Clinical Paper
Craniofacial Anomalies

Prognosis for craniofacial fibrous dysplasia after incomplete resection: age and serum alkaline phosphatase


Abstract. Complete resection is usually impossible for fibrous dysplasia (FD) involving the cranial base. Incomplete resection could be followed by regrowth of FD, but there is no method for indicating disease progress. Serum alkaline phosphatase (ALP) is significantly high in patients with FD. The authors investigate the relationship between ALP, progress of FD, and age at surgery. 18 patients with craniofacial FD were separated into 3 groups: Group A, complete resection; Group B, incomplete resection followed by regrowth of FD; and Group C, incomplete resection but no regrowth of FD. Medical records and CT scans were reviewed retrospectively. ALP levels were obtained preoperatively, postoperatively and every year during follow-up. The relation between ALP and regrowth and that between age at surgery and regrowth were investigated. There was no recurrence in Group A (n = 4). Regrowth in Group B (n = 7) was preceded by an abrupt increase in ALP. In Group C (n = 7), no regrowth was observed and ALP was maintained within the normal range. 6 patients (85%) in Group B and 2 (28%) in Group C were under 17 years old. The results revealed that the level of postoperative serum ALP could be a reliable marker for predicting the progress of craniofacial FD.

Keywords: craniofacial fibrous dysplasia; incomplete resection; age; alkaline phosphatase; prognostic factor.
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Although it is a benign osteopathy, fibrous dysplasia (FD) manifests with clinically malignant symptoms characterized by replacement of the normal bone with fibrous-osseous tissues. This is due to the primary developmental abnormality of the bone-forming mesenchymal tissue. The molecular etiology is somatic activating mutations in osteoprogenitor cells of the cAMP regulating protein Gsα, which is coded by the GNAS gene.

In general, the pathological process of craniofacial FD begins in childhood and progresses through puberty and adolescence. The progression usually stops after adolescence. Some authors report that the progression of the lesions may continue during adulthood, resulting in facial deformity and functional problems.

There are three main types of FD: monostotic, polyostotic, and McCune-Albright syndrome. The monostotic form is the most common, comprising 70% of cases. 25% of FD involves two or more bones. These lesions may be localized to one region of the body or they may be disseminated, involving almost every bone. These lesions are more likely to continue to progress even after puberty, specially craniofacial lesions.

In craniofacial FD, the base of the skull, especially the sphenoid bone and maxilla,
may be the most common site of involvement. The clinical problems vary according to the anatomical location. It tends to overgrow causing facial asymmetry, disfigurement, exophthalmos, orbital dystopia, and malocclusion. It also has the potential to compress the optic nerve. Malignant transformation is rare but may occur, most likely after radiation therapy with sarcomas being the most common histological type.

The surgical treatment of craniofacial FD consists of conservative shaving (contouring), which may be repeated, or complete resection of the dysplastic bone followed by reconstruction using autologous bone. In the fronto-orbital, zygomatic and upper maxillary areas, total excision and immediate reconstruction produce good functional and esthetic results. The surgical approach and complete resection in the base of the skull are limited and difficult due to sphenoid or ethmoid bone invasion. The timing and extent of surgery is controversial, especially in children with craniofacial FD who have thriving bone metabolism. It is important to observe the progress and regrowth of remnant FD in patients who undergo incomplete resection, but there is no objective and simple method to predict clinical results and progression or regrowth. Some authors recommend serial follow-up for craniofacial FD with computed tomography (CT) to determine progression or regrowth. Serum ALP level and age at the time of surgery were examined during the long-term follow-up.

