Osteogenesis Imperfecta – Experience of Dona Estefânia's Hospital Orthopedics' Department

Osteogenesis Imperfecta – Experiência do Serviço de Ortopedia do Hospital Dona Estefânia

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ABSTRACT

Introduction/Aims: Osteogenesis imperfecta (OI) is a genetic disorder characterized by bone fragility and osteopenia. Treatment involves a multidisciplinary approach and aims to improve the quality of life. The authors aimed to describe the characteristics of a sample of children with OI, to evaluate the treatment and clinical outcome before and after therapy.

Material and Methods: An observational, longitudinal, retrospective and analytic study based on data obtained from the analisys of the clinical files of all patients with OI included in the pamidronate treatment protocol in Dona Estefânia's Hospital. The studied variables were: gender, age at diagnosis, familiar history of OI, age at fracture, fracture location, number of fractures, medical/surgical therapy, age at onset of treatment, number of courses of medical therapy, age at surgical treatment and its complications. A five percent statistics significance level was adopted.

Results: in 21 patients, 61,9% were male and 11 had its OI type registered (five type I, three type III, three type IV). The average age of diagnosis was 20,6 months and there were two diagnostic peaks: the first month - 37%, and 24 months - 26%. On average patients had 0,62 fractures/patient/year, of which 17,4% in the perinatal period and 62% before age three. Most of the fractures occurred in the lower limbs (55,6%). All patients underwent medical treatment, starting at an average of 4,3 years. In follow-up sample (n=14) there was a decrease in the number of fractures after starting treatment with pamidronate (0,76 to 0,35 fractures/patient/year). Intramedullary rods were placed in nine patients (64,3%). In eight patients they were placed in the femur, four unilateral and four bilateral, with no prior history of fracture in three cases. There were no new fractures in the surgically treated bones.

Conclusion: OI is a disease with a wide clinical variability that mainly depends on its type. Despite no cure has been found, medical treatment with biphosphonates and surgical treatment, with intramedullary rods, seems to reduce the incidence of new fracture occurrence.

Keywords: Osteogenesis Imperfecta; Child.

RESUMO

Introdução/Objectivos: A osteogénese imperfeita (OI) é uma doença genética caracterizada por fragilidade óssea e osteopenia. O tratamento implica uma abordagem multidisciplinar e tem como objectivo a melhoria da qualidade de vida. Os autores pretendem descrever as características de uma amostra de crianças com OI, avaliar o tratamento realizado e a evolução clínica pré e pós terapêutica.

Material e Métodos: Estudo observacional, longitudinal, retrospectivo e analítico, com base nos dados obtidos da consulta dos processos de todos os doentes com OI incluídos no protocolo de tratamento com pamidronato no Hospital Dona Estefânia. As variáveis estudadas foram: sexo, idade de diagnóstico, antecedentes familiares de OI, idade de fractura, localização da fractura, número de fracturas, terapêutica médica/cirúrgica, idade de início do tratamento médico, número de ciclos de terapêutica médica, idade da terapêutica cirúrgica, complicações da terapêutica cirúrgica. Adoptou-se um nível de significância de 5%.

Resultados: De 21 doentes, 61,9% eram do sexo masculino e 11 tinham registado o diagnóstico do tipo de OI (cinco do tipo I, três tipo III, três tipo IV). A idade média de diagnóstico foi de 20,6 meses, verificando-se dois picos diagnósticos: no primeiro mês – 37%, e aos 24 meses - 26%. Em média os doentes apresentaram 0,62 fracturas/doente/ano, 17,4% das quais no período perinatal e 62% antes dos três anos de idade. A maioria das fracturas ocorreu nos membros inferiores (55,6%). Todos os doentes realizaram tratamento médico, com início em média aos 4,3 anos. Na amostra com seguimento (n=14) verificou-se diminuição no número de fracturas após o início do tratamento com pamidronato (de 0,76 para 0,35 fracturas/doente/ano). Foram colocadas cavilhas endomedulares em nove doentes (64,3%). Em oito doentes foram colocadas nos fémures, quatro unilaterais e quatro bilaterais, não existindo antecedentes de fractura em três casos. Não se registaram novas fracturas nos ossos encavilhados.

