INDEPENDENT WALK IN OSTEOGENESIS IMPERFECTA

CARMEM LIA MARTINS MOREIRA[1], MARIA ANGELICA DE FARIA DOMINGUES LIMA[2], MARIA HELENA CABRAL DE ALMEIDA CARDOSO[1], SAINT CLAIR DOS SANTOS GOMES JUNIOR[1], PAULA BACELLAR LOPES[1], JUAN CLINTON LLERENA JUNIOR[1].

ABSTRACT

Objectives: Investigation of the locomotion process in patients with osteogenesis imperfecta (OI), and the factors that influence it, with special attention to clinical aspects relating to motor rehabilitation. Methods: a retrospective, cross-sectional study was carried out at the physical therapy outpatient clinic of the Instituto Fernandes Figueira. All patients with a clinical diagnosis of OI were included. Patients with other diseases, and those aged under two years, old were excluded. Epi-Info version 3.4 was used to construct the database, and SPSS version 15 for the statistical analysis. Results: The odds-ratio was used to measure the association between independent walking and clinical characteristics, adopting a level of significance of 5% for the analysis. Results: 69 patients were included. Of these, 43.5% were classified as OI type I; 37.7% as type III and 18.8% as type IV. 76.8% presented long bone deformities. A negative association was observed between hypotonia, number of fractures, and independent walking. A positive association was observed between independent walking and OI type I. Conclusions: physical therapy, as a complementary approach to orthopedics, and the administration of medications of the biophosphonates class, are of fundamental importance for the rehabilitation of motor capacity of individuals with OI. Level of Evidence, cross sectional.

Keywords: Physical therapy. Osteogenesis imperfecta. Gait. Mobility limitation. Cross-sectional studies.

Citation: *Moreira CLM, Lima MAF, Cardoso MHC, Gomes Junior SCS, Lopes PB, Llerene Junior JC. Independent walk in osteogenesis imperfect. Acta Ortop Bras. [online]. 2011;19(5):312-15. Available from URL: http://www.scielo.br/aob.*

INTRODUCTION

Osteogenesis Imperfecta (OI) is a genetically determined condition characterized by substantial bone fragility and osteopenia. It affects about 1:5000-10000 individuals[1] and is a rare and potentially incapacitating disease.

The clinical manifestations include recurrent fractures with secondary deformities, muscle weakness, ligamentous laxity, bluish sclera, dentinogenesis imperfecta, bone pain and early loss of hearing. The clinical heterogeneity is so striking that Sillence's first classification, involving four groups, has been added to and currently totals eight.[2-6]

Several authors have already demonstrated the major physical disability associated with OI, even in patients with the least severe type (type I according to Sillence's classification), related to the presence of deformities that directly affect mobility.[4,7]

In Brazil, the osteogenesis imperfecta issue gained greater visibility from 2001, when treatment for this condition was established as a public health policy. From then on, within the Unified Health System (SUS), the systematic monitoring of individuals with OI has been oriented by the Protocol of Indication of Clinical Treatment of OI, which establishes a therapeutic approach with disodium pamidronate, orthopedic interventions and physiotherapeutic treatment at the Centers of Reference for Treatment of OI (CROIs).

As refers to physiotherapy where the main goal is functional capacitation with motor development stimulation, aiming to perform postural transitions or activities denominated transfer tasks,[8] it is to be expected that its application for the capacitation and rehabilitation of people with OI would be widely discussed. However, the scientific publication geared toward the treatment of the disease accentuates drug therapy with bisphosphonates and surgical techniques,[9] whereas physiotherapy is seldom contemplated.[1,9]

In this regard, the objective of this study is to demonstrate the clinical characteristics of patients with OI, relating them to the orthostatic position and to the acquisition of independent walking from the perspective of the physiotherapy clinic.

MATERIAL AND METHODS

This is a retrospective, cross-sectional study that included patients with clinical diagnosis of OI, carried out at the physiotherapy outpatient clinic of the Instituto Fernandes Figueira (IFF),

All the authors declare that there is no potential conflict of interest referring to this article.

