Fibrous dysplasia of the sinonasal tract and adjacent skull base

Alberto Schreiber[a], *Andrea B. Villaret*[a], *Roberto Maroldi*[b], *and Piero Nicolai*[a]

Purpose of review
Fibrous dysplasia is a rare condition characterized by replacement of normal bone by fibro-osseous connective tissue exhibiting varying degrees of osseous metaplasia, which can affect the craniofacial complex. This article reviews the recent literature with the intent to highlight the innovative information that has contributed to elucidate the pathophysiology, diagnostic criteria, and treatment principles of the disease.

Recent findings
A mutation in the GNAS1 gene on chromosome 20 has been identified as the molecular hallmark of fibrous dysplasia. This finding is not present in ossifying fibroma, which has been traditionally included in differential diagnosis. The concept that asymptomatic patients do not require surgical treatment has been reinforced by a meta-analysis specifically addressing the issue of optic nerve decompression.

Summary
A diagnosis of fibrous dysplasia can be achieved by combined assessment of clinical, radiologic, and pathologic findings. There is general agreement that, when the disease is not associated with symptoms, partial or radical resection is not indicated, but patients do require periodic radiologic evaluations. There is, however, an absolute need for prospective studies to identify factors predicting the possible late growth of the disease and to investigate the efficacy and side-effects of pharmacological treatment with biphosphonates.

Keywords
endoscopic sinus surgery, fibrous dysplasia, optic nerve decompression, skull base lesions

INTRODUCTION

Fibrous dysplasia is a benign, slowly progressing dysplastic process of altered osteogenesis that may occur within a single or multiple bones; in the latter form, it may be associated with endocrinopathies and abnormal pigmentation of the skin. Rather than a true neoplasm, the disease can be regarded as a developmental anomaly in which the normal medullary space of the affected bone is progressively replaced by disorganized fibro-osseous tissue. The disease was first observed more than a century ago by Von Recklinghausen [1] in a group of patients affected by a bone disease that he called osteitis fibrosa generalisata. In 1938, Lichtenstein [2] described eight cases of a fibro-osseous bone disease affecting multiple bones without extraskeletal manifestations using the present day terminology of 'polyostotic fibrous dysplasia'. Subsequently, Lichtenstein and Jaffe [3] noted that the changes might be confined to a single bone and coined the name fibrous dysplasia. In 1968, Ramsey *et al.* [4] proposed a classification system subdividing the disease into three types: type 1, characterized by unique or multiple lesions in a single bone (monostotic); type 2, characterized by multiple lesions involving different bones (polyostotic); and type 3, characterized by dissemination of pathological bone changes connected to other disturbances such as McCune–Albright syndrome (polyostotic fibrous dysplasia, cutaneous pigmentation, and endocrine abnormalities). Monostotic fibrous dysplasia is the most common form (80%), with prevalent involvement of the ribs and femur, and 20% of cases

[a]Department of Otorhinolaryngology and [b]Department of Radiology, University of Brescia, Brescia, Italy

Correspondence to Piero Nicolai, MD, Department of Otorhinolaryngology, University of Brescia, Piazza Spedali Civili 1, 25123 Brescia, Italy. Tel: +39 30 3995319; fax: +39 30 395212; e-mail: pieronicolai@virgilio.it

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KEY POINTS

- Fibrous dysplasia of the craniofacial skeleton frequently involves the skull base.
- Fibrous dysplasia is associated with a mutation in the gene encoding the alpha subunit of the Gs protein located on chromosome 20. This genetic alteration is lacking in ossifying fibroma, a disease that radiologically mimics fibrous dysplasia.
- Surgery is indicated in symptomatic patients. The advantages of treatment should be appropriately weighed against possible complications.
- In lesions encroaching on the optic nerve, prophylactic decompression with the intent to prevent possible visual impairment is not recommended.
- The efficacy of biphosphonates as the sole therapy or as an adjunct to surgery in symptomatic patients needs to be explored in properly designed studies.

localized in the head and neck region [5]. Multiple areas of the skeleton are involved in polyostotic fibrous dysplasia, which overall accounts for 20% of cases; the rate of craniofacial involvement is quite variable, ranging from 50 to 100% [6]. Other than McCune–Albright syndrome, polyostotic fibrous dysplasia may be associated with primary hyperparathyroidism, tuberous sclerosis, and soft-tissue myxomas (Mazabraud's syndrome). Although it can be considered a very rare event, the coexistence of fibrous dysplasia with aneurysmal bone cyst has also been described [7].

