ABSTRACT

Objective: To discuss what has been described so far in the literature regarding the time taken for fracture consolidation in pycnodysostosis. Materials and Methods: Thirteen new cases were studied, as available from the medical records and radiographic examinations, thus encompassing a total of 44 fractures in patients evaluated between November 1970 and August 2004 at the Orthopedics Hospital, Goiânia. Field research, simultaneous clinical monitoring for new fractures in two patients and retrospective evaluation of medical records were undertaken. The purpose was to determine the total number of fractures in each patient and to determine which of these were viable for this study. The patient group was composed of three women and two men of mean age 51.4 years. The tibia was the bone most affected, followed by the femur. Fractures for which the follow-up was done at another clinic were excluded. Results: Out of the 12 fractures that were considered fully suitable for the study, nine occurred in femurs (six in the left femur and three in the right femur); one in the right tibia; one in the right clavicle; and one in the left ulna. Among these 12 fractures, eight developed pseudarthrosis after an average of 29.25 months; three consolidated well after an average of 5.83 months; and one evolved with delayed consolidation in just 2 months. Conclusion: In combination with genetic and micromorphological evaluations, further studies are awaited for reconfirmation of the diagnosis of such a rare clinical entity.

Keywords – Pseudarthrosis; Bone Diseases, Developmental; Fractures, Spontaneous; Fracture Consolidation

INTRODUCTION

Pycnodysostosis is a disease within the group of craniofacial bone dysplasias, which have universal distribution and a high association with consanguinity, because of genetic inheritance. Over the course of life, the bones of patients affected by this disease because increasing sclerotic, basically because of a failure of osteoclastic activity due to mutations in the gene for the cathepsin K enzyme, which is located on chromosome 1q21. Therefore, the increased bone density in these patients leads to fractures caused by minimal trauma. Such fractures generally occur in the lower limbs and the current treatment is mainly directed towards the symptoms, with emphasis on fracture prevention. Deformities of the long bones due to skewed consolidation are also common.

This skeletal dysplasia is characterized by significantly small stature, short limbs and osteosclerosis, with a tendency towards multiple bone fractures. The
clavicles are dysplastic, with partial distal aplasia of the acromion\textsuperscript{(3,5,7)}.

The main radiographic characteristic is increased bone density throughout the skeleton, with diffuse sclerosis. Although the medullary canal is small and imperfect, it is present and always shows evidence of hematopoiesis\textsuperscript{(5)}.

Also according to the radiographic characteristics, the clavicles are dysplastic, hypoplastic or aplastic in their acromial portion. In the hip, the femoral heads may be flattened; the femoral necks may be short and deformed, with a tendency towards coxa valga\textsuperscript{(7)}.

Therefore, the aim of this work was, in a certain way, to discuss what has been described in the literature regarding the time taken for fracture consolidation in cases of pycnodysostosis. Some references are confusing in their presentation of the topic, while others categorically maintain the position that there is normal cure demand for fractures within this pathological condition, and a few take the position of the present study but without the due relevance that the topic requires.

Clinical experience, together with recent molecular studies on pycnodysostosis, has shown that a further problem can be added to the extensive clinical list relating to this disease: delayed consolidation and pseudarthrosis as habitual entities.

**MATERIALS AND METHODS**

This was a retrospective descriptive study in which 13 new cases of pycnodysostosis were selected. For reasons of availability of medical files and radiographic examinations, as well as access to patients, five case totaling 44 fractures and encompassing patients evaluated between November 1970 and August 2004, at the Orthopedics Hospital, Goiânia, also formed part of this work.

Field research, simultaneous clinical monitoring for new fractures in two patients and retrospective evaluation of medical records were undertaken. The purpose was to determine the total number of fractures in each patient and to determine which of these fractures were valid for this study, i.e. which of them required time and serial quality of monitoring, with comprehensive medical files and sequential or final radiographic examinations of good quality in order to determine the consolidation, delays in consolidation or pseudarthrosis.