1 – Department of Genetic Medicine – Fernandes Figueira National Institute of Women's and Children's Health – Oswaldo Cruz Foundation, Rio de Janeiro – RJ
2 – Genetic Medicine – National Cancer Institute – Rio de Janeiro – RJ

Work done at the Fernandes Figueira National Institute of Women's and Children's Health – Oswaldo Cruz Foundation, Rio de Janeiro – RJ. Brazil.
Mailing Address: Departamento de Genética Médica do Instituto Fernandes Figueira. Av. Rui Barbosa, 716, Flamengo, Rio de Janeiro – RJ. Brazil. Postal Code: 22250-020.
Email: cardosomhca@iff.fiocruz.br8, c.lia9@globo.com

Article received on 7/28/10 and accepted on 8/19/10.

maternal-infant unit of Fundação Oswaldo Cruz (FIOCRUZ). IFF/FIOCRUZ was accredited as general coordinator of all the Brazilian CROIs and since 2001 has been responding to the needs of the highest number of individuals with the disease in the country, also acting as a pioneer in the preparation of a specific Physiotherapy Program targeting these patients.

Selection of the sample

The clinical laboratorial diagnosis of OI, defined by: bone fragility characterized by repetitive fractures; family history positive for OI; blue sclera; early deafness; low stature; dentinogenesis imperfecta; alterations in radiography compatible with OI and osteoporosis evaluated through bone densitometry, was considered an inclusion criterion.

The exclusion criteria were comorbidities and age below two years at the time of the physiotherapy assessment.

Data gathering

The demographic and clinical data were obtained from the medical records and by the physiotherapy assessment tool[10], which records information about: gestational and neonatal histories; motor development; activities of daily living; physical examination; and evaluation of functional capacity that involves measuring the range of motion through goniometry, posture transition and displacements. Posture transitions and displacements are part of the assessment of gross motor function (GMFM - Gross Motor Function Measure).

From the viewpoint of physiotherapy, the following clinical characteristics were contemplated as factors that could influence independent displacement, *a priori*: type of OI, joint hypermobility, hypotonia, number of fractures and deformity of long bones. The type of OI was classified according to Sillence et al.[4] Hypermobility was evaluated by measuring joint amplitude (goniometry), considered present when the amplitude of most of the individual's joints was within the range of normality. Long bone deformities were evaluated through inspection, palpation, as proposed by Sillence et al.[4] and radiographs of long bones, flagged when there was at least one long bone outside the adequate biomechanical alignment. The number of fractures was obtained by recording clinical consultations and radiographic evidence was recorded when registered at CROI/IFF. Hypotonia was diagnosed according to the criteria proposed by Dubowitz[11] and Reed,[12] and was characterized by the decrease of resistance to passive manipulation, recognizing the hypotonic individual as exhibiting reduced resistance of the muscles to passive movement, absence or decrease of myotactic reflexes, fixed posture of abduction with external rotation of coxofemoral joint and flaccid extension of the arms.

Statistical analysis

A bivariate analysis was conducted initially, employing Fisher's, chi-square, Mann-Whitney and Wilcoxon tests, with independent orthostatic position and independent walking as outcomes.

The Relative Risk was used to measure the association of the variables of interest to physiotherapy with the orthostatic position and independent walking.

A logistic model was used to identify factors that have a negative effect on independent walking capacity, which is obviously the most important outcome.

The significance level of 5% and confidence interval of 95% were adopted for the bivariate and multivariate analyses. Epi-Info 3.4 was used to construct the database and SPSS version 15 for the statistical analysis.

The research project that serves as the basis of this study was approved by the Committee of Ethics in Research on Humans of IFF-FIOCRUZ through report no. CAAE-0022.0.008.000-08, cover page 201496.