Most lesions are diagnosed before the age of 30 years with no sex predilection. The skull base is the most common site of involvement when the disease involves the craniofacial skeleton [8▪▪]. Although fibrous dysplasia growth has been traditionally described as self-limiting after puberty, there is evidence that the lesion can be diagnosed in adulthood or occurs as regrowth after partial surgical resection performed in an apparently stabilized lesion. Another peculiarity of the biological behavior of fibrous dysplasia is the possibility of malignant degeneration, which is observed in 0.4–4% of cases [9]; the most common histotypes are osteosarcoma, fibrosarcoma, and chondrosarcoma, which occur in the third or fourth decade of life. Reported cases of sarcomatous degeneration are more common after radiation therapy and in polyostotic fibrous dysplasia.

Herein, we review the clinico-pathological features of fibrous dysplasia with special reference to advances in the management of lesions involving the sinonasal tract and its surroundings.

HISTOPATHOLOGY, ETIOPATHOGENESIS, AND DIFFERENTIAL DIAGNOSIS

Histologically, fibrous dysplasia is characterized by replacement of medullary bone by abnormal fibrous tissue with variable cellularity and density associated with trabeculae of woven bone with an irregular shape and lacking osteoblastic rimming. Fibrous dysplasia foci are typically not encapsulated and there is fusing and blending between normal and abnormal bone, making the margins of this lesion impossible to verify [10]. Eversole *et al.* [11▪] detailed the histological changes that occur during progression of the disease. Active osteogenesis with osteoblasts surrounding thin osteoid trabeculae and a hypercellular, proliferative, fibroblastic component without pleomorphisms are observed in the early formative phase. Subsequently, the bony trabeculae thicken and assume a typical aspect described as 'Chinese or Hebrew letters' or 'alphabet soup', whereas fibrous tissue continues to be hypercellular. The stabilized form of the disease is characterized by extensive remodeling that may result in a mosaic pattern of resting and reversal lines.

In the past, several hypotheses (i.e., posttraumatic, malformation, and hormonal) have been proposed to explain the origin of fibrous dysplasia, but it was only in the early 1990s that studies on the genetic substrate of the disease shed light on its pathophysiology [12,13]. An activating missense mutation on chromosome 20 in the gene encoding the alpha subunit of the G_s protein (GNAS gene), which results in prolonged adenylyl cyclase activity and a subsequent increase in intracellular cAMP, was first described in patients with McCune–Albright syndrome [12,13], and subsequently even in monostotic and polyostotic fibrous dysplasia [14,15]. The mutation occurs early in embryogenesis and therefore affects cells that are then distributed in a mosaic pattern. The proportion and distribution of affected cells in endocrine and nonendocrine tissues are determined by the precise stage of development at which the mutation occurred. Thus, mutational events that occur later in embryogenesis are likely to give rise to fewer mutant cells and a milder phenotype than mutational events that occur very early [16]. The modifications of biological pathways produced by gene mutation have been recently summarized by Garcia *et al.* [17▪▪]. Activation of Gsalfa/PKA/CREB pathway induces overexpression of c-fos in mesenchymal precursor cells, which interferes with normal osteoblastic differentiation. The increase in cAMP could have a two-fold effect: downregulation of the osteoblastic transcription factor Runx2, contributing to abnormal osteoblastic differentiation, and osteoclast recruitment and activation with

consequent bone resorption, via an increase in interleukin 6 levels.

