

CASE REPORT

Diagnostic difficulties in fibrous dysplasia – a 5-case series and a literature review

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ABSTRACT

Fibrous dysplasia is an uncommon disorder of the skeleton bones characterized by proliferation of fibro-osseous tissue. It can affect any skeleton bone. In case of craniofacial involvement, the symptoms occur earlier than in other regions; deformed facial aspect or/and pain are the main complaints. The best imagistic evaluation is a CT scan and it should be performed at any age. In case the clinical and imagistic evaluations raise the suspicion of a malignant disease, a biopsy must be taken. Given the rare incidence of the disease, it is difficult to confirm it even after the CT examination. A trained and experienced radiologist is the key, as he is the one who can measure and compare the bone densities, differentiating it from Paget disease, sarcoma, type I neurofibromatosis or osteofibrous dysplasia. Regular check-ups are indicated, including control CT scans. In this article, we will discuss about the main diagnostic and therapeutic features of this controversial disease, focusing on our clinical experience.

KEYWORDS: dysplasia, headache, CT scan, endoscopic surgery, biopsy

INTRODUCTION

Fibrous dysplasia (FD) is a very rare condition, a bone disease characterized by areas of abnormal growth or lesions in one or several bony structures. The process is related with the mutation in the gene that encodes the subunit of a stimulatory G protein ($G\alpha$)^{1,2} located on chromosome 20 (20q13.2-13.3)^{3,4}, manifested as a localized defect in osteoblastic differentiation and maturation; the osteoblastic cells elaborate a fibrous tissue in the bone marrow instead of normal bone.

Fibrous dysplasia of the bone is a non-heritable disease, which can occur in any bone. It is not a form of cancer and does not increase a person's susceptibility to cancer. Fibrous dysplasia represents about 5% of all benign bone tumors⁴. This rare disorder is usually diagnosed in childhood or early adulthood; about 75% of the cases are found under the age of 30 years⁵. There is no recognized gender predilection, males and females of any race being equally affected⁶. The true incidence of this disorder is unknown and many patients are asymptomatic. In some cases, it is discovered incidentally on an X-ray for another condition.

In symptomatic FD patients, pain is a common sign⁷.

The diagnostic algorithm in case of FD includes radiologic imaging and bone biopsy. Computed tomography (CT) and magnetic resonance imaging (MRI) are useful for evaluating the bony lesions and soft tissue components⁸.

FD has no etiological known cure, the surgical treatment being directed towards complications. Some authors mentioned good results with bisphosphonate therapy for patients with fibrous dysplasia⁹⁻¹¹.

OUR EXPERIENCE

Between 2010 and 2012, in the ENT Department of “Sfanta Maria” Clinical Hospital, were admitted 5 cases of fibrous dysplasia. All of the patients were women, aged between 12-69 years. Their final diagnose was established by clinical and imagistic criteria. Intraoperative endoscopic visualization of the involved bony structures did not raise the suspicion of a malignant tumor, so the FD diagnose was built without anatomopathological confirmation, as the risk of intra and postoperative complications was high.

Case 1

Female patient, 69 years old, refers to the clinic complaining of bilateral nasal obstruction started 5 years prior to presentation, aggravated in the past year. She was diagnosed with frontal fibrous dysplasia in her childhood (Figure 1a, 1b).

Anterior rhinoscopy revealed a large non-infiltrative tumoral mass that entirely occupied the right nasal cavity up to the limen nasi and the posterior part of the right nasal fossa. A cranio-facial computer to-

mography was required in order to establish the demarcation limit between the deformed bones (Figure 1c) and the obstructive mass. The CT-scan showed a non-homogeneous mass, with contrast opacification, filling the right ethmoidal and maxillary sinuses, the rhinopharynx, the right nasal fossa and the third posterior part of the left fossa (Figure 1d).

