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Ciências da Saúde

Osteogenesis imperfecta: Clinical characteristics and treatment approach of patients from Manaus, Amazonas, Brazil

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Resumo

Introdução: A osteogenese imperfeita é uma doença genética do tecido conjuntivo, decorrente de anormalidades quantitativas e/ou qualitativas do colágeno tipo I. O objetivo deste estudo é descrever as características clínicas e de tratamento de pacientes com OI do ambulatório de doenças osteometabólicas do Manaus. **Metodologia:** Trata-se de um estudo retrospectivo, descritivo em protuários médicos de 2002 a 2018. **Resultados:** Nossa amostra consistiu de 6 pacientes. O tipo I foi identificado em 50% dos pacientes e tipo IV nos demais 50%. Todos os pacientes apresentavam graus de parentesco, e o principal tratamento utilizado foram bifosfonatos. **Conclusão:** Identificamos um diagnóstico tardio nessa amostra, principalmente decorrente da variabilidade clínica da doença. Médicos precisam estar atentos para as principais formas clínicas, de forma que um diagnóstico precoce possa ser feito, prevenindo complicações como fraturas.

Abstract

Background: Osteogenesis imperfecta (OI) is a connective tissue genetic disorder due to quantitative and/or qualitative abnormalities of type I collagen. The objective of this study is to describe the clinical and treatment characteristics of patients with OI from an ambulatory clinic treating osteometabolic diseases from Manaus. **Methods:** Retrospective descriptive study of medical records from 2002 to 2018. **Results:** Our sample consisted of six patients with OI. Type I was observed in 50% of patients, while type IV was observed in the remaining 50%. All the patients were related, and the main treatment approach was the prescription of a bisphosphonate. **Conclusion:** We identified a delayed diagnosis in our sample due to the many possible different clinical features of the disease. The clinical doctor should pay attention to the signs and symptoms, in order to make an early diagnosis and prevent complications (such as fractures).

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Introduction

Osteogenesis imperfecta (OI), or brittle bone disease, is a genetic autosomal dominant condition affecting the extracellular matrix of connective tissue and is characterized by high bone turnover and osteopenia. The prevalence of OI is estimated to be between approximately 1 and 2 per 20,000 people (SAM & DHARMALINGAM, 2017; BACON & CROWLEY, 2017; MARINI, 2018).

Diagnosis is by clinical and radiological observation. According to the disease severity, a classification has been proposed by Silence, ranging from I to IV. Recently, OI type V has been described, which is based on specific phenotypic traits. There are other types and classifications that have been described, but the most commonly used is the Silence classification with the addition of type V (PALOMO & VILAÇA & LAZARETTI-CASTRO, 2017; GIMENO-MARTOS *et al., 2017;* TOURNIS & DEDE, 2017; MORELLO, 2018).

Since it is a rare condition, this study aimed at characterizing the clinical patterns and treatment of patients with OI in an ambulatory clinic treating osteometabolic diseases in a tertiary hospital.

Methods

This is a retrospective study from the medical records of patients with OI from Ambulatório Araújo Lima, Manaus – AM, Brazil. All patients with the diagnosis of OI were included. In order to identify the patients with OI, the charts from patients with osteometabolic diseases were reviewed from 2002 to 2018. This research was approved by the Ethics Committee of Universidade Federal do Amazonas (CAAE 02533612.7.0000.5020).

Out of the 354 patient charts that were reviewed, we found six patients with OI. The diagnosis was based on clinical and radiological features. The data collected included age at diagnosis, disease type, family history and clinical characteristics of the disorder.

Results

Our sample consisted of six patients with OI. The main epidemiological characteristics are included in Table 1. The male/female ratio was 1:5. The age at diagnosis ranged from 2 months to 69 years old, with a median age of 24 years old. Type I was observed in 50% of the patients, while type IV was observed in the remaining 50%.

Table 1: Epidemiological characteristics of the patients with osteogenesis imperfecta

Patient	Sex	Age of Diagnosis (years)	Type	Family History
1	F	12	I	+
2	F	9	IV	++
3	F	40	I	+
4	F	12	IV	+
5	M	69	IV	++
6	F	41 days	I	+

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Heredity was an important factor in our sample, as all of the patients had a positive family history for OI. Two of the patients had more than one first-degree relative with the disease. All patients were related, and patients 4 and 5 had many family members with the disease, as seen in Figure 1.