As for most benign fibro-osseous lesions, a definitive diagnosis of fibrous dysplasia can rarely be rendered on the basis of microscopic features alone, and other findings such as age and sex together with radiologic presentation need to be considered [11▪]. Ossifying fibroma presents more histologic similarities and radiologic overlapping features with fibrous dysplasia: Voytek *et al.* [18] concluded that they could be considered as diseases at either end of a single morphological spectrum. However, the clinical course of the two diseases is quite different, with fibrous dysplasia having the tendency to stabilize after adolescence and ossifying fibroma progressing in size, so achieving a correct diagnosis is relevant from a therapeutic standpoint. Toyosawa *et al.* [19] have recently provided a clue to distinguish the two entities, by demonstrating with immunohistochemistry and PCR analysis of GNAS mutations, respectively, the abundance of osteocalcin and the presence of mutations in fibrous dysplasia only. These findings suggest that they are probably distinct disease entities.

CLINICO-RADIOLOGIC PROFILE

Patients with fibrous dysplasia are frequently asymptomatic and diagnosis may be incidental after imaging examination performed for other reasons. When signs and symptoms become evident, they are strictly related to the site and size of the lesion. The most common clinical presentation of fibrous dysplasia in the head and neck area is facial asymmetry, followed by ocular symptoms, headache, and hearing loss [8▪▪]. When the lesion involves the sinonasal tract, symptoms suggestive of recurrent rhinosinusitis (nasal obstruction, pain, and hypo/anosmia) or trigeminal neuralgia are frequently reported [20]. Severe impairment of sinus outflow may even lead to the formation of a secondary mucocele [21] or to periorbital abscess [22]. Diplopia, proptosis, and epiphora may be observed when the lesion displaces the orbital content, while compression of the optic nerve can be associated with impairment of visual acuity. Occasionally, fibrous dysplasia may extend intracranially and produce pneumocephalus, meningitis, cerebrospinal fluid leak, or neurologic changes [23]. Patients with McCune–Albright syndrome typically present with endocrine dysfunctions, which include precocious puberty, hypersecretion of growth hormone (GH), hyperprolactinemia, hyperthyroidism, adrenal hyperplasia causing hypercortisolism and Cushing's syndrome, and nonendocrine manifestations such as cutaneous hyperpigmentation and renal phosphate wasting, in a different association.

The role of endoscopic evaluation in diagnosis of fibrous dysplasia is quite limited, as the examination is often negative, or it shows an expansile lesion covered by normal mucosa in a minority of cases. Imaging techniques are therefore essential in diagnosis and defining the site, the extent, and the relationship of the lesion with adjacent structures. Fibrous dysplasia is detected by imaging techniques as an intramedullary, expansile, and well defined lesion [24,25]. The cortical rim lining of fibrous dysplasia shows a variable thickness and mineralization because of the mass effect of the medullary lesion. The rim conforms to the general shape of the involved bone, albeit enlarged. On conventional radiography, most fibrous dysplasia lesions show variable degrees of hazy radio-opacity with a ground-glass appearance. The grade of indistinctness of the bony trabeculae directly correlates with the histopathology of fibrous dysplasia, reflecting the balance between the radio-lucent fibrous tissue and the radio-opaque mineralized woven bone [26]. In fact, fibrous dysplasia lesions may present almost completely as radio-lucent or radio-opaque (sclerotic) intramedullary bone lesions. A cystic-like appearance – complete radio-lucency – may correspond to areas of necrosis [27].

In 1957, Fries [28] described three possible patterns of craniofacial fibrous dysplasia: pagetoid (56%), sclerotic (23%), and cystic (21%), all characterized by a lesion expanding the bone. In the pagetoid pattern, a patchy mixing of fibrous tissue and woven bone accounts for alternating areas of radio-lucency and radio-opacity, similar to Paget's disease. In the sclerotic and cystic forms, there is the predominance of woven bone and fibrous tissue, respectively.

The most common findings of fibrous dysplasia on computed tomography (CT) are an expanded bone with ground-glass appearance [29,30]. As for conventional radiography, the ground-glass appearance depends on the degree of metaplastic bone formation. Therefore, at CT fibrous dysplasia may range from a radio-lucent lesion, difficult to differentiate from a simple bone cyst, to a radio-opaque lesion with preponderance of dense osseous tissue [5,31,32]. CT overcomes the geometric limitations of conventional radiography and precisely demonstrates the narrowing of neural and vascular foramina because of progressive bone expansion (Figs 1 and 2). On magnetic resonance (MR), the diagnosis may be easier only if fibrous dysplasia causes a bone expansion that conforms to the original shape of the involved bone. Otherwise, proper diagnosis is difficult because of unspecific signal features