The endoscopic endonasal removal of the tumor was performed, under general anesthesia. The piece-meal resection was possible up to the olfactory fossa, without



Figure 1a Lateral view of the frontal dysplastic process and its posterior limit



Figure 1b Anterior view of the frontal deformity caused by FD



Figure 1c Axial CT scan of the skull showing a large, mutilating, FD of the frontal bone

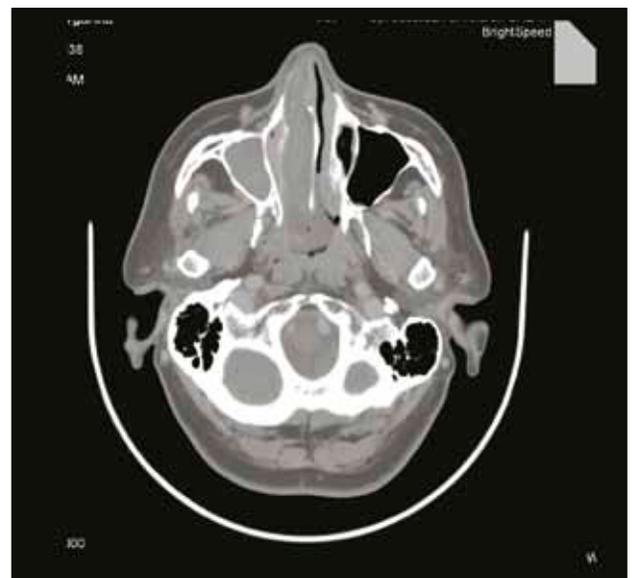


Figure 1d Axial CT section of the tumoral mass involving the right part of the naso-sinusal cavities and the rhinopharynx

any iatrogenic CSF fistula. The frozen histopathological sections examination showed the reactive nature of the lesion, with inflammatory cells, without malignant expression. On further examination, the anatomopathologist recognized only inflammatory polyps.

In this case, the new symptomatology was not a complication of the fibrous dysplasia. Even though our clinical experience indicated the possibility of an esthesioneuroblastoma originated from the cribriform plate, the decisive diagnostic was established by the histopathologic examination.

Postoperative outcome was free of incidents. When discharged, the patient received nasal corticotherapy and saline nasal showers. The twelve-month follow-up showed the absence of nasal tumoral relapse.

In this case, FD represented a radiological finding, without clinical connection with the current obstructive tumor and the patient's complaints. No treatment was needed for FD.

Case 2

A 65-year-old patient was admitted to investigate the cause of her right hemicrania. The headache had started 2 years before, had become persistent, accom-

panied by retro-orbital pressure and chronic posterior rhinorrhea. From her medical history, we acknowledged a bilateral concha bullosa resection a year before. Endonasal examination, revealing hypertrophic turbinates, was limited by a deviated nasal septum and a hypertrophic superior turbinate. The radiologist described a hypoplastic left sphenoidal sinus, with thick walls and dense fluid, partially densified (Figure 2a, 2b).

Although for us the CT images were representative for fibrous dysplasia, the late manifestation (untypical for fibrous dysplasia) and the imagist's opinion determined us to further investigate. Under general anesthesia, after the resection of the bullosa of the superior turbinate, the Onodi cell was reachable and surgically drained. We could not identify the natural ostium of the sphenoid sinus; the anterior wall of the sphenoid was compact, covered by normal mucosa – clinical finding that confirmed the sphenoidal fibrous dysplasia, mainly of the clivus (Figure 2c). It was important to exclude a tumor or chronic sphenoidal sinusitis.

The patient received symptomatic medical treatment in order to reduce the chronic rhinorrhea and the headache.



Figure 2a Cranio-facial CT scan, coronal slice - "hypoplastic" sphenoidal sinus

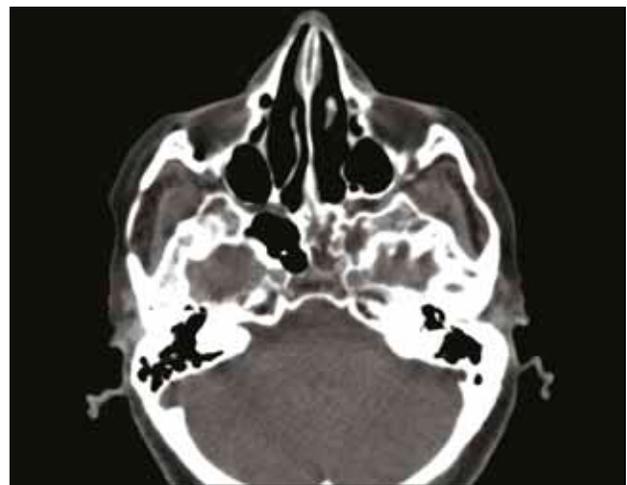


Figure 2b Axial CT scan of the skull – non-homogenous mass occupying the right sphenoidal body and its left wing