RESULTS

Between 2004 and 2008 the physiotherapy service of the Program for Treatment of Osteogenesis Imperfecta of CROI/IFF assessed 92 patients. Of these, four were excluded due to comorbidities – Down syndrome, sickle cell anemia, fetal alcohol syndrome and West's syndrome -, and another 19 as they were under two years old at the time of the first assessment, totaling 69 individuals in the sample presented here. Most of the patients were female (58%). The age of the analyzed individuals ranged between 2 and 37.6 years, with mean age of 10 years. As regards the type of OI, the patients were classified according to Sillence[4] (1979) as OI type I - 30 individuals (43.5%); OI type III - 26 (37.7%); and OI type IV - 13 (18.8%). The clinical characteristics associated with each one of these groups are summarized in Table 1.

The deformities were observed more frequently in lower limbs than in upper limbs. Femurs and tibias were the long bones affected most often, followed by humerus, fibula, radius and ulna. Besides the long bone deformities, in 24 (35.3%) patients there was deformity of the spinal column (kyphosis, lordosis and scoliosis). As regards the outcomes independent orthostatic position and also independent walking acquisition, the results are summarized in Table 2.

Table 1. *Clinical characteristics by types of OI.*

	OI Type			Total
	I	III	IV	
Deformity				
Present	16	25	12	53 (76.8%)
Absent	14	1	1	16 (23.2%)
Hypotonia				
Present	18	26	11	55 (79.7%)
Absent	12	0	2	14 (20.3%)
Joint hypermobility				
Present	21	26	11	58 (84.1%)
Absent	9	0	2	11 (15.9%)
Number of fractures (mean)*	8.76 (1-48)	51.26 (2-200)	20.58 (2-15)	27.1

*The analysis by OI subgroup was performed when possible. * Wilcoxon non-parametric test, p-value<0.001*

Table 2. *Orthostatic position and independent walking outcomes, bivariate analysis.*

	Orthostatic position			Walks independently		
	Yes	No	p-value	Yes	No	p-value
Age (years) (mean/ median)*	9.76 / 9.29 (N= 42)	10.36 / 11.33 (N = 27)	>0.05	9.04/7.5 (N=33)	8.69/11.2 (N=36)	<0.05
Joint hypermobility#						
Present	32	26	<0.05	24	2	<0.05
Absent	10	1		9	35	
Hypotonia#						
Present	28	27	<0.0001	20	35	<0.0001
Absent	14	0		13	1	
Type of OI§						
I	28	2	<0.0001	27	3	<0.0001
III	7	19		2	24	
IV	7	6		4	9	
Deformity#						
Present	26	27	<0.0001	18	35	<0.0001
Absent	16	0		15	1	

** Mann-Whitney test. # Fisher test. § chi-square test.*

On the other hand, the multivariate analysis process focused on the main outcome (independent walking) included the variables: hypotonia; deformities of lower limbs and spinal column; number of fractures; joint hypermobility and type of OI. The first analysis revealed significance with regards to the type of OI, hypotonia and the number of fractures. Accordingly, another analysis was conducted with a basis on these three variables, with results shown in Table 3.

Table 3. *Multivariate model considering the independent walking outcome.*

	Relative risk	CI (95%)	p-value
Hypotonia	0.023	0.01 – 0.412	0.01
Type I OI	6.248	2.096 – 18.624	0.001
Number of fractures	0.897	0.825 – 0.974	0.01

DISCUSSION

Although no differences are observed in the frequency of OI between the sexes, in our sample we observed a discrete predominance of female individuals, which we consider a fortuitous observation.

The actual prevalence of the groups according to the Sillence classification is unknown, yet some authors report that type I is observed the most,[4,13] similar to our findings.

Both outcomes, orthostatic position and independent walking, showed association with variables of interest to physiotherapy clinics such as hypotonia, joint hypermobility and deformities that, in turn, are also linked to the typological classification of OI. Independent walking is an important motor development goal in children with OI as well, but requires initial training promoted by the orthostatic position, so as to favor weight bearing and unloading on the lower limbs and to promote active bone strengthening.[8]

Considering that walking is said to be acquired when the child can take at least three steps without support, and the mean acquisition age is at 13 months,[14] it is befitting to question the statistically significant association between independent walking outcome and the age variable. We can probably put forth the hypothesis that the explanation for such fact resides in a discreet prevalence, among our patients, of OI type I, the mildest form of the disease, where disability is not so evident.