Conclusão: A OI é uma doença com uma ampla variabilidade clínica que depende maioritariamente do seu tipo. Apesar de não existir tratamento curativo, o tratamento médico com bifosfonatos e o tratamento cirúrgico, com colocação de cavilhas endomedulares, parece reduzir a incidência de novas fracturas.

Palavras-chave: Osteogénese Imperfeita; Criança.

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INTRODUCTION

Osteogenesis imperfecta (OI) is a rare hereditary disease of the connective tissue, defined by bone fragility and osteopenia.[1,1,2,3] It is the most frequent genetic bone disease with an estimated prevalence between 1 : 10 000 – 20 000 births although milder forms are probably underdiagnosed.[1,3-5] Even though 0.008% of the world population is affected by OI, it is assumed that currently there are half a million patients worldwide. There are no national records in Portugal but a recent report estimates there may be 660 carriers of this condition of which only approximately 50 are currently diagnosed and followed up.[6] OI clinical presentation is extremely variable, including increased susceptibility to fractures, reduced bone mass, short stature, skeletal progressive deformities, bluish sclera, dentinogenesis imperfecta, laxity of the ligaments and hearing loss.[1,3-5]

Prognosis depends on the type of OI.[1,4] This issue can be addressed under a clinical perspective with the classification described by Sillence in four clinical types,[7] or in a classification based primarily on the genetic component. This latter classification groups nine subtypes in which severity increases progressively as follows: Type I < IV, V, VI, IX < III, VII, VIII < II.[4] Independent walking and autonomy are influenced by the number of fractures and deformities and the age at which they start.[3]

In about 90%, OI is the result of autosomal dominant mutations in one of two genes – COL1A1 and COL1A2, which codify chains of collagen type I.[1,2,4,8] The defects may be quantitative (mild to moderate forms) or qualitative (major or lethal forms).[4,5] More recently, mutations in genes involved in the hydroxylation of collagen type I proline were described.[4,] A type X was described, with a much more serious phenotype associated to mutations in a protease inhibitor. Types V and VI have an unknown etiology.[4]

Clinical and functional variability of this entity requires a multidisciplinary approach.[1] Treatment of OI depends on its severity and on patient's age.[4] There is no cure for OI,[1,5] so therefore the treatment aim is to improve functional capacity of patients, adopting strategies that optimize independence and social integration, beyond exclusively improving muscle and/or joint deficits.[3-5]

Treatment relies on three main aspects: medical treatment, using bisphosphonates, orthopedic surgery, application of intramedullary rods and rehabilitation.[3] Pamidronate increases bone mass, reduces musculoskeletal pain, increases vertebral body height and reduces fracture frequency in children.[6,8,9] Telescopic intramedullary rods have proved to be the most efficient treatment for fracture prevention and correction and for long bone deformities, improving patient walking capacity and leading to a successful rehabilitation, even in the most affected patients.[3,4] Physiotherapy, using orthoses, represent a fundamental role in preventing muscular atrophy, ankylosis and loss of autonomy.[3]

With the present work, the authors propose to describe the characteristics of a cohort of children with OI, in order to evaluate treatment by comparing pre and post-therapeutic clinical progress.

MATERIAL AND METHODS

Variables: glongitudinal, gender and age; Study type: observational, longitudinal, retrospective and analytical.

Population and cohort: children and adolescents (less than 18 years of age) with an OI diagnosis. The sample included all children with OI followed in this Department and included in a treatment protocol with pamidronate since 2001.

Duration and period: data collection took place during March 2011. The study period started at the time of inclusion of the patient with the longest follow-up until the moment of data collection. It took place from the beginning of May 1995 ending in March 2011.