Figure 2c Skull CT scan - sagittal section - arrow pointing the transformed clivus

Case 3

Not having a definite diagnosis after being investigated in another clinic, a 39-year-old patient asked our medical opinion. She complained of intense left hemicrania and ipsilateral nasal obstruction with 3-month onset, symptoms slightly improving after nonsteroidal anti-inflammatory drugs. At the previous evaluation, before any imaging examination, a biopsy was taken from the rhinopharynx. The histopathologist described chronic rhinopharyngitis, with reactive lymphoid tissue. The cranial MRI subsequently performed revealed an effusive process enveloping the clivus, the left pterygopalatine fossa, the left sphenoid sinus, bulging in the cavum (Figure 3a).

Our nasal examination revealed hypertrophic inferior turbinate, congested nasal mucosa and the bulging of the sphenoid-ethmoidal area. Under endoscopic guidance, we performed left sphenoidotomy. Contradicting the MRI, the objective findings were: normal sphenoidal mucosa, absence of tumoral mass or mucopus; several fragments of tissue were prelevated from the rhinopharynx and from the hyperplastic ethmoidal mucosa – examination showed the same reactive tissue. Perioperative, steroidal treatment diminished the intensity of hemicrania.



Figure 3a Sagittal MRI - scan of the skull base

Clinical and paraclinical investigations suggested a fibrous dysplasia. To confirm this suspicion, a skull CT-scan was performed 7 days after the surgery, showing characteristic modifications in the bony sphenoid structure (Figure 3b).

Case 4

A 29-year-old female patient was admitted in our Department for dizziness, insecure walking and anxiety. A cranio-facial angio-MRI, taken 6 weeks before, described a thickened bone at the anterior wall of the maxillary sinus, inhomogeneous, up to 16 mm width, resembling fibrous dysplasia (Figure 4a, 4b) – with the recommendation of a skull CT scan.

Clinical ENT examination was normal. Additional vertigo tests were performed: no nystagmus, negative head-shaking-test, negative head-impulse-test, negative Romberg test, normal eye tracking, normal saccades, non-deviating segments, negative standing tests. All hearing investigations were normal (pure tone audiometry, BERA), including tympanogram - bilateral type A curve.

Due to the normal results of all clinical investigations and the radiologist's recommendation, the patient performed a cranio-facial CT scan. The osseous



Figure 3b Cranio-facial CT scan (coronal slice) – the half left sphenoid body modified by FD



Figure 4a Cranio-facial MRI, coronal slice - osseous tumor involving the anterior maxillary bone (arrows pointing the superior and inferior limit)

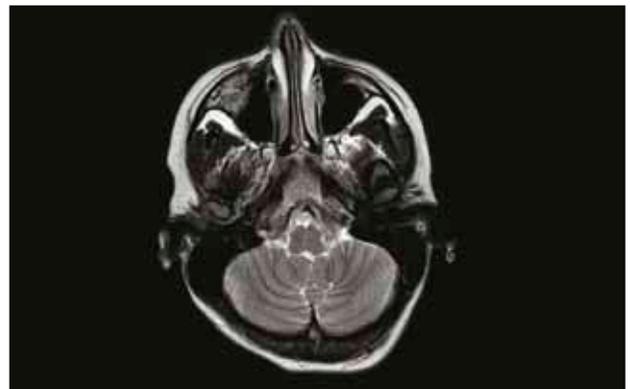


Figure 4b Axial MRI-scan showing the FD in the anterior wall of the right maxillary sinus

