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Temporal analysis of therapeutic approaches to osteogenesis imperfecta in the context of pediatric orthopedics - an update

Abstract

Osteogenesis Imperfecta (OI), popularly known as brittle bone disease, is characterized by bone fragility and deformities, as well as fractures caused by minor trauma. Prevention to reduce the number of fractures, treatment of fractures and surgical correction of deformities are a challenge for orthopaedic surgeons in their therapeutic management. The aim of this study is to analyze the therapeutic approaches to osteogenesis imperfecta in Brazil from 2013 to 2022. This is a retrospective qualitative and quantitative clinical investigation, in which the information was obtained from the Ministry of Health databases (TABNET), made available by the Department of Informatics of the Unified Health System (DATASUS), using the health science descriptors: "osteogenesis imperfecta", "pediatrics" and "bone fractures". It can be seen that between 2013 and 2022, 9,461 treatments for osteogenesis imperfecta were recorded in Brazil, so even though it is considered a rare pathology, it has a significant number of cases. Thus, the long-term aim of therapeutic interventions is for these children to live independently and develop the life skills that will enable them to coordinate their own care.

Keywords: osteogenesis imperfect, pediatrics, bone fractures

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Introduction

The conceptual change in osteogenesis imperfecta (OI) over the years has been scientifically translated into therapeutic possibilities. The theory of alterations in the genes that produce collagen, once not amenable to treatment, clinically classified into four types, is now understood as a set of genetic alterations, amenable to classification into at least eight different forms, and therapeutic prospects. It is worth highlighting the evolution of medical knowledge in recognizing that improving the quality of life of those with this disease is a treatment, given its limited prognosis.[1,2]

Mutations in the genes that produce collagen, located on chromosomes 7 and 17, are not mandatory for the diagnosis, since there are several patients clinically diagnosed as having OI who do not have mutations in the genes that code for collagen production, compatible with the classification in which there is hypertrophic growth and the presence of a pseudoglioma.[3–6] In the case of rhizomelic OI, there is a genetic alteration on the short arm of chromosome 3, where there are no genes coding for collagen production.[7,8] Statistically and with well-established case studies, there is recessive transmission in an indigenous tribe in Quebec, while the majority of OI cases are recent mutations and dominant transmission in an affected family.[8,9]

It follows the criteria of Sillence et al, from Australia, to classify OI into I to IV. Type I includes patients with slight forms, normal height, few fractures, no major deformation of the long bones or dentinogenesis imperfecta. Type II is the most severe and the vast majority of patients die in the perinatal period. Type III is the typical case that appears in books, with patients affected to a moderate to severe degree, triangular facies, short stature, deformity of the long bones and dentinogenesis imperfecta.[10,11] The remaining patients are classified as type IV. This last group is extremely heterogeneous, varying not only in severity but also in clinical characteristics and, consequently, systemic involvement.[12,13] The presence or absence of bluish sclerae has been proposed to differentiate type I from type IV, but this characteristic can be present in any type of OI and even in normal individuals, making its differentiation complex.[14]

Clinical and histomorphometric factors are evaluated to subclassify type IV into at least five other types. OI with hypertrophic callus and ossification of the interosseous membrane of the forearm, referred to as "type V" in the literature, consists of patients who develop huge repair calluses around fractures, with a differential diagnosis of neoplastic processes and there are occasions when they may even lead to limb amputation, due to the severity of the case and difficult handling.[15,16] It is also possible to see a limitation of movement, such as pronosupination, due to calcification of the interosseous membrane between the radius and ulna.

In the past, the treatment of OI was limited to conservative measures, with minimal physical activity and occasional surgical correction of deformities. Later, pharmacological treatment was tried with: vitamin C, vitamin D, fluoride, magnesium, anabolic steroids, calcitonin, growth hormone and bone marrow transplants.[16–18] None of these treatments have been shown to be useful or at least effective in OI.[18–,20] Requiring a change in the therapeutic approach, thanks to technological evolution, the currently prescribed use of bisphosphonates as a treatment for OI has changed the quality of life of patients with OI, and the possibilities of surgical treatment of deformities have been significantly extended, due to the pharmacokinetics of inhibition of bone resorption, even though the mechanism of action is not well explained in the literature, the stimulation of osteoclast apoptosis ends up delaying, consequently, the programmed cell death of osteoblasts. [21–23]

Prevention to reduce the number of fractures, treatment of fractures and surgical correction of deformities are a challenge for orthopedists in their therapeutic management. Scientifically, hydrotherapy has been used and seems to have significant value. On the other hand, the

use of casts or braces should be as brief as possible, since prolonged immobilization leads to greater bone weakening due to disuse, and is strategically the starting point for a series of consecutive and concurrent osteotomies (Sofield operation), enabling intramedullary splinting of the resulting correct bone axis.[24–26]

This clinically heterogeneous and rare genetic connective tissue disease is marked by low bone density and increased bone fragility, resulting in increased susceptibility to fractures, underestimated growth anomalies and deformities, with an incidence of 1 in every 10,000 to 20,000 births.[27–30] Since there is no genetic cure for OI, the management of the disease aims to reduce symptoms through a multidisciplinary approach consisting of orthopedic interventions, pharmacological agents, physiotherapy and rehabilitation.[31–33] The aim of this study is therefore to analyze the therapeutic approaches to osteogenesis imperfecta in Brazil over the period from 2013 to 2022.