Collection methods and information sources: Data have been collected through consultation of medical and nursing records.

Conceptual and operational definition of variables:

Age at diagnosis, defined as the number of full years, or months in the case of infants, at the moment of diagnosis;

Family history of OI, defined as the presence or absence of family members with an established diagnosis of OI;

Age of fracture, defined as the number of full years, or months in the case of infants, when fracture occurred;

Type of OI: defined according to the clinical classification of Sillence:[7] I – mild, little or no deformity; II – perinatal death; III – major bone deformity; IV – moderate bone deformity;

Fracture location, defined as the anatomical location of the fracture, set in *upper limb*, *lower limb* and *other locations*, including collar bone and spine;

1. **Number of fractures,** defined as the number of fractures pre and post medical and/or surgical treatment. This variable has been subdivided in fractures/year/patient (ratio between number of fractures and years of patient follow-up), fractures/patient (number of fractures per patient) and fractures/bone (number of fractures in a certain bone);
2. **Medical/surgical treatment**, defined as treatment with pamidronate / placement of intramedullary rods, respectively;
3. **Age of initial medical treatment**, defined as number of full years of age, or months in the case of infants, when medical treatment is started;
4. **Course of medical treatment**, defined as a set of three intravenous pamidronate infusions in three consecutive days in an adequate frequency for the patient's age: less than two years (0.5 mg/kg/day; every two months), between two and three years (0.75 mg/kg/day; every three months) and more than three years (1 mg/kg/day; every four months);
5. **Number of medical treatment courses**, defined as the number of full treatment courses with pamidronate that were administered;

6. **Age at surgical treatment** defined as the number of full years, or months in the case of infants, at the moment of placement of intramedullary rods;
7. **Complications of surgical treatment**, defined as complications directly attributed to the placement of intramedullary rods;

Collection and data treatment: all data have been collected through patient and nursing files. Data was codified and recorded on informatic support Excel 2007® (Microsoft Corporation, USA) having been treated with the statistical software SPSS 17.0Ò (SPSS Inc, Chicago, IL)

Data analysis: data description was based on frequency distribution, central tendency measures and dispersion measures. Non-parametrical tests were used for the statistical analysis of medical treatment efficacy (Wilcoxon Test for paired samples). A significance level of 5% was used for decision-making.

RESULTS

The studied cohort (*n* = 21) showed a predominance of males 61,9(13 boys – 61.9% and 8 girls – 38.1%). The average age at OI diagnosis (*n* = 19) was 20.6 months. Diagnosis was obtained under 27 months of age, except in two cases, when it occurred at four and nine years of age, respectively. Two diagnostic peaks were observed: at the first month (37%) and at 24 months (26%) of age (Table 1). A family history of the disease, always in first grade relatives was documented in only 33% (*n* = 7) of the cohort. In 57% of cases there was more than one relative with the disease (*n* = 12). In 11 children, OI type I was defined (five of type I; three of dois type III; three of type IVum).

Table 1 - Description of the 21 children in the study.

Patient	Gender	Age at diagnosis	Follow-up (years)	OI Family History	Fractures			Treatment
					Lower limbs	Upper limbs	Others	
1	M	5 days	3.3	N	6	6	-	B + S
2	M	at birth	3	N	4	-	-	B
3	F	at birth	10.7	N	1	3	-	B
4	F	2 years	6.6	N	2	1	1	B
5	F	18 months	9.4	Y	1	4	1	B
6	F	*in-utero*	11.2	N	3	1	-	B + S
7	M	2 years	1.6	Y	1	1	-	B
8	M	14 months	6	Y	4	-	-	B + S
9	M	2 years	15.3	N	3	-	-	B + S
10	F	1 day	13	N	1	2	-	B
11	M	2 years	3	N	2	1	-	B
12	F	2 years	2.6	N	2	-	-	B
13	M	at birth	7.3	Y	3	1	-	B + S
14	M	9 months	0.6	Y	1	3	-	B
15	F	*in-utero*	4.4	Y	2	-	-	B
16	M	18 months	8.4	Y	2	1	-	B + S
17	M	4 years	6.25	N	3	3	3	B
18	M	?	?	N	-	2	1	B
19	M	9 years	7.7	N	1	-	-	B + S
20	F	?	?	N	3	3	-	B + S
21	M	2 years	10	N	5	2	-	B + S

