Fibrous Dysplasia of Craniomaxillofacial Bones - A Clinical Study of 18 Cases and Review of the Literature

SUMMARY

Aim. The purpose of this study was to evaluate our experience with treatment and outcome of 18 cases of fibrous dysplasia (FD) that were treated in our clinic.

Materials and Methods. We present 18 cases of FD of craniomaxillofacial bones. 7 patients were affected by the polyostotic type of the disease, 2 by McCune Albright Syndrome (MAS) and 9 by the monostotic type. One patient with monostotic type developed malignant transformation (osteosarcoma). All the patients were treated with conservative surgical procedures as the primary treatment, mainly for aesthetic reasons. 2 patients required subsequent surgery to reduce furthermore bone enlargement. 2 patients received supplementary treatment with bisphosphonates (BPs).

Results. The follow-up for all patients ranged from 3 to 14 years. Cosmetic results and local control of the disease proved satisfactory for most patients.

Conclusions. The opinions about surgical procedures for the treatment of FD are controversial. Many authors believe that radical surgical excision permits an immediate functional and aesthetic result. BPs may have a significant role for the therapy of FD.

Keywords: Fibrous Dysplasia; Bisphosphonates; Osteosarcoma

Introduction

Fibrous dysplasia (FD) is a benign fibro-osseous lesion in which fibrous tissue and abnormal bone replace the normal bone. It presents about 2.5% of bone disorders and 7% of benign tumors1-3. 3 forms of FD are usually distinguished: a) monostotic form, presenting in early adolescence as a single localized bone lesion; b) polyostotic form, typically presenting in the late childhood and affecting multiple skeletal sites; and c) polyostotic form associated with endocrinopathies and skin pigmentation (café au lait spots), known as the McCune-Albright syndrome (MAS)4-7.

Monostotic FD is much more common than the polyostotic form, accounting for as many as 80% of the cases8. Jaw involvement is common in this form of the disease, with the maxilla to be affected more frequently. Maxillary lesions may extend to involve the maxillary sinus, zygoma, sphenoid bone, temporal bone and floor of the orbit. This polyostotic form of the FD, with involvement of several adjacent bones, has been referred as craniofacial FD. The most common site of mandibular involvement is in the body portion6,9-11.

Many studies have been made in the past 10 years in an effort to approximate the pathophysiology of FD. It is now recognized that FD is caused by the missense mutations of the gene encoding the “a” subunit of the G protein (Gsa) that stimulates cAMP formation, resulting in an increased cAMP concentration in genetically changed cells. This increased signalling though the cAMP pathway has been shown to be responsible for the clinical characteristics of monostotic and polyostotic FD, pituitary adenoma and MAS12-14. The diagnosis of FD is based on clinical, radiographic, and histological features. The most common clinical sign is swelling or deformity of the affected bone. When the disease concerns the craniofacial form, it can be presented with nasal
obstruction, sinusitis, hearing loss, headache, diplopia, proptosis or loss of vision\textsuperscript{11,15}. Radiological features can be cystic, sclerotic or pagetoid, often with typical “ground glass” appearance caused by the mixture of fibrous and osseous elements\textsuperscript{4,6,16}. An important distinguishing feature of FD is the poorly defined radiographic margins of the lesion. The process appears to blend into the surrounding normal bone without evidence of a circumscribed border. Histopathological view shows that the lesion consists of areas of fibrous tissue interwoven with newly formed bone. The fibrous tissue may be extensive or limited and may vary within areas of the same lesion\textsuperscript{7,17,18}.

3 main histological types have been identified: 1) the “Chinese letters” model, 2) the “pagetoid” model, and 3) the “hypercellular” model. Each of these is differentiated on the basis of the architecture and cellularity of the osseous tissue\textsuperscript{4,5,19}.

The purpose of this study was to evaluate our experience with the presentation, treatment and outcome of 18 cases of FD that were treated in the Clinic of Oral and Maxillofacial Surgery at the hospital “G Papanikolaou” in Thessaloniki. We also reviewed the methods of treatment as they presented in the recent literature.