Materials and methods

The study was carried out by retrospective review of medical records and CT scans of 18 patients who were treated for craniofacial FD. The 18 patients had given their written consent and the study was performed in accordance with the guidelines of the Declaration of Helsinki. The patients who were pregnant, had liver disease or chololithiasis, or were using oral contraceptives were excluded. No patients demonstrated the typical symptoms of the McCune Albright syndrome, which was confirmed by endocrinology. 15 patients (83%) had monostotic lesion and 3 patients (17%) had polyostotic lesions. The monostotic lesions often involved adjacent craniofacial bones (the maxillary, zygomatic, sphenoid, nasal, or frontal bone) as indicated by the term ‘monofocal’, describing a condition where several adjacent skeletal segments in a single area are affected. The indications for surgery were aesthetic reason (67%), exophthalmos (28%), and optic nerve compression (6%). The age of the patients at the time of surgery ranged from 9 to 45 years (average 19.3 years). 7 patients underwent surgery after the age of 17 years, while 11 patients had surgery before 17 years of age. The follow-up period varied from 3 to 16 years (average 7.7 years). CT scans were obtained only when regrowth of FD was suspected, based on clinical findings. Clinical photographs were obtained every year during the follow-up period. Serum ALP levels were obtained before surgery, immediately after surgery, and every year during the follow-up period.

The 18 patients were divided into three groups. Group A was composed of patients who received complete resection. Group B patients received incomplete resection and had regrowth of FD. Group C comprised patients who received incomplete resection but had no regrowth of FD. Surgery was defined as incomplete resection as long as there was a remaining lesion (however small it was) after resection. Groups B and C were examined by comparing the postoperative serum ALP levels and regrowth. The association between regrowth and postoperative serum ALP levels was investigated. The influence of age at the time of surgery was also examined during the long-term follow-up.

Results

Among 18 patients, complete resection was performed in 4 possible cases (22%), and the remaining 14 patients (78%) underwent incomplete resection. Of the 14 patients who received incomplete resection, contouring surgery (shaving of the protruding part of the lesion) was carried out in 5 patients, and partial resection surgery in 7 patients because lesions were widely present in the sphenoid or ethmoid. One patient underwent partial resection after receiving contouring surgery because of regrowth of FD (Table 1). There was no complication related to the surgery. Group A patients (n = 4) achieved complete remission clinically and radiologically without recurrence during follow-up periods ranging from 4 to 16 years. In this patient group, postoperative ALP remained within the normal range (Table 2).

Of the 14 patients who received partial resection, the authors observed regrowth of FD through clinical findings and confirmed it with CT scans in 7 patients (Group B; Table 3). An abrupt drop in ALP was observed immediately after surgery. This revealed that the decreased ALP levels were attributable to the effect of surgery. Regarding the age of patient at the time of surgery, the reduction was not due to the natural history of FD. The mean time interval between the operation and regrowth was 4.4 years. Tumour invasion to the autologous grafted bone was detected in two patients (case numbers 8 and 11) (Fig. 1). The 7 patients with regrowth had abnormally high postoperative ALP levels at a time point during the follow-up period (Table 3). The time point of the abrupt rise in ALP was correlated with the regrowth of FD, confirmed by CT scans. Among these 7 patients, 6 underwent surgery before

<table>
<thead>
<tr>
<th>Extent of resection</th>
<th>No. of cases</th>
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<tr>
<td>Complete resection and autologous bone graft</td>
<td>4 (22%)</td>
</tr>
<tr>
<td>Incomplete resection</td>
<td>14 (78%)</td>
</tr>
<tr>
<td>Partial resection and autologous bone graft</td>
<td>8 (44%)</td>
</tr>
<tr>
<td>Contouring surgery</td>
<td>5 (28%)</td>
</tr>
<tr>
<td>Contouring surgery followed by Partial resection and autologous bone graft</td>
<td>1 (6%)</td>
</tr>
<tr>
<td>Total</td>
<td>18 (100%)</td>
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</table>

Table 1. Extent of resection. Complete resection was carried out in 4 patients (22%). Incomplete resection was carried out in 14 patients (78%). Autologous bone grafts were used in 13 patients (72%).
Table 2. The patients who received complete resection (Group A). The authors did not observe regrowth or morbidity during the follow-up period. The immediate postoperative ALP levels were lower than preoperative levels in all patients. The serial ALP values were maintained within the normal range during the long-term follow-up period.