Legend: M – Male; F – Female; N – No; Y – Yes; B – Bisphosphonates treatment (Pamidronate); S – Surgery; ? – not known.

A total of 90 fractures occurred, with an average of 4.3 fractures per patient. In the 19 children in which diagnosis date was known, there was an average follow-up of 6.9 years (0.6 – 15.3 years) and 0.62 fractures/patient/year.

In terms of fracture location, 55.6% (*n* = 50) occurred in the lower limbs, followed by the upper limbs, responsible for 37.8% (*n* = 34) of the fractures. In 6.7% (*n* = 6), fractures occurred in other locations, particularly in the collar bone, ribs and spine.

From all fractures (*n* = 90), it was possible to determine the age in which they occurred in 82% (*n* = 74), with 62% (*n* = 46) occurring in the three first years of life. Perinatal fractures occurred in 17.5% (*n* = 13). The average age was 3.75 years (ranging from *in utero* to 14.6 years).

Fifty fractures occurred in the lower limbs and we could not determine the age when they occurred in eleven patients. From the 39 fractures in which the age at which they occurred was known, the average age was 3.55 years (ranging from *in utero* to 14.6 years). Two thirds of these fractures occurred in the three first years of life.

Of the 34 upper limb fractures, it was possible to determine the age in which they occurred in 31 cases. The average age was 4.17 years (ranging from *in utero* to 12.1 years). The three first years of life correspond to more than half of the cases (54.8%), with another peak during the sixth year of life (16.1%).

The average age in which the collar bone and spine fractures occurred was 2.33 years. Collar bone fractures exclusively occurred during childbirth and the single case of spinal fracture occurred at the age of nine.

In terms of medical treatment, all patients were treated with pamidronate. It was possible to determine the number of courses in only 14 patients, with an average of 6.5 courses/patient (2 – 13 courses).

Medical treatment average starting age (*n* = 18) was 50 months (2 – 120 months) with 55.6% of the cases starting treatment before 36 months (Fig 1). On average, the time span between OI diagnosis and the beginning of medical treatment was three years and four months (ranging from 2 months to 10 years).

Transfer to other hospitals explains the lack of follow-up in seven patients. After starting treatment, the remaining 14 patients presented 1.57 fractures/patient, corresponding to 0.37 fractures/patient/year and seven patients did not present new fractures during an average follow-up of four years and two months (Fig 1). In these patients where follow-up was possible (*n* = 14) there were on average 3.3 fractures per patient before starting treatment, representing 0.76 fractures/patient/year. We did not find statistically relevant differences between the average fracture/patient before and after treatment (*p* = 0.63 – Wilcoxon Test).

In these cases, where follow-up was possible (*n* = 14), intramedullary rods were placed in nine children (64.3%), with an average number of 1.7 rods per patient. Most were applied to the femur, unilaterally and bilaterally, both with four cases. A humerus, a tibia and an ulna were also

Figure 1 - Pre and post-treatment clinical progress with Pamidronate.

operated.

Prior to operation, the average fracture number was approximately 1.4. No new fractures occurred after surgery. A rod was placed in three patients, despite the absence of a previous bone fracture.

The average age for the first intervention was 7.7 years (2.5 – 15 years). All described surgeries occurred in the last three years. About one month after intervention, intramedullary rod migration occurred in one case, requiring surgical revision, without any further complications.