**Materials and Methods**

In this study we described 18 cases of FD of craniofacial bones. The patients, 11 males and 7 females, were treated in our clinic at the “G Papanikolaou” hospital at Thessaloniki. The patient’s age ranged from 8 to 48 years and the mean age was 17.8 years. 7 had the polyostic type of the disease, 2 had MAS, and 9 had the monostotic type of the disease. 1 patient of our study (No 12) with monostotic type of the FD developed osteosarcoma 4 years after the first surgical procedure (osseous contouring). The age and sex distribution, as well as, the areas of involvement are shown in table 1.

The most common clinical feature was an osseous hard painless protrusion of the face or an asymptomatic swelling in the oral cavity. 2 patients (No 1 and 18) with spread of the lesion in temporal, sphenoid and frontal bones had exophthalmos, without diplopia or reduced visual activity (Fig. 1). Radiographically, the lesions were defined as unilocular radiolucent areas (Fig. 2) or as densely radiopaque masses with diffused margins (“ground glass” appearance - Figs. 3 and 4).

After an incisional biopsy the diagnosis of FD was established for all lesions (Fig. 5). All the patients were treated with conservative surgical procedures (osseous contouring), as primary treatment, mainly for aesthetic reasons (asymmetry or protrusion of facial bones). 2 patients (No 4 and 11) required subsequent surgery to reduce furthermore bone enlargement. 2 patients (No 1 and 18) received supplementary treatment with bisphosphonates. For the patient No 12 with malignant transformation (osteosarcoma - Fig. 6), segmental mandibulectomy was required, followed by implantation of iliac bone graft. All the treatment procedures, for all patients, are listed in table 1.
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are very occasionally seen lining their margins. Over time, FD may show maturation, which is characterized by formation of lamellar bone and parallel arrangement of trabeculae. It is proven, in serial biopsies, that lamellar maturation does occur, and the lesions that contain appreciable quantities of lamellar bone, always come from older patients and the lesion is likely to have been of relatively long duration.4-6,17.

The lesions of FD tend towards stabilization with the completion of normal skeletal growth. Thus lesions in children may grow actively for a period and then become quiescent when the skeletal growth has been completed. On the other hand, lesions that have been quiescent for some time may undergo a phase of renewed growth. This may occur in adults, who may be aware that a quiescent lesion from their childhood could be reactive.7

Results

The follow-up for all patients ranged from 3 to 14 years. Cosmetic results and local control of the disease proved satisfactory for most patients. The results and the follow-up of all patients are listed in table 1.

Discussion

FD is a lesion in which normal medullary bone is gradually replaced by generally loose, cellular fibrous tissue, composed of irregularly shaped trabeculae of immature bone. The trabeculae consist at first of osteoid, later becoming well calcified, and rows of osteoblasts...
Table I. Fibrous Dysplasia of cranio-maxillofacial region