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Sex</th>
<th>Age (year) at operation</th>
<th>ALP (IU/L)</th>
<th>Follow-up (years)</th>
<th>Location of lesion</th>
<th>Type of FD</th>
<th>Type of operation</th>
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<td>91</td>
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<td>Mo</td>
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<td>F</td>
<td>13</td>
<td>357</td>
<td>210</td>
<td>201</td>
<td>104</td>
<td>82</td>
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</tr>
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</table>

ALP, alkaline phosphatase (normal range: 60–300 IU/L for 14 years and less, 38–115 IU for over 14 years). F, frontal; T, temporal; Z, zygomatic; Ma, maxilla; Mo, monostotic; CR, complete resection; CB, autologous calvarial bone graft; RB, autologous rib bone graft.

Table 3. The patients who received incomplete resection followed by regrowth of FD (Group B). ALP levels abruptly rose during the follow-up period in all patients. The time point of increased ALP was well correlated with regrowth of FD in all patients. Six patients (85%) were under 17 years old at the time of surgery. Two patients underwent surgery twice (cases 5 and 7).

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Sex</th>
<th>Age (year) at operation</th>
<th>ALP (IU/L)</th>
<th>Follow-up (years)</th>
<th>Location of lesion</th>
<th>Type of FD</th>
<th>Type of operation</th>
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Table 4. The patients who received incomplete resection without regrowth of FD (Group C). The postoperative serial ALP values were maintained within the normal range during the long-term follow-up period in all patients. Two patients (28%) were under 17 years old at the time of surgery.

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Sex</th>
<th>Age (year) at operation</th>
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<th>Type of FD</th>
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<td>E, A and Ma</td>
<td>Mo</td>
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<td>Po</td>
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<td>F, P and E</td>
<td>Mo</td>
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<td>E and Ma</td>
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<tr>
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Higher ALP than normal range regarding the age.
the age of 17 years, and 1 after the age of
17 years.

Of 7 patients in Group C with incom-
plete resection, regrowth of FD was
not observed during the follow-up
period. The immediate postoperative
ALP levels and the serial follow-up of
ALP showed it had been maintained
within the normal range. The authors
did not observe an abrupt increase or
decrease of ALP during the follow-up
period (Table 4). Two patients were
under 17 years old at the time of surgery,
and five patients were over 17 years old.
All 7 patients had a quiescent remnant
lesion with no disease progression
(Table 4).

Discussion

FD is one of the craniofacial bone
tumours most frequently encountered
by oral and maxillofacial surgeons. The
optimum treatment for craniofacial
FD has been controversial for a long
time. Recent advances in craniofacial
surgical techniques have led to complete
resection and autologous bone graft
becoming an ideal treatment modal-
ity. Despite these developments in
 craniofacial surgical techniques, com-
plete resection of craniofacial FD is
not achievable at high frequencies.
This could be attributed to the complex
anatomical structure of the craniofacial
area, a low rate of malignant change, and
the limitation of approach during sur-
gery. The authors considered whether
complete resection is the best treatment
modality for patients with FD and the
factors that can be used to predict prog-
nosis during follow-up.