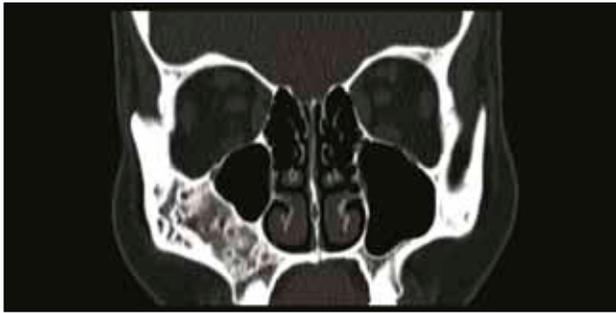


Figure 4c Cranio-facial CT section, coronal slice – non-infiltrative aspect of FD

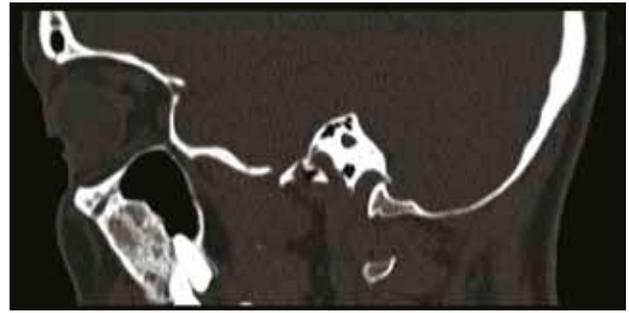


Figure 4d Sagittal view of the right maxillary sinus showing no protrusion through the anterior wall

lesion involved the anterior wall of the right maxillary sinus, measuring 20/14/18 mm, reducing the volume of the sinus cavity, with no protrusion through the anterior sinus wall (Figure 4c, 4d).

In this case, no aggressive treatment was needed. As long as the FD is not mutilating or invalidating, surgery is not indicated. Radiological follow-up is required every year.

Case 5

A 12-year-old teenager, with autoimmune thyroiditis, accusing severe headache in the fronto-temporal areas, first appeared 2 months before, was admitted in our ENT Clinic. The patient had been diagnosed and treated for acute sphenoiditis two weeks before the admission in our department. At the admission time, no clinical and endoscopic endonasal signs of sinusitis were present, but the headache lingered on.

The cranio-facial CT scan (Figure 5a, 5b) and the MRI (Figure 5c) scan (native and with contrast) revealed dysplasia of the posterior sphenoid wall and of the clivus, questioning the existence of a chronic inflammatory process of the sphenoid bone. The neurosurgical examination recommended skull base intervention with the biopsy of the suspicious tumoral mass.

Having the parents' approval, we proceeded with the endoscopic assessment of the naso-sinusal cavities: bilateral permeable sphenoidal ostia, normal endonasal mucosa, without pathological secretions; no bi-optic tissue was prelevated.

All factors put together (age, cephalalgia, clinical and imaging aspects) advocated for clivus fibrous dysplasia. Our recommendation was periodical check-ups and painkillers when needed.

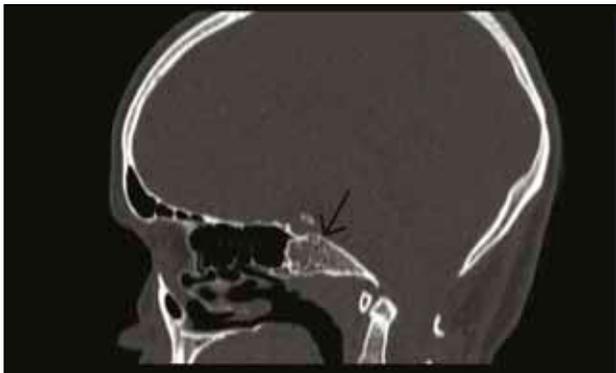


Figure 5a CT scan – sagittal view – modified clivus (arrow pointing)