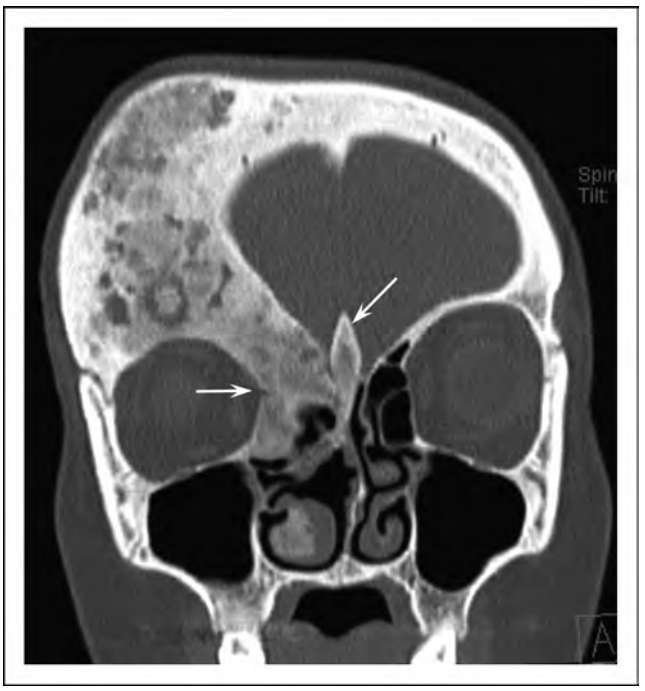

FIGURE 1. Fibrous dysplasia in a 53-year-old woman. Computed tomography shows extensive diploic widening of right frontal bone and ethmoid bone, involving the crista galli (oblique arrow). Though enlarged, both bones conform to their original shape. Their nonhomogeneous content suggests a mixing of fibrous and mineralized bone. The right orbital cavity is narrowed, and the anterior ethmoid artery channel is partially detectable (horizontal arrow).

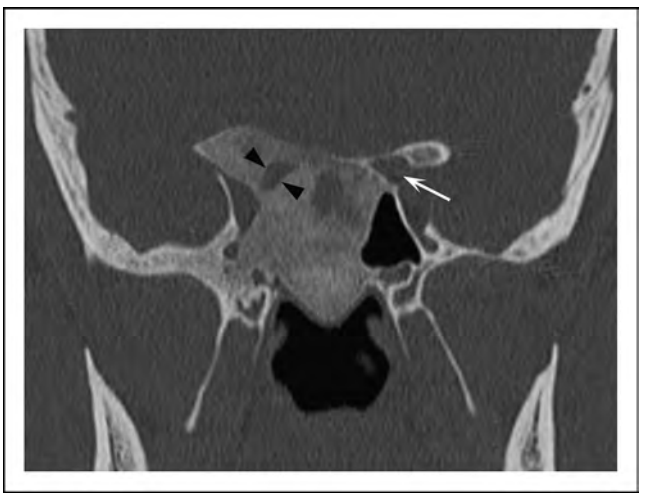

FIGURE 2. Fibrous dysplasia in a 40-year-old man. Computed tomography shows the involvement of the sphenoid bone. The coronal plane section clearly demonstrates narrowing of the right optic nerve canal (black arrowheads) because of enlargement of the right nonpneumatized sphenoid sinus and right lesser wing. Incomplete mineralization of the fibrous dysplasia within the right sphenoid sinus can be observed (left optic canal, white arrow).

[20,24,33,34]. In fact, the signal intensity on T1-weighted images may vary, depending on the ratio between fibrous and mineralized tissue, which is more hypointense when bone predominates. In addition, on T2-weighted images, bright signal intensity may be observed in lesions with high fibrous content and cystic spaces. The fibrous tissue in fibrous dysplasia is well vascularized and enhances intensively after contrast agent administration [30,35]. Although MR may not differentiate fibrous dysplasia on the basis of signal intensity as effectively as CT, it is highly accurate to analyze the spatial relationship with critical structures (Fig. 3), such as the orbit, dura, cranial nerves, cavernous sinus, and internal carotid artery, in addition to identifying possible complications (mucocele and abscess).