No other imaging examination formed part of the evaluation on the patients. There were two old anatomicopathological examinations relating to a patient that only confirmed the sclerotic nature of the condition and the presence of hematopoiesis, as well as ruling out malignancy, but without adding anything else.

The inclusion criteria covered the patient’s age, sex, color, total number of fractures, fractures valid for the study, type of treatment and duration of follow-up (clinical or surgical). The cases that did not cover these issues or that in some manner could not be included in such a restricted question of such a rare pathological condition have only been cited in reconstructing the kinship between the family members in this study, and they form part of another study in preparation that has the aim of reporting these cases and their genetic mapping.

The etiology of the fractures, which was initially posted as an inclusion criterion, was subsequently shown to be unnecessary because all of the fractures were due to mild trauma such as falls from the patients’ own height or stress fractures. Obviously, all of them are classified as pathological fractures.

Fractures for which the follow-up was done at another clinic, fractures that were diagnosed as clinical findings and did not motivate the patient to seek medical assistance at the time of the trauma and fractures that had too few radiographic examinations to allow us to show the evaluation of the case were excluded. Thus, 12 fractures were followed up between November 1970 and August 2004 at our clinic, with a mean follow-up of 59.08 months, ranging from two to 187 months. Radiographs produced on average every two months and complete medical files describing the treatment proposed and the prognostic evolution to cure or non-union were present in all these cases.

The patient group was composed of three women and two men. These patients’ mean age was 51.4 years, ranging from 39 to 64 years. Three patients formed part of the same family (two were siblings). The other two patients did not have kinship with the family, or with each other. Four of the patients were white and one was black (Table 1).

In total, over the courses of their lives, these patients presented 44 reported fractures, as confirmed in the medical files and through radiographic examinations.

The tibia was the bone most affected, with 25 fractures. This was followed by the femur, with 14 fractures; the clavicle and acromion, with two each; and the ulna, with one fracture (Figure 1). There was no predominance of the side affected, with 21 fractures occurring...
on the left side and 23 on the right side (Figure 2).

The patient and bone affected, length of specific follow-up for each of these 12 fractures and the kinship with other patients with pycnodysostosis who were excluded from this study are presented in Table 2.

**Table 1** – Characterization of the patients according to age, sex and color.

| Summary of the patients | Number | Patient | Age (years) | Sex | Color |
|-------------------------|--------|---------|-------------|-----|-------|
|                         | 1      | MLV     | 51          | F   | White |
|                         | 2      | IMSS    | 39          | F   | White |
|                         | 3      | VSN     | 47          | M   | White |
|                         | 4      | MPS     | 64          | F   | Black |
|                         | 5      | HNS     | 56          | M   | White |

**RESULTS**

Out of the 12 fractures that were considered fully suitable for this study, nine occurred in femurs (six in the left femur and three in the right femur); one in the right tibia; one in the right clavicle; and one in the left ulna (Figure 3). In total, there were seven fractures on the left side and five on the right side.

Patient 1 was first seen at this hospital in November 1970, because of a diaphyseal fracture of the right femur (Figure 4).

**Table 2** – Correlation of the patients with pycnodysostosis according to the valid fracture and relatives affected.

| Patient | Bone fractured | Length of follow-up | Relatives affected | Observations |
|---------|----------------|---------------------|--------------------|--------------|
| 1       | Right femur    | 3 M                 |                    |              |
|         | Left femur     | 108 M               |                    |              |
|         | Left ulna      | 4 M                 |                    |              |
|         | Right clavicle | 120 M               |                    |              |
| 2       | Left femur     | 187 M               | Sister No. 3       | Three sisters and parents are normal |
|         | Right femur    | 28 M                | Second-degree female cousin No. 5 and six second-degree male cousins |
| 3       | Right tibia    | 2 M                 | Brother No. 2      | Three sisters and parents are normal |
|         |                |                      | Second-degree female cousin No. 5 and six second-degree male cousins |
| 4       | Right femur    | 108 M               | Adopted female patient. Does not know her relatives. | * Associated fracture of synthesis material |
|         | Left femur     | 18 M                |                    |              |
|         | Left femur *   | 56 M                |                    |              |
|         | Left femur *   | 49 M                |                    |              |
| 5       | Left femur     | 26 M                | One brother and father | Three siblings and parents are normal |
|         |                |                      | Paternal aunt |              |
|         |                |                      | Second-degree male cousin Nos. 2 and 3 and five other second-degree male cousins |