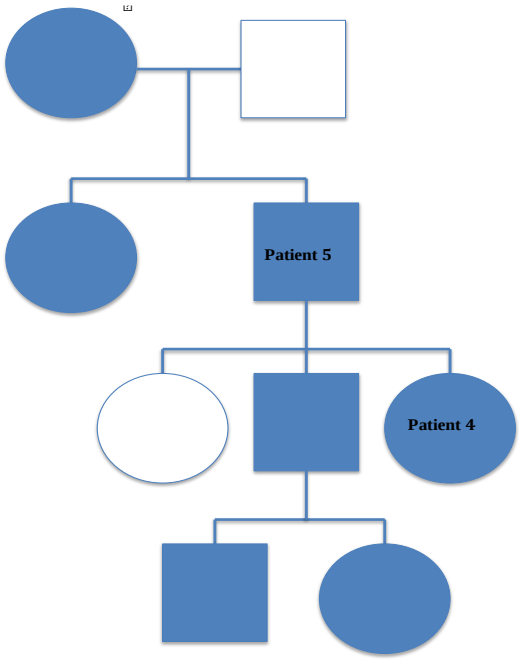

Figure 1: Genogram of patients 4 and 5

Concerning the clinical features, the characteristics are seen in Table 2. Blue sclera (Figure 2) was the most common feature and was present in all patients. Pectus carinatum, joint laxity and lordosis were quite frequent and were present in half of the patients. Triangular face, prominent forehead and proptosis were found only in-patient number 2.

Dentinogenesis imperfecta (DI) (Figure 3) was observed in patients 3 and 6; both patients are related, and patient 6 presented with clinical aspects as soon as she was born, being diagnosed by 41 days of life. A total of 55 fractures was registered, ranging from 0 to 33, with a median of 9.2 fractures per patient. None of the patients underwent genetic analysis.

The main treatment approach was bisphosphonates; 50% of patients were treated with alendronate and the remaining 50% with pamidronate.

Discussion

OI is a rare disease caused mainly (85–90%) by autosomal dominant mutations in either the COL1A1 or COL1A2 gene. There are two types of defects. The quantitative defects produce normal type I collagen, but in reduced amounts. These cases normally present with mild phenotypes (MARINI, 2018; PALOMO & VILAÇA & LAZARETTI-CASTRO, 2017; GIMENO-MARTOS *et al., 2017;* TOURNIS & DEDE, 2017; MORELLO, 2018; FABRE & BAGGENSTOSS, 2017; ZHANG *et al*. 2016).

Table 2: Clinical features of the patients with osteogenesis imperfecta

Patient	Blue Sclerae	DI	Hearing Loss	PC	Lordosis	Joint Laxity	Nº of Fractures	Height (m)
1	+	-	-	-	+	-	0	1,52
2	+	-	-	+	+	+	15	1,57
3	+	+	-	-	+	+	8	1,50
4	+	-	-	+	-	-	15	1,40
5	+	-	-	-	-	-	32	1,56
6	+	+	-	+	-	+	1	NR

PC = Pectus Carinatum
NR: not relevant, because the patient is a child

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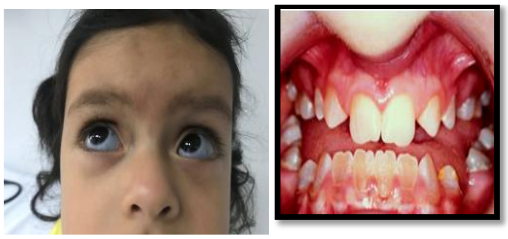

Figure 2A and 2B: Blue sclerae and dentinogenesis imperfecta

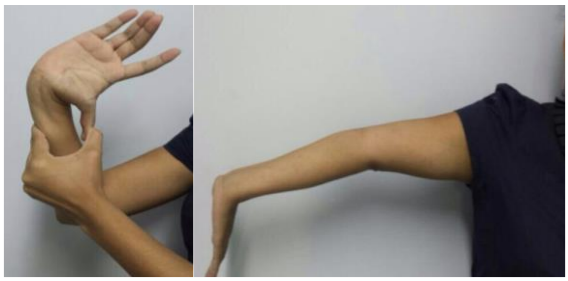

Figure 3A and 3B: Joint laxity

The qualitative defects affect the structure. Usually, the glycine is replaced by another amino acid, causing a structural defect in the collagen triple helix, resulting in moderate and severe phenotypes. The defective protein accumulates in the endoplasmic reticulum, causing an enlargement of the endoplasmic reticulum and delayed secretion into the extracellular matrix (MARINI, 2018; PALOMO & VILAÇA & LAZARETTI-CASTRO, 2017; GIMENO-MARTOS *et al., 2017;* TOURNIS & DEDE, 2017).