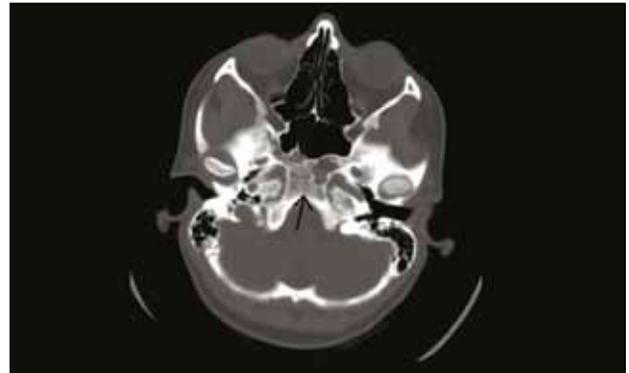


Figure 5b CT scan – axial view – clear sphenoidal sinuses and the FD of the clivus (arrow pointing)

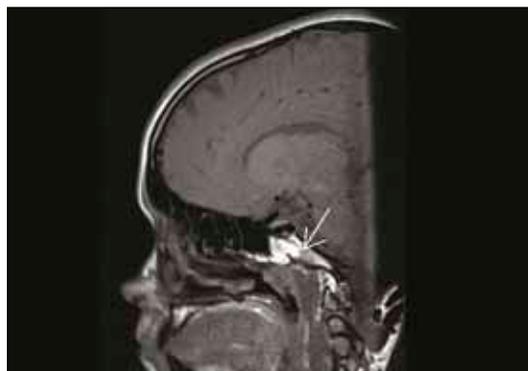


Figure 5c MRI-scan, sagittal section: sphenoidal process resembling an inflammatory lesion (arrow pointing)

DISCUSSIONS

GENERAL CLINICAL CHARACTERISTICS

The main types of fibrous dysplasia include monostotic FD, polyostotic FD and McCune-Albright syndrome. The main characteristics of these subtypes are as follows:

- Monostotic fibrous dysplasia – only one bone is affected.
 - It is by far the most common and accounts for 70-80% of cases⁸.
 - Monostotic destruction affects the ribs 28% - most common, proximal femur 23%, tibia¹², craniofacial bones 10-25%¹³, humerus.
 - Following the ribs and long bones, craniofacial bones are the second most common site of involvement¹⁴ and comprise 25% of the cases¹⁵.
 - However, fibrous dysplasia of paranasal sinuses is rare¹⁶.
 - Among fibrous dysplasia of the head and neck, the maxilla and mandible are the most frequent sites to be involved, followed by the frontal, parietal and occipital bones¹⁷.
- Polyostotic fibrous dysplasia – two or more bones are affected.
 - The association of multiple skull and facial bones is considered to be 50% of the polyostotic form¹⁰.
- McCune-Albright syndrome – fibrous dysplasia can be associated with hormone disturbances and skin pigment changes.
 - The incidence of McCune-Albright syndrome is about 10% of all FD.
 - Females are affected more often than males¹⁸.

FD is a paucisymptomatic disease. When symptoms occur, they can include:

- Bone pain – caused by the expansion of bone or the pressure of the expanding bone against a nerve.

- Unusual gait – for example, walking with short steps, rocking from side to side when walking, limping.
- Irregular bone growth.
- Bone deformity.
- Increased susceptibility to bone fractures.
- Nerve entrapment.
- Visual complications (occur when the sphenoidal complex is involved)¹⁹.
- Arthritis (in the hip and knee joints).

Most commonly, fibrous dysplasia is asymptomatic until there is encroachment upon adjacent vital structures. Leeds and al. consider that facial asymmetry is the most common sign of fibrous dysplasia in the head and neck, followed by pain, ocular proptosis and neurological changes²⁰. In our days, Rahman et al. suggest another classification for signs and symptoms of FD in the cervico-facial area²¹ (Table 1).

Rarely, fibrous dysplasia may be associated with abnormalities in the hormone-producing glands of the endocrine system²², as:

- Very early puberty (precocious puberty in girls²³ with onset before 10 years of age)
- Overactive pituitary gland, which could lead to abnormal height
- Thyroid gland problems: hyperthyroidism, hyperparathyroidism; renal stones, calcinosis, diabetes mellitus, Cushing's syndrome.
- Changes in skin color - light brown spots (café au lait)²⁴.

INVESTIGATIONS

Some investigations must be performed in order to confirm the diagnosis or to determine the extension of the disorder:

- Medical history.
- Physical examination.
- Blood tests.
- Endocrine screening.