<table>
<thead>
<tr>
<th>No</th>
<th>Sex</th>
<th>Age</th>
<th>Location</th>
<th>Treatment</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>8y</td>
<td>Mandible (R) (body, ramus, condyle), maxilla (R), zygomatic bone and arch</td>
<td>Conservative surgery (osseous contouring of the mandible, maxilla and condylectomy)</td>
<td>5 years later the lesion spread in sphenoid, temporal and frontal bones. Treatment with bisphosphonates: 180mg pamidronate intravenous every 6-months (60mg/day during 3 days). 3 years later the lesion is remarkably stable.</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>20y</td>
<td>Maxilla (R) premolar-molar region, zygomatic bone, most of the maxillary sinus replaced by the lesion</td>
<td>Conservative surgery (osseous contouring of the maxilla)</td>
<td>5 years later the maxillary sinus is partially occupied by the lesion</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>12y</td>
<td>Maxilla anterior portion crossing midline until premolar region (R)</td>
<td>Conservative surgery (osseous contouring of the maxilla)</td>
<td>8 years later without clinical and radiographic features.</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>10y</td>
<td>Most of the maxilla, zygomatic complex and most of the maxillary sinus (R)</td>
<td>4 conservative surgical procedures (osseous contouring of the maxilla, intraoral approach). 2 surgical excisions of masses of anterior maxilla, zygomatic bone and orbital rim (extraoral approach).</td>
<td>4 years after the last surgical procedures and 12 years after the first conservative surgical procedure, was not observed progression of the disease.</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>24y</td>
<td>Mandible (R) premolar-molar region</td>
<td>Conservative surgery (osseous contouring of the mandible)</td>
<td>6 years later was no observable progression of the disease.</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>48y</td>
<td>Maxilla (R) premolar-molar region, zygomatic bone with spread in maxillary sinus</td>
<td>Conservative surgery (osseous contouring of the maxilla and zygomatic bone)</td>
<td>8 years later the lesion is remarkable stable</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>18y</td>
<td>Maxilla (R) premolar-molar region</td>
<td>Conservative surgery (osseous contouring of the maxilla)</td>
<td>7 years later there are not clinical or radiographic features of the disease.</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>12y</td>
<td>Mandible anterior portion crossing midline until premolar (R)</td>
<td>1 surgical conservative procedure (osseous contouring of the mandible). 4 years later malignant transformation of the lesion (osteosarcoma). Fast growing painful swelling with spread in the soft tissues. Partial mandibulectomy and reconstruction with iliac bone graft.</td>
<td>14 years after the second radical surgical procedure the patient is free of the disease.</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>11y</td>
<td>Mandible (L) premolar-molar region</td>
<td>Conservative surgery (osseous contouring of the mandible)</td>
<td>8 years later the lesion is remarkable stable</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>12y</td>
<td>Maxilla (R) premolar-molar region, zygomatic bone and maxillary sinus</td>
<td>Conservative surgery (osseous contouring)</td>
<td>7 years later the patient is free of the disease</td>
</tr>
<tr>
<td>11</td>
<td>F</td>
<td>30y</td>
<td>Maxilla anterior portion</td>
<td>Conservative surgery (osseous contouring)</td>
<td>7 years later the patient is free of the disease</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>10y</td>
<td>Maxilla anterior and premolar region (R)</td>
<td>Conservative surgery (osseous contouring)</td>
<td>12 years later the patient is free of the disease</td>
</tr>
<tr>
<td>13</td>
<td>M</td>
<td>13y</td>
<td>Maxilla premolar-molar region with spread in the maxillary sinus</td>
<td>Conservative surgery (osseous contouring)</td>
<td>17 years later the patient is free of the disease</td>
</tr>
<tr>
<td>14</td>
<td>M</td>
<td>17y</td>
<td>Maxilla anterior region</td>
<td>Conservative surgery (osseous contouring)</td>
<td>13 years later the patient is free of the disease</td>
</tr>
<tr>
<td>15</td>
<td>F</td>
<td>31y</td>
<td>Maxilla (R) premolar-molar region</td>
<td>Conservative surgery (osseous contouring)</td>
<td>12 years later there was not observed progression of the disease</td>
</tr>
<tr>
<td>16</td>
<td>M</td>
<td>11y</td>
<td>Maxilla premolar-molar region (L) with spread in the maxillary sinus</td>
<td>Conservative surgery (osseous contouring)</td>
<td>10 years later a part of maxillary sinus is occupied by the lesion</td>
</tr>
<tr>
<td>17</td>
<td>M</td>
<td>9y</td>
<td>Mandible molar region (R), temporal and frontal bones, base of the skull, foramen (R), café au lait pigmentation, precocious puberty</td>
<td>Osseous recontouring for the lesion of the mandible</td>
<td>3 years later stabilization of the disease process. The patient refused any more following</td>
</tr>
<tr>
<td>18</td>
<td>M</td>
<td>26y</td>
<td>Mandible premolar-molar region (L), maxilla premolar-molar region (R), sphenoid bone and zygomatic maxillary complex (R), frontal bones, arm (R), café au lait pigmentation, hyperparathyroidism</td>
<td>Two conservative surgical procedures for aesthetic reasons (asymmetry of the mandible and protrusion of the zygomatic and frontal areas).</td>
<td>One year later treatment with bisphosphonates. 180mg pamidronate intravenous every 6 months (60mg/day during 3 days). 3 years later the disease is under control (no further spread of the disease).</td>
</tr>
</tbody>
</table>
The aim of treatment of FD is to achieve a cosmetic and functional satisfactory result. The surgical treatment is based on 2 different approaches, conservative (shaving or osseous contouring) or radical excision followed by immediate reconstruction. Conservative surgical treatment may be recommended as primary treatment until the lesion shows less growth and its activity is reduced as adulthood is near. It is estimated that between 25% and 50% of patients will show further post-operative growth after surgical procedure. This post-operative growth appears more common in younger patients, suggesting that surgical procedures should be delayed as long as possible. The advances in surgical techniques can significantly reduce the risk and the complexity of radical excision; so, many authors in favour of radical surgical treatment, which permits the complete removal of the lesion followed by immediate reconstruction with free-vascularised flaps.