Among the bone lesions that mimic fibrous dysplasia are those – like ossifying fibroma and Paget's disease – characterized by bone expansion, preserved cortical rim, variable degree of medullary mineralization and radio-opacity. Though imaging findings are usually insufficient to precisely discriminate fibrous dysplasia from ossifying fibroma, a multiloculated lesion, bordered by a peripheral eggshell-like dense rim on CT [36], suggests a diagnosis of ossifying fibroma.

Moreover, the CT appearance of Paget's disease may often be confused with fibrous dysplasia [31], particularly because of diploic widening and the simultaneous presence of mixed lytic and sclerotic changes. Fibrous dysplasia can be reliably differentiated because of its ground-glass appearance and sinus involvement (particularly the sphenoid sinus). In Paget's disease, the symmetry of skull involvement is considered the most valuable sign for differential diagnosis [31].

TREATMENT STRATEGIES

In view of the rarity of fibrous dysplasia, only a few long-term studies are available and the patient cohorts are almost invariably limited in number; as a consequence, no treatment guidelines exist. Although in the past surgical resection was the only therapeutic option, in recent years some promising results have been reported regarding the administration of biphosphonates (pamidronate, alendronate, and zoledronic acid) [37,38]. Treatment planning must take into account several factors (i.e., natural history of the disease, presence of symptoms, site of the lesion, and the relationship with critical anatomic structures). Whenever surgery is considered, the morbidity of the intervention should be weighed against the potential benefits of achieving relief of symptoms or

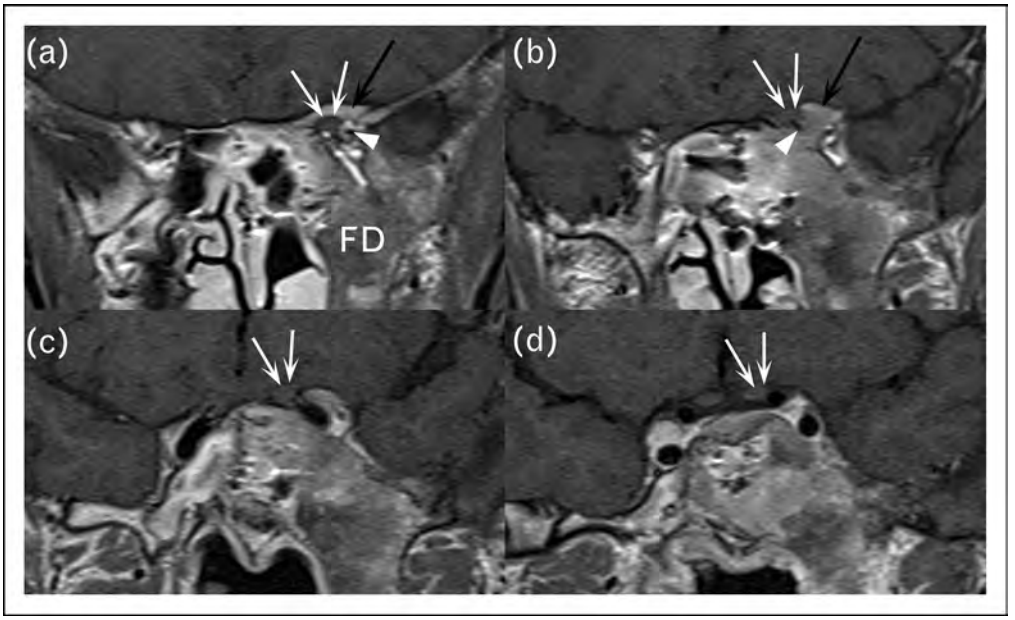

FIGURE 3. (a–d). Fibrous dysplasia in a 40-year-old men. Magnetic resonance in the coronal plane, T1-weighted image after contrast agent administration. Fibrous dysplasia of left sphenoid bone. In (a) and (b), the left optic nerve (white arrows) and ophthalmic artery (arrowhead) are surrounded by the fibrous dysplasia involving the lesser wing (black arrows), the sphenoid sinus, and pterygoid process (fibrous dysplasia). (c) and (d) show the course of the left optic nerve towards the chiasm. Nonhomogeneous enhancement of fibrous dysplasia is demonstrated after contrast agent administration.

improving aesthetic deformities. As stated by Chen and Noordhoff [39], 'any aggressive surgery should not cause a more severe functional or aesthetic disturbance'.