Methodology

This study is a qualitative-quantitative, retrospective clinical investigation, studying therapeutic approaches to osteogenesis imperfecta in Brazil, in which the information was obtained from the Brazilian Ministry of Health's databases (TABNET), made available by the Department of Information Technology of the Unified Health System (DATASUS), available at http://www.data-sus.gov.br. As this is a public domain database, it was not necessary to submit the project to the Research Ethics Committee.[34]

The research presents health data and involves the category of treatment instituted in cases of osteogenesis imperfecta. The study sample consisted of patients diagnosed with osteogenesis imperfecta who underwent some type of treatment between 2013 and 2022 in Brazil. Microsoft Excel 2019 was used to analyze and create the data and graphs.

Inclusion criteria

The criteria for including the articles were: studies that include the treatment and prognosis of patients diagnosed with osteogenesis imperfecta; studies that are more than 10 years old; articles whose titles and abstracts are related to the theme proposed by the study; articles in Portuguese, English and Spanish.

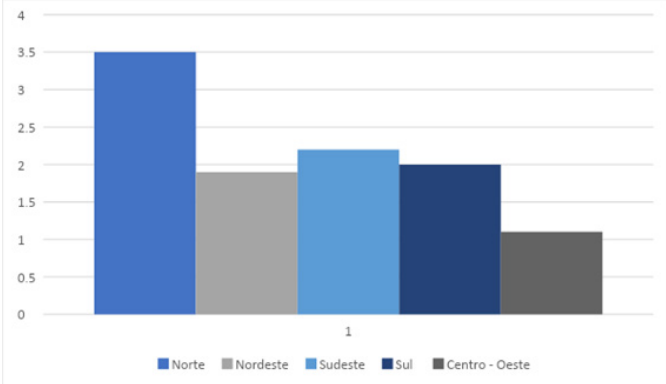
The exclusion criteria were articles unrelated to the research topic; studies analyzing osteosarcoma in the adult population; articles whose language differed from those mentioned above.

The articles used were selected from the SciELO, PubMed and LILACS databases. The terms "osteogenesis imperfecta, "osteogenesis" and "pediatrics" were chosen from the Health Sciences Descriptors platform at <https://decs.bvsalud.org/>.

Results

Between 2013 and 2022, 9,461 treatments for osteogenesis imperfecta were recorded in Brazil, with the highest incidence in 2019 (1,204 cases) and the lowest in 2020 (692 cases). The Northeast had the highest number of notifications (35.1%), followed by the South (26.1%) (Table 1). The Federal District was the federal unit responsible for 1,317 procedures carried out in the period, Bahia came second with 1,270. The average number of days spent in hospital was 1.9, totaling 18,110 days. The North region recorded a considerably higher number than the average, 3.5 days (Graph 1).[35]

Most of the care was provided by the public health network (86.5%), representing a total expenditure of approximately R$5,700,000.00. The Northeast of Brazil recorded the highest investments, approximately R$ 2,000,000.00. With regard to the number of deaths resulting from osteogenesis imperfecta, there were 11 deaths during the entire period.[35]



Graph 1 Mean length of hospital stay due to osteogenesis imperfecta in Brazil.

Table 1 Treatments for osteogenesis imperfecta performed in Brazil during the years 2013 – 2022

Region	Treatments
Northeast	3.327
South	2.478
Southeast	2.224
Midwest	1.371
North	61

Discussion

Even though osteogenesis imperfecta is a genetic disease considered rare, a considerable number of incidences were recorded during the study period. A total of 9,461 cases of treatment for the condition were reported, of which the highest rate was in the Northeast, followed by the South, with the highest percentage of treatments being carried out in the public health system. The Northern region had the lowest records, but the length of hospital stay per patient treated was significantly higher than the other regions, at 3.5 days compared to the average of 1.9 days. It is therefore clear that greater local financial investment is needed in order to improve therapeutic quality and consequently reduce hospital stays.[35]