Source: Orthopedic Hospital, Goiânia.

**Figure 1** – Characterization of the study sample according to the bone affected, Goiânia, Goiás, 2010.

**Figure 2** – Characterization of the study sample according to the side affected, Goiânia, Goiás, 2010.
The remaining patients, respective fractures and variables are presented in Table 3.

The fractures described followed an initial treatment as recommended for habitual fracture at the time of the fracture. Three cases required placement of a bone graft: two through the surgeon’s choice, in primary fractures. In one fracture (ulna), conservative treatment had already been attempted. One case was due to refracture associated with the synthesis material. Four patients were treated conservatively; seven, surgically; and one patient is currently awaiting treatment. Out of the 12 fractures, eight (66.66%) evolved with pseudarthrosis over a mean time of 29.25 months, ranging from three to 62 months. Three (25%) consolidated well, over a mean of 5.83 months, ranging from 2.5 to 10 months. One patient (8.33%) evolved with delayed consolidation in only two months, with no initial formation of callus, in conservative treatment for fracture of the middle third of the tibia.

Out of the eight fractures that evolved with pseudarthrosis, six had been treated surgically and two, conservatively. Likewise, among the three fractures that evolved with good consolidation in a timely manner, two were treated surgically and one, conservatively.

Two fractures that consolidated well were in the same female patient (2) (the only fractures presented by this patient in this study). However, her brother (patient 3) presented early delay in consolidation in another type of fracture.

The other patients evolved with a high rate of pseudarthrosis.

Table 3 – Characterization of the patients with pycnodysostosis according to the valid fractures and results obtained, Goiânia.

| Patient | Fracture | LFU* | Follow-up | Treatment |
|---------|----------|------|-----------|-----------|
| 1       | Diaphyseal - right femur | 3 M | Hospitalized | Skeletal traction + plaster from pelvis to foot |
|         | STC** – left femur | 108 M | Monthly outpatient | Surgery: DCP plate with 8 holes + bone graft |
|         | Proximal ⅓ - left ulna | 4 M | Weekly outpatient | Plaster from axilla to palm |
|         | Middle ⅓ - right clavicle | 120 M | Weekly outpatient | Eight plaster casts |
| 2       | Diaphyseal – left femur | 187 M | Weekly and monthly outpatient | Surgery: DCP plate with 10 holes |
|         | Diaphyseal – right femur | 28 M | Monthly outpatient | Surgery: DCP plate with 10 holes |
| 3       | Middle ⅓ - right tibia | 2 M | Weekly outpatient | Plaster cast boot |
| 4       | STC – right femur | 108 M | Yearly outpatient | Surgery: Jewett |
|         | STC – left femur | 18 M | Monthly outpatient | Surgery: Richards |
|         | Diaphyseal – left femur | 56 M | Monthly outpatient | Surgery: Richards + bone graft |
|         | STC – left femur | 49 M | Monthly outpatient | Awaiting surgery |
| 5       | STC – left femur | 26 M | Monthly outpatient | Surgery: Richards |

*LFU: length of follow-up; **STC: subtrochanteric.

Source: Orthopedic Hospital, Goiânia
DISCUSSION

The time taken for a fracture to consolidate cannot be arbitrarily established. There are no data regarding the nature and duration of fracture consolidation in cases of pycnodysostosis(8).