Table 1
Classification of the signs and symptoms (after Rahman et al.²¹)

Objective	Subjective
Facial asymmetry (86%)	Blurred vision (24%)
Tumor Mass (64%)	Headache (20%)
Eyelid position abnormalities (10%)	Diplopia (8%)
Loss of visual field (8%)	
Sinusitis (8%)	
Epiphora (7%)	
Hearing loss (3%)	
Epistaxis (3%)	

- Imaging tests.
 - X-ray examinations, computerized tomography or magnetic resonance imaging scans may be used to determine the extension.
 - Radiographic examination usually reveals a well-circumscribed lesion occupying all or a portion of the shaft of the long bone involved, with a foggy appearance of the matrix. There is a narrow area of transition and no periosteal reaction or soft tissue mass²⁵.
 - EOS X-ray Imaging System creates 3-dimensional models from two planar images. Unlike a CT scan, EOS images are taken while the patient is in an upright or standing position, enabling improved diagnosis due to weight-bearing positioning.
 - Dental radiographs (e.g. Orthopantomograph and dental films) to examine lesions around the dentition.
 - CT scans of the bones can provide detailed information about the bone tissue. The description “ground glass appearance” is described in 56% of cases¹⁰; sometimes endosteal scalloping may be seen⁸. The margin between abnormal and normal bone is often difficult to identify, the two regions blending with each other; however, on occasion, a relatively sharp demarcation may be present⁶.
 - MRI findings are not specific. They do not replace the necessity of a CT examination. MRI appearance is variable, depending on the degree of lucencies versus sclerosis^{6,8}.
- Bone scan using radioactive tracers – e.g. partial multiphase skeletal scintigraphy – shows the increased bone metabolism in the area, useful to demonstrate the extent of the disease²⁶. As a first step in the evaluation, a full-body ⁹⁹Tc-methylene diphosphonate (MDP) bone scan is recommended not only to evaluate the biologic activity of the index lesion, but to detect any additional lesions that may exist throughout the skeleton²⁷.
- Biopsy (i.e. using a hollow needle). Unfortunately, the histology does not predict the biological behaviour of these lesions^{28,29}.
 - It has been suggested that it is possible to obtain a correct diagnosis of fibrous dysplasia without the need for a biopsy^{30,31}.
 - However, biopsy might be needed if the diagnosis is doubtful or malignant transformation is suspected³².

TREATMENT

There is no cure for FD. In this case, the treatments are focused on the complications of the disease. For the quality of life, physiotherapy is indicated to improve joint mobility. Overtreatment of fibrous dysplasia

should be avoided because most patients respond to conservative management. Asymptomatic patients do not need treatment.

Medication

As the pain is the main symptom, once other diseases are excluded, the treatment intention is pain management.

Medical treatment is guided for rickets (softening and weakening of the bones due to deficiency of vitamin D, calcium, or phosphate), hormone imbalances, medication to strengthen bones (such as drugs commonly used in the treatment of osteoporosis).

Many authors can be credited with reporting the initial European experience with bisphosphonate therapy for patients with fibrous dysplasia⁹⁻¹¹. Osteoporosis medications, particularly pamidronate (a second-generation bisphosphonate), may help strengthen bones affected by fibrous dysplasia, as it is a potent inhibitor of bone resorption³³⁻³⁵ and has a lasting effect on bone turnover. This can relieve pain and help reduce the risk of fractures. Liens et al. supplemented this treatment with calcium (500 to 1500 mg/day) and vitamin D (800 to 1200 IU/day)¹⁰.

Some authors suggest applying calcitonin in combination with surgical treatment. Calcitonin treatment aims local bone calcification, which leads to reduction in bleeding during the bone remodelling³⁶.

Useful biomarkers such as serum alkaline phosphatase and urinary hydroxyproline can be used to monitor response in the nonsurgical treatment of the disease rather for diagnosis^{37,38}.

Surgery

In those cases refractory to medical treatment, surgery - in experienced hands - can result in a good functional and cosmetic outcome³⁹.

Because extensive removal of FD is associated with a low rate of tumor recurrence, this type of surgery was especially recommended for children with low predicted surgical morbidity and for symptomatic patients⁴⁰.