Regarding disease prognosis, the
importance of age at the time of surgery
and the possibility of complete resection
has been emphasized during follow-up.
The ideal treatment for craniofacial FD is
complete resection and immediate recon-
struction with autogenous bone. In the
present cases of complete resection, the
authors did not observe recurrence dur-
ing the long-term follow-up periods. In

Fig. 1. (Case 11) A 9-year-old male patient who had an incomplete resection. (Above, left) Preoperative view showing the right fronto-orbital
bulging and orbital dystopia. (Above, right) Postoperative view after 15 years with recurrence of fibrous dysplasia. (Below, left) Postoperative CT
scan after 1 year showing the autogenous bone graft of fronto-temporal region. (Below, right) Postoperative CT scan after 15 years. The fibrous
dysplasia invaded the autogenous bone grafting.
these patients, postoperative serum ALP did not increase once the patient had undergone complete resection, regardless of their age at the time of surgery. The authors postulate that recurrence is rare if the postoperative serum ALP level does not increase after complete resection. In the 14 patients who received incomplete resection, the authors observed regrowth of FD in 7 patients. The authors think that regrowth is related to two factors: the age of patient at the time of surgery and the level of serum ALP. ALP is an enzyme distributed widely throughout the human body, especially abundant in the bones, liver, intestines and placenta. The serum ALP level may be elevated in various liver diseases (e.g., hepatitis, cholelithiasis and tumour in the liver or the bile duct) or metabolic diseases, such as osteoporosis. The authors realized that an increased level of serum ALP was also noticed in the previously treated FD patients in their hospital. Collins et al. also reported that ALP could be a marker of skeletal burden in FD.

In Group C, the postoperative serum ALP level did not increase. The serum ALP was elevated in two Group B patients who showed invasion of FD to the analogous grafted bone on the follow-up CT scan. Regarding the age of patients at the time of surgery, most Group B (86%) and Group C (71%) patients received incomplete resection before 17 years of age.

Based on these facts, the authors assumed that the elevation of serum ALP level after incomplete resection may be a factor strongly associated with regrowth or disease prognosis, because regrowth was found in all 7 patients who had increased ALP after partial resection, whereas no regrowth was found in all 7 patients who maintained normal ALP levels.

When the authors examined age at the time of surgery they found that 6 patients who underwent incomplete resection under the age of 17 years had a tendency for regrowth. Five other patients who underwent incomplete resection after the age of 17 years usually maintained normal levels of postoperative serum ALP.

There was a high tendency for regrowth of FD if surgery was carried out before the age of 17 years or there were high levels of postoperative serum ALP. The authors have also taken into consideration that their theory might leave room for controversy regarding high serum ALP levels in patient who underwent surgery before the age of 17 years. Children may have higher levels of serum ALP than adults, even in the normal situation; studies have shown a correlation between serum ALP and growth spurts in children, in which hormones play a crucial role. The authors refute such arguments because the serum ALP level begins to drop until it reaches the normal adult level by the age of 11–12 years in females and 13–14 years in males and in this study, most patients received surgery after these ages. The authors regard postoperative serum ALP as a prognostic factor because most of the postoperative ALP values were obtained when the patients were adults.

Based on these results, the authors propose a treatment principle for craniofacial FD patients. First, for patients who are good candidates for complete resection, it is preferable to perform the resection regardless of their age. Particularly when the lesions are located in the fronto-temporal area, complete resection should be performed regardless of age. For those for whom complete resection is impossible, the age of the patient and the serum ALP level should be taken into consideration. Postoperative regrowth should be monitored carefully through a series of postoperative serum ALP levels. If the patient is older than 17 years and is in a condition that does not allow complete resection, partial resection is recommended because regrowth is not significantly probable. Surgery merely for aesthetic purposes is sufficient in patients older than 17 years, regardless of their preoperative serum ALP levels.

Patients for whom incomplete resection of FD is inevitable, should be observed closely for regrowth during the follow-up period. The authors’ long-term follow-up data revealed that the postoperative serum ALP level could be a reliable and simple marker for predicting the progression of the disease in craniofacial FD patients.

Competing interests
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References


Address:
Won-Jai Lee
Department of Plastic & Reconstructive Surgery
Yonsei University
College of Medicine
134 Shinchon-dong
Seodaemun-gu
Seoul
Republic of Korea
Tel.: +82 2 2228 2219
Fax: +82 2 393 6947
E-mail: pswjlee@yuhs.ac

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