Although fibrous dysplasia is considered to stabilize after skeletal maturation, there is evidence that some lesions continue to grow even after puberty or can reactivate under specific circumstances like pregnancy. These possibilities are unpredictable based on clinical and radiological findings, as it is impossible to anticipate whether a malignant transformation will eventually occur. Therefore, monitoring the lesion with periodic imaging examinations is mandatory when a 'wait and see' policy is adopted. When surgery is planned to correct an aesthetic alteration not associated with symptoms, it is usually postponed until lesion growth subsides. The occurrence of symptoms related to sinus obstruction, compression of the orbital content or optic nerve, or intracranial extension, which can occur suddenly, leading to the diagnosis of fibrous dysplasia, or develop in a previously diagnosed patient, is a clear indication that surgery is required in the short term or even as an emergency procedure, as in the case of sudden impairment of vision from optic nerve compression.

Although in the past conservative contouring of bone was the recommended treatment, in recent years a more aggressive management philosophy has developed in view of the improvement of surgical techniques and the more liberal use of free flaps for reconstruction. One additional argument in favor of radical excision is the exceedingly rare observation of recurrence [40], while regrowth occurs in up to 50% of patients receiving partial removal [41]. Chen and Noordhoff [39] provided some practical general principles on surgical management of craniomaxillofacial fibrous dysplasia, which are still valid, based on the classification of the anatomic area into four major zones. Zone 1 is the facial area above the maxillary alveolar bone, where radical resection and reconstruction are feasible without adverse cosmetic or functional disturbance. Zone 2 corresponds to the hair-bearing cranium, where cosmetic appearance is less affected than in Zone 1, and treatment can be reasonably more conservative. Zone 3 includes the central cranial base, petrous, mastoid, and pterygoid region, where major vessels and nerves can be encased by the lesion. In view of the nonnegligible associated morbidity, surgery is justified only when symptoms are present. Zone 4 encompasses the teeth-bearing bones. The recommendation of the authors favored a conservative attitude, while at present the availability of sophisticated free flaps such as fibula, iliac crest, and scapula enables radical resection and adequate dental rehabilitation with osteointegrated implants [40].

The progressive expansion of the indications of endoscopic sinus surgery has favored the involvement of rhinosurgeons in many steps of the management of fibrous dysplasia. An endoscopic approach is obviously ideal to obtain a biopsy in deeply located lesions, when differential diagnosis is not clear at imaging and a tissue sample is required, to improve the drainage of a sinus when the fibrous dysplasia focus is impacting on the outflow, causing a sinusitis or a mucocele [42], or to completely remove a symptomatic lesion in the rare cases where no major morbidity is expected [43]. However, the most challenging area where endoscopic surgery is involved is the management of optic nerve encasement, with consequent possible visual loss due to nerve ischemia and compression. Since its first description in 1998 by Luxenberger *et al.* [44], endoscopic optic nerve decompression has become widely accepted as the approach of choice for posttraumatic injuries and subsequently for benign lesions compressing the nerve and accessible through the nose, such as fibrous dysplasia. However, controversies exist on its indications, and the issue has been the subject of critical re-evaluations to determine if asymptomatic patients should be regularly monitored or if they should receive prophylactic decompression of the nerve, which potentially exposes the patient to the risk of visual impairment or blindness. Lee *et al.* [45] performed a well designed case–control study on 38 patients with fibrous dysplasia of the lesser sphenoid wing, who underwent a detailed neuro-ophthalmologic examination and CT to measure the extent of involvement and area of the optic canals. The major conclusion was that prophylactic decompression of the optic nerve could not be recommended based on imaging alone, as the results of radiologic measurements did not correlate with visual loss. A complete ophthalmologic evaluation (best corrected visual acuity, visual field, color vision, and examination of the fundus) was advocated for the early detection of the most subtle changes. Cutler *et al.* [46] performed a retrospective analysis on patient records, endocrine testing, computed tomography, and neuro-ophthalmologic examination in 91 patients with craniofacial fibrous dysplasia involving the optic nerves: 17% of nerves were less than 50% encased, 22% were 50–99% encased, and 61% were 100% encased. Overall, only 13 (six prophylactic and seven therapeutic) nerve decompressions were performed. Similarly to Lee *et al.* [45], the authors found that the majority of optic nerves encased with fibrous dysplasia did not present symptoms of optic neuropathy and appeared to be stable over time. GH excess was associated with nerve encasement and optic neuropathy.