It is called brittle bone disease, a rare bone pathology characterized by bone vulnerability, fractures with no or little trauma, short stature, bone pain, deformities of the long bones, low muscle mass, hypermobility and, in some individuals, bluish sclera.[36,37] It is a pathology with variable clinical manifestations and is classified into four types based on the severity of symptoms and signs, according to the Sillence classification: types I and IV are mild and moderate, type II lethal and type III progressively deforming and severe.[38,39]

The biomechanical properties of bones in individuals with OI are different from those of healthy individuals; the bones are denser, more fragile and have low resistance to torsional forces, even against slight repetitive stress.[40] The incidence of fractures remains high during the pre-school and school years, but after adolescence they become rarer.[41] Susceptibility decreases with puberty, but in female patients the risk increases again after the menopause.[42]

The therapeutic goal in OI varies according to phenotype and mobility status. Children with uncomplicated type I OI can have physical activity levels similar to healthy individuals.[43] For this reason,

orthopedic and rehabilitation treatments for mild OI consist of treating fractures. In this circumstance, medical follow-up serves mainly to detect complications, such as vertebral compression fractures.[44–46] In contrast, moderate to severe OI is often associated with deformities of the long bones, reduced mobility and scoliosis, requiring orthopedic and rehabilitation interventions, which are essential for the correct treatment of these patients.[47]

The bisphosphonate therapy option has been administered to children with OI for three decades and is by far the most widely used medical treatment modality.[48] Several studies have reported that the therapy leads to an increase in bone mineral density (BMD) in the spine and at various other sites in the skeleton.[49–51] It is not surprising, since bone formation activity is very high during growth, and even more so in severe OI, and has no relation to bone resorption in skeletal sites subject to bone modeling.[52] Anti-osteoclast treatment reliably increases bone mass while skeletal growth continues.[53]

As a result, both oral and intravenous bisphosphonates appear to be related to a lower rate of long-bone fractures in children with OI.[45,53,54] The reported reductions in the fracture rate are in the order of 30% to 60%, indicating some therapeutic efficacy, although a large number of long bone fractures still occur. A recent study followed a group of 37 children with moderate to severe OI for fifteen years after starting treatment with intravenous bisphosphonates and showed a median of 5 tibial and 6 femoral fractures per patient.[53] So, long-bone fractures remain a major problem, even with bisphosphonates.[54]

However, several factors contribute to the persistence of high rates of long bone fractures during treatment. Children with OI have a small bone cross-section in the diaphysis of their long bones, indicating a decrease in periosteal bone growth.[55] The total volumetric BMD of the diaphysis of long bones is abnormally high, in contrast to the low BMD at the metaphyseal sites.[56] Another reason that contributes to these fractures is bone deformities, which do not respond to any known therapeutic alternative and are corrected by surgery.[57] Regardless of the continued occurrence of these fractures, treatment with intravenous bisphosphonates is known to improve mobility, especially when started in the first few years of life. Long-term follow-up suggests that most children with type IV OI are able to walk independently, while those with type III OI are able to live independently even with restricted mobility.[57]

Surgical treatment is often necessary to treat bone fractures, correct remaining deformities from previous fractures and prevent new fractures. Individuals are fragile, making it a delicate but essential treatment for neonates and pre-school children with OI. Its purpose is to reduce the period of immobilization in all surgical treatments, avoiding iatrogenic reduction in bone mass and new fractures. Efforts are made to correct misalignments, especially in the legs of ambulatory children, because of the risk of fractures in the child's development. The conventional procedure includes multiple osteotomies of the curved bone and intramedullary fixation with Kirschner wires (K-wires) or Kuntscher or Rush screws. Protective braces or orthoses are fitted to the lower extremities to prevent stress fractures in the event of misalignment. It helps them to achieve a standing posture and learn to walk. Physiotherapy is considered important, with newborns the focus is on developing their sense of self and mobility. In pre-school children with a severe type of OI, the aim is the child's independence and ability to solve everyday tasks. The long-term aim of therapeutic interventions is for children to live independently and develop the life skills that will enable them to coordinate their own care.

Conclusion

OI is a skeletal dysplasia caused by mutations in the genes encoding type I collagen (COL1A1 and COL1A2), with variable manifestations including low bone mineral density (BMD), recurrent bone fractures, bone deformities, chronic pain and scoliosis. The typical clinical description includes blue discoloration of the sclera and dental anomalies called dentinogenesis imperfecta, being extra-skeletal features. So far, there is no cure for OI. However, its symptoms can be controlled through the administration of bisphosphonates, physiotherapy and surgery. Pharmacological therapy decreases bone turnover, reduces fracture rates and improves bone mineral density. In this way, children become able to coordinate their activities and their own care.

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None.

Conflict of interest

The authors declared no conflict of interest.

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