Chen and Noordhoff22 and Ricalde and Horswell15 divided the craniofacial skeleton into 4 zones according to surgical, aesthetic and functional criteria. They proposed conservative treatment for the alveolar part of the maxilla, the mandible (protection of alveolar ridges and teeth) and for cranial base. On the other hand they suggested radical excision for the fronto-orbital area and maxillo-zygomatic complex.

Valentini et al11 refer in their study that among 68 patients who underwent surgery, 61 had radical excision, six received conservative treatment and a patient with mandibular involvement received radical excision and immediate reconstruction with a free fibula flap. No disease recurrence was observed in cases treated with complete excision, whereas a case of mandibular involvement treated with remodelling, required further surgery. The same authors support the radical treatment even in cases involving the maxilla and the mandible, and the use of conservative surgical treatment only in polyostic cases and cases of MAS. In their experience, the radical excision approach prevents the occurrence of relapses and eliminates the illness. Posnick10 also states that the treatment of choice should be radical excision for an immediate functional and aesthetic result. Kreutziger23 believes that the conservative treatment is unable to eliminate the lesions. Zenn and Zuniga20, in considering the numerous relapses following conservative treatment, are in favour of radical treatment in FD of the mandible. The controversial opinions about radical excision concern the management of FD involving alveolar bone and cases in which the optic nerve canal is involved, particularly in patients with normal vision. Furthermore, other authors24 consider being better to follow the progression of the illness than to perform an early prophylactic decompression with incalculable consequences.

For the patients of our study we used the conservative surgical treatment with satisfactory results (Table 1). For mandibular lesions (No 1, 5, 8, 9, 17 and 18), the primary treatment always included a correction of deformations and asymmetry. For the patient No 1 the surgical treatment was completed with condylectomy. For the patient No 8 with malignant transformation (osteosarcoma), the final surgical treatment was radical excision (partial mandibulectomy) and reconstruction with iliac bone graft. For maxillary and zygomatic complex lesions (No 1-4, 6, 7, 10-16, 18) conservative surgical treatment was the only treatment. 2 patients (No 4 and 11) required subsequent surgery to reduce further bone enlargement; the patient No 11 is free of the disease (Table 1). 2 patients of our study with FD of craniofacial bones (No 1 and No 18) had some of these symptoms that are related to the involvement of craniofacial bones (asymmetry, protrusion of facial bones, headache and exophthalmos).

The management of FD involving craniofacial sites can be challenging. Most patients with craniofacial FD have functional and cosmetic problems. These may include swelling or facial asymmetry, headache, malocclusion, sinusitis, telecanthus, exophthalmos etc. In such cases, with many vital structures in the involved area, radical resection of FD in the craniofacial and skull base area may not be possible. Furthermore, the available reconstruction options, especially in paediatric and adolescent patient population, are not optimal. The use of bisphosphonates (BPs) could be an alternative solution when surgical approach is difficult or impossible.