Surgery is required in order to:

- Reduce a fracture.
- Correct a deformity.
- Correct a difference in limb lengths.
- Remove an affected area of bone.
- Relieve pressure on a nerve, particularly if the lesion is in the skull or face.

Surgery may involve replacing the excised bone lesion with bone grafted from another part of the body or from a deceased donor bone.

Radiation

It is not used to treat fibrous dysplasia. In case of a FD patient who receives radiotherapy for another dis-

ease, the clinician should be aware of the possibility of malignant transformation; even if it is a rare event, it can be precipitated by radiation therapy⁴¹.

Malignant change to osteosarcoma or other forms of sarcoma⁴² has been reported to occur in less than 1% of cases of FD⁴³⁻⁴⁷.

On average, 13.5 years pass between diagnosis and progression of osteosarcoma, fibrosarcoma, chondrosarcoma, or giant cell sarcoma⁴⁸.

DIFFICULTIES IN DIFFERENTIAL DIAGNOSIS

- Paget's disease
 - The resorptive phase of Paget's disease radiographically may resemble fibrous dysplasia.
 - The disorder is characterized by a generalized widening and often bowing of the long bones and thickening of the skull⁴⁹.
 - It is distinguishable from fibrous dysplasia by the accompanying marked elevation in serum alkaline phosphatase levels⁴ and, histologically, it has a mosaic bone pattern.
- Neurofibromatosis type I
 - The difficulty to differentiate these two entities consists in their common features: café au lait spots, bony dysplasia (especially tibia) and sphenoid wing dysplasia.
 - Characteristically, the von Recklinghausen patients have learning disabilities, iris hamartomas (Lisch nodules) and one or more neurofibromas.
 - The osseous lesions are rare.
 - When ribs are affected, the radiological aspect is like a ribbon – thinned and attenuated appearance of ribs.
- Osteofibrous dysplasia
 - Also known as ossifying fibroma.
 - It is usually identified in children younger than 10 years of age, and has a remarkable radiographic resemblance to fibrous dysplasia⁵⁰.
 - It is the most common benign tumor occurring in the paranasal sinuses. The fronto-ethmoid region is the most common site of origin.
 - It is a well-demarcated benign fibro-osseous tumour with capsule, a tiny sclerotic shell composed of metaplastic-sclerotic bone, fibrous tissue and varying amounts of osteoid⁵¹. Fibrous dysplasia is not well circumscribed, and its borders are difficult to define.
 - It appears locally aggressive, with cortical disruption and involvement of many adjacent anatomical structures⁵².
- Sometimes, highly cellular areas of fibrous dysplasia may be diagnosed incorrectly as sarcoma. Focal areas of hyaline cartilage can dominate the microscopic picture, resulting in misdiagnosis of cartilaginous tumor⁵³.

CRANIO-FACIAL FEATURES OF FIBROUS DYSPLASIA

The diagnosis of monostotic fibrous dysplasia is based on clinical, radiographic and histopathological findings.

The craniofacial form occurs typically around 10 years of age and then progresses throughout adolescence⁵⁴.

According to Mirra concept, "when a single bone (monostotic) is affected, it probably represents a forme fruste of the more severe form (polyostotic)." He stated that the craniofacial bones affected by fibrous dysplasia are in the following order: frontal > sphenoid > ethmoid > maxilla > mandible > zygoma > parietal > occipital > temporal⁵⁵.

The most common presenting features included atypical facial pain and headache, complaints referable to the sinuses, proptosis and diplopia, hearing loss and facial numbness⁵⁶.

Monostotic fibrous dysplasia of the clivus is extremely rare^{57, 58}.

Previously, only a few cases of FD of the clivus have been reported in the literature^{57, 59}.

CONCLUSIONS

Fibrous dysplasia is a genetic nonhereditary disease. The diagnosis of FD is established by clinical and imaging criteria. If malignant tumor is not suspected, the bone biopsy is not strictly necessary. Mainly, the treatment is focused to solve complications or to alleviate pain, the most common symptom in FD. Frequently, it manifests and is diagnosed in childhood. It has no etiological treatment.

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