In normal bones, union is considered to be delayed when consolidation does not occur within a timely average for the site and type of fracture (usually three to six months). A diagnosis of non-union cannot be justified until clinical or radiological evidence shows that consolidation ceased and that achieving union is highly unlikely. The final status of a non-united fracture is the formation of pseudarthrosis. Judet and Judet differentiated two basic types of pseudarthrosis: hypertrophic cases (capable of a biological reaction) and atrophic cases (incapable of this reaction)(9).

Although the causes of delayed consolidation and pseudarthrosis are unknown, several local and systemic factors contribute towards its development, namely: fracture type and site, presence of infection, type of fixation, duration of immobilization, use of alcohol and tobacco, metabolic and nutritional status, irradiation of the bone or any constitutional alteration.

In pycnodysostosis, bone reabsorption is defective, but not completely inhibited. In fact, it seems that there is a biochemical non-osteoclastic alternative for degradation of the bone matrix: cells with metalloproteinase activity degrade the matrix left by the osteoclasts.

However, the mechanism, function and form of degradation of the two routes are distinct, and the functioning of just one may change the bone microenvironment, thereby also contributing towards changes in osteoblastic function(10). This may modify the sclerotic phenotype and the consolidation pattern of the frequent fractures presented by patients with this disease.

Degradation of the bone matrix is a fundamental step in promoting bone neo-apposition. Recent studies have also shown that osteoclastic dysfunction is associated with bone formation deficit that is dependent on age and on the mechanical loads(10). In other words, osteoclastic dysfunction thus increases the bone volume and hence paralyses not only the osteoclastic function but also the osteoblastic function.

The homogeneity of the bone matrix is severely affected and the structure of the lamellar bone suffers many consequences, with trabeculae that no longer form lines in the direction of the mechanical stress, which explains the great contradiction regarding bone fragility in cases of pycnodysostosis. There is a reflection of this in the collagen fibrils and their alignment of mineral particles, which are found to be reduced, thus influencing the bone regeneration and fracture consolidation.

The finding that 66% of the pathological fractures associated with pycnodysostosis presented pseudarthrosis confirms this theory and raises issues regarding what the best treatment methods for these fractures would be and regarding what the expected consolidation time for such restricted cases would be.

It is known that the use of osteosynthesis with plates and screws is only efficient when there is a gap of less than or equal to 1 mm between the fragments, and that this consolidation takes place without the formation of a callus, through primary contact of cortical bone(11), which thus does not favor this form of treatment for cases of pycnodysostosis.

However, the use of nails, which would lead to the formation of bone callus, is difficult in a pathological condition with major abnormalities of the medulla (Figure 5) and bone length(12). Conservative treatment is known to produce pseudarthrosis(9) and is extremely incapacitating, in treatments for fractures of the long bones of the lower limbs in adults.

The use of bone grafts for this pathological condition is not yet well established. It is not known to what point there may be degradation of the allogenic bone matrix, and tests using morphogenetic bone proteins still lack good results in evaluations on normal bone.

Figure 5 – Macroscopic appearance of lack of medulla in pycnodysostosis, which unlike osteopetrosis, is not confirmed on radiography and in practice.
CONCLUSIONS

Although many studies have affirmed that the time taken for consolidation in cases of pycnodysostosis is normal, doubts have been raised regarding this matter and with the passage of time. It seems obvious, with clinical experience from such patients, that despite the treatment used and failures that have occurred, the consolidation pattern in cases of pycnodysostosis (whether endosteal or periosteal) dictated its own speed. This was a slow speed, with a tendency towards pseudarthrosis, and was highly dependent on the intrinsically altered blastic and clastic functions. The matter now depends on the sequence of micromorphological studies with synthesis materials, genetic mapping and further retrospective studies, given that prospective studies would face the barrier of rarity in the sampling, for reconfirmation of the certainties.

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