines. At one of the patients observed a titular nodular formation in the parotidian region, imagines not found in the literature.

As a personal finding is that, the osseous abnormalities were more pregnant in the group of patients without dermal neurofibromas, only with hyperpigmented spots. We do not have an explanation of this fact but it is difficult to believe that is a simple coincidence. It is necessary more studies to prove if exist a correlation between the two forms of dermal presentation of NF1 and the grade of osseous involvement.

Finally, with the exception of three patients, all the others (indifferent of the form of dermal presentation) had a short and very short stature. The macrocephaly was evident at the patient with hypostature, but in none of them cannot be observed a correlation with some grade of intellectual deficit.

☞ Conclusions

The patients with NF1 has osseous abnormalities specific of the disease as well as dysplasia, scoliosis, pseudoarthrosis, often gentle but sometimes extremely severe. The most severe osseous involvement are presented in the cases when these development early in the childhood. Other times the osseous abnormalities are clinical asymptomatic, their finding been clinical incidental. We want to have a separate mention for the maxillary and mandible involvement, which according to our information is not a rare form.

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