DISCUSSION

The cohort presented in this study (*n* = 21), although small, represents a relevant number of cases, taking into account that there are only approximately 100 OI cases diagnosed and in follow-up in Portugal, including adults and children.[6]

Our cohort showed a male : female ratio of 2:1. There are however no descriptions of gender predominance in this disease, in accordance with the autosomal genetic transmission (dominant and rarely recessive) mode of inheritance.[4] In our group of patients, only 33% presented with a positive OI family history. Taking into account that about 75% of the OI cases present an autosomal dominant transmission and that the recessive cases are rare (consequently each parent is a gene carrier), this fact seems to be related to parental mosaicism (recently considered as an etiological factor in 16% of autosomal dominant cases)[10] or *de novo* mutations (25% of OI cases).

In terms of the age at diagnosis, this depends on disease subtype. In our group of patients, genetic and clinical characterization is still pending in ten cases, at the time of writing. Therefore, we may just analyse the collected data and infer the subtype by classical case descriptions. In our group of patients, 37% (*n* = 7) were diagnosed in the perinatal period, what is typical of the more severe phenotypes such as OI type II and III.[4] In 37%, the diagnosis was made between the ages of 18-24 months, after which all children should have started walking. These may be due to milder OI subtypes, I and IV, which are characteristically diagnosed at these ages. We must emphasize the possibility that a delayed diagnosis is due to clinicians lack of awareness regarding the disease characteristics, compounded by the probability that 25% of cases were due to a *de novo* mutation and an apparently high mosaicism frequency**.**

OI is characterized by bone fragility and osteopenia, allowing for fractures due to minor or even spontaneous trauma.[1-3]

Clinical presentation is very variable, mainly in what refers to fracture susceptibilty.[1,3-5] This depends, among other factors, on the OI type and on the age of the patients. On average, 2 fractures/year occur in moderate-severe OI types (III, IV, V, VI).[2] In this study, OI type was only available in 11 patients, which may be explained by multiple factors, namely incomplete records, diagnostic uncertainty and a requirement for genetic confirmation of diagnosis. On average, there were 0.76 fractures/patient/year, in the 21 children included in the study. This fracture frequency may be explained by the presence of different OI types in the studied population and by the treatment which was carried out. The likely presence of moderate to severe forms of the disease may explain a percentage of 17.5% of fractures in the perinatal period.[1,4]

In this disease, in the pediatric period, mainly in more intense bone growing periods, the fracture incidence is higher, reducing considerably after puberty.[4,8] Almost two thirds of the fractures (62%) occurred in the three first years of life, in this study. The fact that it is a period of intense bone growth, coinciding with the acquisition of important motor skills such as walking, sets a greater accident and trauma risk, increasing the risk of fracture.

More than half of fractures (55.6%) occurred in the lower limbs, subjected to a higher charge and with a relevant risk of trauma, even more important in the younger children. The falls may also have contributed to the significant percentage of fractures in the upper limbs.

In the studied patient group, all patients were treated with bisphosphonates (pamidronate). Treatment was started, on average, 40 months after OI diagnosis and, in 52.4% of the cases started before 36 months of age. Treatment delay may relate to the fact that it was only initiated in this Department in 2001, at the time addressing children with a previous OI diagnosis (five cases). It may also be related to a delay in the referral process and follow-up of the patients until they reached our speciality.

There is no description of an adequate time to start treatment with bisphosphonates and it is indicated after OI diagnosis,[4] having been successfully carried out in children under three months of age.[11] Medical treatment aims to increase bone mineralization, with a consequent reduction of the number of fractures and improvement of quality of life.[9] In our patients, treatment resulted in a reduction of the number of fractures to approximately half of the previous rate (from 0.76 to 0.37 fractures/patient/year) and even if this reduction lacks statistical significance, we propose it sustained an improvement in the quality of life of these children. In a study carried out by Glorieux,[12] fracture rate changed from 2.3 to 0.6 fractures/patient/year after starting treatment with pamidronate. These results may be influenced by age, OI severity, ambulation capacity and social environment.[11] We are unable to attribute this improvement to bisphosphonate use alone without taking into account surgical treatment.