The conclusions of the previous studies [45,46] have been reinforced by a recent meta-analysis performed by Amit *et al.* [8▪▪] with the intent to evaluate the efficacy and outcome of decompression of the optic nerve in asymptomatic patients with optic canal narrowing. Criteria for inclusion were preoperative or postoperative histopathological diagnosis of fibrous dysplasia; radiologically demonstrated optic canal narrowing; pretreatment and posttreatment visual status (based on visual fields and visual acuity or patient visual status report); and at least 4 months of follow-up. A total of 198 patients were included in the study. One-half had optic nerve decompression (71 therapeutic and 28 prophylactic), whereas the other half were followed conservatively with serial radiographs and ophthalmologic evaluations. In asymptomatic patients, the results revealed stable vision in 87% of patients receiving decompression and 97% of patients not undergoing surgery ($P < 0.001$). Impairment of vision over many years is a rare event that can be associated with the concomitant presence of cystic lesions (i.e., mucocele, hemorrhage, and aneurysmal bone cyst) other than GH excess.

As for surgical therapy, medical treatment in fibrous dysplasia is also restricted to relieving symptoms [5]. Assuming that resorption of surrounding bone by osteoclasts of the advancing edge represents the critical step towards expansion [47], the use of drugs that inhibit osteoblastic resorption, such as biphosphonates, has been proposed. Open studies on small numbers of patients indicated that successful control of pain and stabilization of the disease can be obtained both clinically and radiologically [48]. Only one study [37] has specifically addressed the efficacy of biphosphonates in fibrous dysplasia of the head and neck. In six children with a progressive lesion receiving pamidronate infusions (1 mg/kg i.v. for 3 days, every 4–6 months), pain relief was achieved in all cases, a decrease in swelling in three, and stabilization in three patients. Radiological investigation revealed no progression, but a reduction in size and calcification of osteolytic lesions. Oral alendronate has been shown to satisfactorily control headache in patients with fibrous dysplasia of the skull that is not amenable to surgery [49].

Radiotherapy is strongly contraindicated because of the poor radiosensitivity of the lesion, the negative effects on the growth centers in young patients, and the risk of sarcomatous transformation [20].

Imaging evaluation plays a key role in monitoring patients with diagnosed fibrous dysplasia, who require periodic evaluations not only when a 'wait and see' policy is adopted but also after surgery,

especially in the case of partial resection. MRI is the ideal examination, as the patient is not exposed to radiation. Clinical suspicion of malignant degeneration is usually alerted by a rapid increase in size associated with pain; typical imaging findings consist of bone destruction and soft tissue invasion. Recently, serum alkaline phosphatase has been demonstrated to be a reliable indicator for disease progression in the postoperative setting [41]. Finally, in patients affected by McCune–Albright syndrome, ophthalmologic, neurologic, and endocrinologic evaluation should be performed every 6 months [50].

CONCLUSION

Fibrous dysplasia is a benign disease commonly diagnosed in the first three decades of life that should be included in the differential diagnosis of fibro-osseous lesions of the craniofacial complex. In view of its rarity, our present knowledge on the disease is based on the data reported in studies with a level of evidence of 3a [8▪▪], and it is not surprising that treatment guidelines are lacking. According to current recommendations, treatment should be reserved to patients with signs/symptoms, with surgery being the method of choice. The entity of resection (partial or radical) should be modulated based on the site of the lesion and consequently on the possibility of ensuing complications. The encouraging results reported in the use of medical treatment with biphosphonates mandate that prospective studies are planned to definitively analyze their efficacy and morbidity and to assess their role in a multimodal approach.

Acknowledgements

None.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

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

- ▪ of special interest
- ▪▪ of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 74).

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