Skeletal deformities are observed in many genetic disorders and most studies related to them emphasize that an imbalance of muscle tone, strength or actual immobility may increase the risks of acquiring them.[14,15]

The frequency of deformity observed in long bones was high (76.8%). According to other authors, they were noticed most in Sillence type III patients.[16] Now as regards the vertebral deformities found, it can be affirmed that they are related to the hypotonia observed in our patients, which reinforces the need for early mobility and strengthening of the trunk muscles, since they tend to progress during adolescence.[8]

Almost 80% of the patients in our sample exhibited some degree of hypotonia, a distinctive characteristic in the patients classified with type III (100% of these). The connection with muscle tone in the cases of OI occurs due to the clinical sign of hypotonia originating from limited strength and from lack of resistance, and is often characterized in children by a tendency to fix/secure the weight-bearing joints or to assume positions that provide a broad base of support to maximize their stability.[15]

In the case of the presence of hypotonia in all the cases classified as OI type III, the hypothesis that can be put forward is that it is explained by the occurrence of fractures leading to prolonged secondary immobility, to deformities and, not less importantly, to the bone pain that leads to the tendency toward inertia.

Accordingly, at CROI/IFF, aware of the influence of hypotonia for gain of mobility, we have included in the physiotherapy program an approach geared toward the progressive increase of gain of muscle strength of the trunk and lower limbs, through intensification of the physiotherapy activities that promote body positions in space, allowing better interaction with the vestibular system and consequently improving muscle tone.[17]

Hypermobility was also very frequent in this population (recorded in almost 85% of the individuals), yet did not appear to have any influence on independent walking, based on the multivariate analysis performed. In practice, hypermobility is not as detrimental to physiotherapy work, yet hypotonia substantially hampers gain of function in an individual who can hardly rely on the tensile strength provided by the tendons. Hyperextendable joints are commonly observed in children with hypotonicity.[8,15]

In addition, if the patient exhibits deformities, muscle strength is dissipated and biomechanical alignment modified, undermining a particular function.[18]

A bias of this study was the method used to record the number of fractures, since we did not always have access to radiological confirmation of all the fractures that had occurred, sometimes relying only on old radiographs or the memory of the patient or relatives for a correct record of these events. Indeed, repetitive fractures are notable clinical characteristics of OI and the quantity of fractures occurring during the lifetime serves as support for clinical classification. Recent studies demonstrate that it is possible to reduce this occurrence using bisphosphonates.[19,20]

The implication of fractures at physiotherapy clinics transcends simple temporary immobility as a means of reinforcing hypotonia and the discontinuation of the physiotherapy work. These episodes increase the fear of bone fragility, preventing, at times, the performance of tasks by the individual with OI or of its manipulation by family members. This becomes more evident in small children, where the mothers seldom handle their children, depriving them of a good tactile-kinesthetic-vestibular perception, which ends up entailing a muscle tone regulation deficit.

Also related to the issue of fractures, secondary deformities resulting from fractures, which in the multivariate analysis did not show statistical significance, may also constitute another bias directly linked to the size of our sample. To this effect, more in-depth analyses adding data from the network of Brazilian CROIs, will certainly be useful for the establishment of a more specific association.

CONCLUSION

The experience of CROI/IFF demonstrated that physiotherapy work, as a means of support to orthopedic interventions and to therapy with bisphosphonates, is a tool of vital importance to the improvement of the motor capacity of individuals with OI. Its action should target joint stress during strength gain activities, particularly when there is hypotonia, and more neutral biomechanical alignment.

Finally, in view of the experience acquired and of the results achieved, and as regards physiotherapy as supplementary treatment, we recommend paying special attention to: i) postural positioning to minimize the risks of fractures and soft tissue restrictions, ii) the incentive of mobility in a safe environment as early as possible and also after a fracture to avoid muscle atrophy and the limitation of movements with the intention of preserving bone resistance, iii) the mobility desired by the patient and, finally, iv) balance and functional independence.