The use of BPs in the treatment of FD has increased in the recent years, with encouraging reports of successful control and stabilization of the disease, both clinically and radiologically. Chapurlat et al3 evaluated the long-term effects of intravenous pamidronate in 20 patients with FD. They received course of 180mg of intravenous pamidronate every 6 months (60 mg/day during 3 days by infusion). The mean duration of follow-up was 39 months. They found a decrease in bone pain and improvement in the radiographic appearance of the lesions. The same authors reported another study of 58 patients with FD. All patients who had bone pain referred significantly decreased intensity. Furthermore, 50% of patients showed radiographic improvement (development of new bone)20. Kos et al27 referred in their study the results of the treatment with pamidronate in 6 children with progressive FD located in the mandible, maxilla or cranial base. All patients received pamidronate infusions (1 mg/kg iv.) for 3 days, every 4-6 months. Pain relief was achieved in all cases, the local bone density increased and there was no further spread of the disease in any of the patients. Chao et al28 examined the effects of high-dose oral alendronate (40 mg daily) for 6 months on 3 adult patient with severe headache due to FD of the skull. The patients underwent clinical follow-up 1, 3 and 6 months. All 3 patients demonstrated a significant decrease in pain levels and there was no evidence of tumour growth during the follow-up period.
We used BPs, after initial treatment, for 2 patients of our study, No 1 with polyostotic FD of craniofacial bones and No 18 with MAS. The therapeutic intravenous dose of pamidronate was 180 mg every 6 months (60 mg/day during 3 days). This therapeutic shape is referred in the literature by many authors\(^1,28,29,30\). The results were satisfactory (Table 1).

All the reported studies concerning the treatment of FD with BPs contain small number of patients, and the most of these are uncontrolled. So, the results of these studies are important but are not established. For this reason, the results of our 2 patients treated with BPs, as supplementary treatment, are not remarkable.

The incidence of malignant transformation of FD is rare, accounting less than 1% of cases\(^31\). 60% of this alteration is into osteosarcoma (OS)\(^32\). Although the incidence of transformation is higher in polyostotic type (4%) compared to this of the monostotic type (0.5%)\(^33\), most cases reported overall, as our case, are associated with the latter due to the larger number of patients suffering from monostotic FD\(^33,34\). Many authors emphasize the role of radiation in FD for sarcomatous transformation, with a time interval ranging from 10 to 35 years from the irradiation until the development of OS\(^35-38\). On the contrary, there are several reports of spontaneous transformation without any stimulating factor or condition including radiation\(^39-42\), as it had happened in the patient of our study. The appearance of soft tissue mass within the lesion and the spread of the lesion to the surrounding soft tissues or below the interior nerve canal are characterized as strong clinical features of malignant transformation\(^31,43\).

Treatment of OS arising in FD is radical surgical excision\(^6,44\) and this method of treatment we used for the patient of our study (partial mandibulectomy) with good results (Table 1).

In conclusion, the management of craniofacial FD is very complex. Nowadays, many authors are in favour of radical surgical treatment, which permits the complete removal of the lesion, with good aesthetic and functional results. BPs may have a significant role for the treatment of FD. The sudden increase of the lesion, and its spread into surrounding soft tissues, may be considered as alarming features for further investigation of malignant transformation.

**Clinical Relevance of the Study**

Scientific rationale: FD employs as a disease that among others affects the bones of the skull, which is of personal concern to clinicians. The experience of our clinic when treating these patients, record and evaluate the results of surgical treatment in particular. Simultaneously, it is a comprehensive review of the literature and recorded therapeutic methods used up to now.

Principal findings: Surgical approach (conservative or radical) is considered by most as treatment of choice for FD of the facial bones.

Practical implications: However, in recent years, drug therapy with bisphosphonates has advanced to play the main role.

**References**

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