The first descriptions of using pamidronate in treatment of patients with severe OI occurred in 1998[13] and since then we find different studies in literature that evaluate bisphosphonate treatment in OI. These analysis are difficult to compare as they share the characteristics of being non- randomized trials, with small study populations, little experience in pediatric age and different evaluation criteria.[2,5,14,16] While it seems demonstrated that bisphosphonates are useful in increasing bone density,[9] the level of impact on reduction of number of fractures or bone pain remains questionable. According to Glorieux[12] the benefits of using bisphosphonates

are clear, namely reducing number of fractures and pain, increasing muscular mass and growth velocity. However, the author also remarks some deleterious aspects related to their use, such as reduction of bone remodelling and growing cartilage reabsorption and cure delay in osteotomy locations.[12]

In the treatment of children with OI, the use of bisphosphonates has recently been described as beneficial in the reduction of surgical interventions required for fracture treatment. It has been claimed this would constitute an improvement in the quality of life of these children.[17]

The role of vitamin D in genetic bone diseases has been insufficiently studied in the pediatric age. A recent study by Edouard,[18] revealed a positive correlation between vitamin D levels and lumbar bone mineral density. Vitamin D supplementation in these cases of OI would have a positive impact in increasing bone density and could be recommended in these patients.

In the present study, rods were placed in 64.3% (*n* = 9) of the patients followed and after this treatment no new fracture occurred. Timely surgery with placement of intramedullary rods and osteotomy prevents and corrects deformities of long bones, reducing fracture frequency.[1,3-5] Indication for these interventions is more frequent in the femur and the tibia, while humeral fixation is less frequent and there is rarely an indication for forearm intervention,[4] as we observed in our study.

Intramedullary rod placement before the age of three and a half in lower limbs improves psychomotor development.[4] In this study, the average age of patients that underwent rod placement was 7.7 years. However, and given that consensus about surgical approach in OI is relatively recent, we should remark that all surgeries were carried out in the last three years. Rod migration is a major complication[4], and it occurred in one case of our cohort. New fractures may still occur but, in these cases, rods prevent misalignement, reduce cure time and the need to use splints or casting.[4]

The present study presents some limitations. It is a retrospective study, with a convenience sample that only included patients followed in a Pediatric Hospital. Being non representative, we may not infer any results for other populations. Nevertheless, the sample includes 21 individuals, which represents about one fifth of OI diagnosis in Portugal and as such involves a considerable number of patients, taking into account the rarity of the disease. On the other hand, data collection was based on the analysis of handwritten clinical files and manuscript records, therefore information may have been lost along the years or may have never been recorded, explaining some information loss in this study. In addition, data analysis did not consider the different types of OI, as in some cases this information was not available, the follow-up period was not uniform and in 17.8% of the cases the age at which fractures occurred was unknown. The joint evaluation of surgical and medical treatment (with bisphosphonates), was not assessed in some cases, nor the impact of other treatments. The authors consider that in future studies it would be interesting to evaluate functionality, pain and quality of life before and after treatment, and also to evaluate improvement in bone density and impact of bisphosphonate treatment on the number of fractures.

CONCLUSION

Our results demonstrate the complexity of OI diagnosis and treatment. A high degree of clinical heterogeneity according to the different OI types result in different treatment objectives in these patients in order to obtain *normal* life in the milder forms or maximal autonomy and fracture risk reduction in the moderate-severe forms.

In the present study, we observed that the association between medical and surgical treatment brings obvious benefits with the reduction of number of fractures, reinforcing the notion that a multidisciplinary approach is essential in these patients. In this context, all efforts should concentrate in this objective, allowing for a better quality of life in these patients.

CONFLICT OF INTERESTS

Authors declare the absence of any conflict of interests.

SPONSORSHIP SOURCES

Authors declare the absence of any sponsorship sources.

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