The clinical presentation includes osteopenia, recurrent fractures, bowing of long bones, short stature, joint laxity, kyphoscoliosis and extra-skeletal features (SAM & DHARMALINGAM, 2017; PALOMO & VILAÇA & LAZARETTI-CASTRO, 2017).

Blue/grey sclera is a presentation of OI. The colour can stay stable over the years or become less dark over time. Teeth involvement is common, represented by DI. Hearing impairment is quite common, normally presenting between the second and fourth decade of life, progressing over the years (SAM & DHARMALINGAM, 2017; PALOMO &VILAÇA & LAZARETTI-CASTRO, 2017; GONÇALVES & MEYER & SATO, 2017).

In our patients, blue sclera was the most prevalent characteristic, followed by pectus carinatum, joint laxity, lordosis and DI. None of the patients had hearing loss. We emphasize that patients with DI were type I, and this form often shows dental changes. The prevalence in relation to the clinical characteristic of blue sclera was also observed in the study by BRIZOLA et al. (2017) at the Reference Centre for Osteogenesis Imperfecta in Porto Alegre, Brazil, with 71 (93.4%) patients presenting with this physical finding. In addition, in the same study, 21 (27.6%) patients had DI In the study by COSTA et al. (2020), most patients presented with blue sclera as a clinical characteristic, corresponding to 57.9% of the participants.

The classification currently used is the Silence with the addition of type V. Type I is the non-deforming type, with mild presentation and blue sclerae. Type II is the most severe form, in which perinatal lethality is almost a rule, with 90% of the babies dying by 4 weeks of age (SAM & DHARMALINGAM, 2017; PALOMO & VILAÇA & LAZARETTI-CASTRO, 2017; GONÇALVES & MEYER & SATO, 2017).

Type III is a severe form with progressive deformity. Type IV is a moderate form, with variable deformities. Finally, type V is characterized by progressive calcification of the interosseous membrane and hyperplastic callus (SAM & DHARMALINGAM, 2017; PALOMO & VILAÇA & LAZARETTI-CASTRO, 2017; GONÇALVES & MEYER & SATO, 2017).

In the literature, type I is the most common form of OI. The second most common form is contradictory, with some articles identifying type III and others identifying type IV (BRIZOLA *et al*., 2017; ESCOBAR *et al*., 2017; ZHANG *et al*. 2016; LÓPEZ&SANCHO& MARTÍNEZ-FERRER, 2020).

In our sample, half of the patients were classified as type I and the other half as type IV. In the study by BRIZOLA et al. (2017), 41 (51.3%) of the patients were classified as type I, while the second largest portion was classified as types IV and V (27/1). The same occurred in the study by COSTA et al. (2020), in which the most common form was also type I, with 57 (74%) patients, followed by type IV, with 13 (16.9%) patients.

There is no cure for OI. The main treatment goal is to reduce the incidence of fracture and its complications. Standard treatment is with bisphosphonates. They inhibit the bone resorptive activity of osteoclasts and induces their apoptosis; as a result, it preserves bone density. Other effects of bisphosphonates are reshaping of vertebra in vertebral compression fractures in children under development, and pain relief as a result of its anti-inflammatory properties (SAM & DHARMALINGAM, 2017; PALOMO & VILAÇA & LAZARETTI-CASTRO, 2017; MARGINEAN *et al, 2017;* ROUSSEAU&RETROUVEY, 2018; KREIKEMEIER, 2017).

In our study, all patients were treated with bisphosphates. Half were treated with alendronate and the other half with pamidronate. In a study carried out by VANZ et al. (2018), in two referral centres affiliated with universities for the treatment of OI in two southern Brazilian states: Hospital Clínico de Porto Alegre and Hospital Joana Gusmão in Florianópolis, it was found that 25 (48.1%) patients were using pamidronate and only 1 (1.9%) patient was using alendronate.

Even though there is currently no specific treatment to correct the basic defects of OI, patient survival has been increasing, with quality of life being improved by diagnosis and early treatment.

Conclusion

OI is a rare disease with a genetic cause. Blue sclera was the most common presentation, followed by pectus carinatum, joint laxity, lordosis and DI. Due to late diagnoses, a large number of fractures was observed in the sample studied.

Ethics approval and consent to participate

This research was approved by the Ethics Committee of Universidade Federal do Amazonas (CAAE 02533612.7.0000.5020), and the patients consent to participate of the study.

Consent for publication

All the patients consented to the publication of this article.