ACKNOWLEDGEMENTS

The first author, Carmem Lia Martins Moreira, is grateful for the financial support of CAPES.

REFERENCES

1. Engelbert RHH, Uiterwaal CS, Grever WJ, van der Net JJ, Pruijs HE, Helders PJ. Osteogenesis imperfecta in childhood: impairment and disability. A prospective study with 4-year follow-up. *Arch Phys Med Rehabil.* 2004;85:772-8.
2. Glorieux FH, Rauch F, Plotkin H, Ward L, Travers R, Roughley P et al. Type V osteogenesis imperfecta: a new form of brittle bone disease. *J Bone Miner Res.* 2000;15:1650-8.
3. Glorieux FH, Ward LM, Rauch F, Lalic L, Roughley PJ, Travers R. Osteogenesis imperfecta type VI: a form of brittle bone disease with a mineralisation defect. *J Bone Miner Res.* 2002;17:30-8.
4. Sillence DO, Senn A, Danks DM. Genetic heterogeneity in osteogenesis imperfecta. *J Med Genet.* 1979;16:101-16.
5. Ward LM, Rauch F, Travers R, Chabot G, Azouz EM, Lalic L *et al.* Osteogenesis imperfecta type VII: an autosomal recessive form of brittle bone disease. *Bone.* 2002;31: 12-8.
6. Cabral WA, Chang W, Barnes AM, Weis M, Scott MA, Leikin S et al. Prolyl 3-hydroxylase 1 deficiency causes a recessive metabolic bone disorder resembling lethal/severe Osteogenesis imperfecta. Nat Gen. 2007; 39:359-65.
7. Engelbert RH, Beemer FA, van der Graaf Y, Helders PJ. Osteogenesis imperfecta in childhood: impairment and disability – A follow-up study. *Arch Phys Med Rehabil.* 1999;80:896-903.
8. Ratliffe KT. Fisioterapia - clínica pediátrica. São Paulo: Editora Santos; 2000.
9. Rauch F, Glorieux FH. Osteogenesis imperfecta. Lancet. 2004;363:1377-85.
10. Lopes PB. Estudo sobre desenvolvimento motor grosso de crianças do Centro de Referência para osteogênese imperfeita do Instituto Fernandes Figueira/FIOCUZ/RJ [dissertação]. Rio de Janeiro: Instituto Fernandes Figueira; 2009.
11. Dubowitz V. El nino hipotônico. Barcelona: Editorial Pediátrica; 1973.
12. Reed UC. Síndrome da criança hipotônica. In: Diament AG, Cypel S, organizadores. Neurologia infantil. 3a. ed. São Paulo: Atheneu; 1996. p 1130-54.
13. Munns CFJ, Sillence DO. Disorders predisposing to bone fragility and decreased bone density In: Emery and Rimoin's principles and practice of medical genetics. 5th ed. Philadephia: Churchill Livingstone; 2007. p. 3671-91.
14. Gosselin J, Amiel-Tison C. Avaliação Neurológica: do nascimento aos 6 anos. 2a. ed. Porto Alegre: Artmed; 2009.
15. Umphred DA. Reabilitação neurológica. 4a. ed. Barueri: Manole; 2004.
16. Vetter U, Pontz B, Zauner E, Brenner RE, Spranger J. Osteogenesis imperfecta: a clinical study of the first ten years of life. *Calcif Tissue Int.* 1992; 50:36-41.
17. Flehmig I. Texto e atlas do desenvolvimento normal e seus desvios no lactente.. São Paulo: Atheneu; 2002.
18. Hernandez CJ, Keaveny TM. A biomechanical perspective on bone quality. *Bone.* 2006;39:1173-81.
19. Aström E, Söderhäll S. Beneficial effect of bisphosphonate during five years of treatment of severe osteogenesis imperfecta. *Acta Pædiatr.* 1998;87: 64-8.
20. Glorieux FH, Bishop NJ, Plotkin H, Chabot G, Lanoue G, Travers R. Cyclic administration of pamidronate in children with severe osteogenesis imperfecta. *N Eng J Med.* 1998;339:947-52.