Divulgation

This article is unpolished. The authors and reviewers are not related to any conflict of interest during their evaluation. Therefore, the journal Scientia Amazonia holds the copyright reserved, has authorization and permission from authors for the dissemination of this article by electronic means.

Reference

BACON, Siobhan; CROWLEY, Rachel. Developments in rarebonediseasesand mineral disorders. **TherAdvChronicDis**, v. 9, n. 1, p. 51-60, nov./2017.

BRIZOLA, E. *et al*. Clinicalfeaturesandpatternoffracturesatthe time ofdiagnosisofosteogenesisimperfecta in children. **Rev Paul Pediatr**, v. 35, n. 2, p. 171-177, abr./2017.

ESCOBAR, C. *et al*. Osteogênese imperfeita – Experiência do serviço de ortopedia do hospital Dona Estefânia. **Acta MedPort**, v. 26, n. 11, p. 5-11, jan./2013.

FABRE, Larissa; BAGGENSTOSS, Rejane. Osteogênese imperfeita: relato de caso de uma família. **Arq Catarin Med**, v. 43, n. 3, p. 160-170, jun./2017.

GIMENO-MARTOS, S. *et al*. Epidemiología de La osteogénesis imperfecta: una enfermedad rara enlacomunitat valenciana. **RerEspSalud Pública**, v. 91, nov./2017.

GONÇALVES, Gilciane Ribeiro; MEYER, Luiz Ricardo; SATO, Mario Teruo. Osteogênese imperfeita: relato de caso. **RevMed UFPR**, v. 4, n. 2, p. 87-92, abr./2017.

KREIKEMEIER, S. W. R. Bisphosphonate therapy and osteogenesis imperfecta: The livedexperienceof children and their mothers. **J SpecPediatrNurs**, v. 22, n. 4, p. 1, set./2017.

LIN, H. *et al*. Genotypeandphenotypeanalysisof Taiwanesepatientswithosteogenesisimperfecta. **Orphanet J RareDis**, v. 10, p. 152, dez./2015.

LÓPEZ, María Díaz; SANCHO, J. J. A; MARTÍNEZ-FERRER, Àngels. Osteogénesisimperfecta: Descriptión de 15 casos. **ReumatolClin**, v. 15, n. 2, p. 165-168, mar./2020.

MARGINEAN, O. *et al*. Therapywithpamidronate in childrenwithosteogenesisimperfecta. **Drug Des DevelTher**, v. 11, n. p. 2507-2515, ago./2017.

MARINI, J. C. *et al*. Osteogenesisimperfecta. **Nat RevDisPrimers**, njn, v. 18, n. 3, p. 1-19, ago./2018.

MORELLO, Roy. OsteogenesisImperfectaandTherapeutics. **Matrix Biol**, v. 71, n. p. 294-312, mar./2018.

OTAVIO, A. C. D. C. *et al*. Osteogenesisimperfectaandhearingloss: ananalysisofpatientsattendedat a benchmark treatment center in southernBrazil. **EuropeanArchivesof Oto-Rhino-Laryngology volume**, v. 277, n. 4, p. 1005-1012, jan./2020.

PALOMO, Telma; VILAÇA, Tatiane; LAZARETTI-CASTRO, Marise. Osteogenesisimperfecta: diagnosisandtreatment. **CurrOpinEndocrinol Diabetes Obes**, v. 24, n. 6, p. 381-388, dez./2017.

ROUSSEAU, Maxime; RETROUVEY, Jeanmarc; CONSORTIUM, M. O. T. B. B. D. Osteogenesisimperfecta: potentialtherapeutic approaches. **PeerJ**, v. 6, ago./2018.

SAM, Justin Easow; DHARMALINGAM, Mala. OsteogenesisImperfecta. **Indian J EndocrinolMetab**, v. 21, n. 6, p. 803-809, nov./2017.

TOURNIS, Symeon; DEDE, AnastasiaD..Osteogenesisimperfecta – A clinicalupdate. **Metabolism**, v. 80, p. 27-37, mai./2017.

VANZ, A. P. *et al*. Osteogenesis imperfectaandhearingloss: ananalysisof patientsattendedat a benchmark treatment center in southernBrazil. **BMC Pediatrics**, v. 18, n. 1, p. 95, mar./2018.

ZHANG, H. *et al*. Clinicalcharacteristicsandidentificationof novel mutationsof COL1A1 and COL1A2 in 61 Chinesepatientswithosteogenesisimperfecta. **Mol Med Rep**, v. 15, n. 2, p. 1002, dez./2016.