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Assessment of the health status and pharmacological treatment of neonates with osteogenesis imperfecta – 20-year single-centre observations

Ocena stanu zdrowia i leczenia farmakologicznego dzieci z wrodzoną łamliwością kości w okresie noworodkowym – 20-letnie obserwacje jednego ośrodka

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Abstract

Introduction and objective: Osteogenesis imperfecta is a heritable bone dysplasia resulting in reduced bone mineral density. Fractures of long bones, which are the dominant symptom of osteogenesis imperfecta, can be diagnosed already in foetal life. Multiple fractures are associated with severe pain, which may cause deterioration of the newborn's general condition, respiratory and circulatory disorders, and reduced general motor activity. The aim of the study was to summarise the experience resulting from many years of care and treatment of neonates with osteogenesis imperfecta types II and III. **Materials and methods:** The study included 53 newborns with osteogenesis imperfecta hospitalised at the Department of Paediatrics, Newborn Pathology and Bone Metabolic Diseases in the years 2001–2021. All children underwent a babygram and an assessment of their health status, including calcium and phosphorus metabolism parameters. **Results:** In 67.3% of cases, the mother was informed before delivery that she would give birth to a sick child. The general condition of the newborns was moderately severe to severe in 43.4%. Physical examination revealed abnormal body proportions related to previous fractures in 98.1% of patients, including long bones of limbs. More than 10 fresh bone fractures were diagnosed in 34% of children. **Conclusions:** Prenatal diagnosis of osteogenesis imperfecta indicates its severe course (multiple fractures) in the neonatal period. Therefore, it requires care in a specialised centre that will provide safe, symptomatic pharmacological treatment (bisphosphonates) to reduce both pain and the risk of further bone fractures.

Keywords: newborns, osteogenesis imperfecta, fractures bone

Streszczenie

Wprowadzenie i cel: Wrodzona łamliwość kości jest uwarunkowaną genetycznie dysplazją kostną przebiegającą ze zmniejszoną gęstością mineralną kości. Złamania kości długich jako dominujący objaw wrodzonej łamliwości kości mogą być rozpoznawane już w okresie życia płodowego. Konsekwencją licznych złamań są silne dolegliwości bólowe, które mogą stanowić przyczynę pogorszenia stanu ogólnego noworodka, zaburzeń oddychania i krążenia, obniżenia ogólnej aktywności ruchowej. Celem pracy jest podsumowanie doświadczeń wynikających z wieloletniej opieki nad dziećmi z ciężką (typ III) i skrajnie ciężką (typ II) postacią wrodzonej łamliwości kości w okresie noworodkowym i ich leczenia w ciągu 20 lat. **Materiał i metody:** Badaniem objęto 53 noworodki z wrodzoną łamliwością kości hospitalizowane w Klinice Pediatrii, Patologii Noworodka i Chorób Metabolicznych Kości w latach 2001–2021. U wszystkich dzieci wykonano babygram oraz przeprowadzono ocenę stanu zdrowia, w tym parametrów gospodarki wapniowo-fosforowej. **Wyniki:** W przypadku 67,3% noworodków matka została poinformowana przed porodem, że urodzi chore dziecko. Po porodzie stan ogólny u 43,4% dzieci był średnio ciężki oraz ciężki. W badaniu przedmiotowym u 98,1% stwierdzono zaburzenia proporcji ciała związane z podstawową jednostką chorobową oraz z przebytymi złamaniami kości w okresie płodowym. U 34% rozpoznano ponad 10 świeżych złamań kości do momentu

zakończenia hospitalizacji. **Wnioski:** Prenatalne rozpoznanie wrodzonej łamliwości kości wskazuje na jej ciężki przebieg (liczne złamania) w okresie noworodkowym. Chore dziecko wymaga zatem opieki w specjalistycznym ośrodku, w którym zostanie włączone bezpieczne, objawowe leczenie farmakologiczne (bisfosfonianami) zmniejszające dolegliwości bólowe i ryzyko liczniejszych złamań kości.

Słowa kluczowe: noworodki, wrodzona łamliwość kości, złamania kości

INTRODUCTION

Congenital bone fragility or osteogenesis imperfecta (OI) is a bone dysplasia associated with reduced bone mineral density (BMD). It is a rare hereditary connective tissue disorder[1,2], characterised primarily by an increased number of bone fractures and deformities involving the limbs, chest and skull. It is most often caused by mutations in the type I collagen gene encoding α1 and α2 chains: *COL1A1*, less often *COL1A2*, which account for 85–90% of cases[2,3]. The remaining 10% are non-collagen mutations in genes encoding proteins involved in collagen biosynthesis, including: *CRTAP*, *LEPRE1*, *PPIB*, *SERPINH1*, *FKPB10*, *PLOD2*, *SERPINF1*, *WNT1*, *BMP1*, *SP7*[4,5]. The incidence of this rare disorder is estimated at 6–7/100,000 births[6].

Two of the four classic OI types (I–IV) described by Sillence are most often diagnosed in the neonatal period: lethal perinatal type II and progressive-deforming type III[5]. Both these forms share some common features such as the fact that they can be diagnosed already at the age of 18–20 weeks gestation and a very early onset of fractures, which lead to shortening of limbs and skeletal deformities[5].

Fractures may occur during intrauterine life or at various times after birth; they can affect all bones, but most often involve the long bones and ribs[7,8]. These are spontaneous, low-energy fractures that may be caused by even a minor trauma. Multiple fractures cause very severe pain, which may lead to deterioration of the newborn's general condition, respiratory and circulatory disorders, and reduced general motor activity, which may lead to concomitant infections and the need for intensive care[5,9–11].

The aim of the study was to summarise the experience acquired during many years of care for neonates with severe (type III) and extremely severe (type II) forms of osteogenesis imperfecta and their treatment over 20 years.

MATERIALS AND METHODS

We analysed the records of patients with OI diagnosed in the neonatal period who were admitted to the Department of Paediatrics, Newborn Pathology and Bone Metabolic Diseases of the Medical University of Lodz for diagnosis and treatment over a 20-year period. The following data were assessed: perinatal history, gender, number of postpartum fractures on babygram, feeding method, as well as the length of hospital stay, complications arising during hospitalisation and the need for intensive care unit (ICU) treatment.

The analysis included 53 patients diagnosed with OI in the neonatal period. Children were classified into groups based the number of fractures on postnatal babygram, as well as the need for ICU admission. We verified whether the subgroups differed in perinatal history, length of hospital stay, feeding method, and the occurrence of anaemia and pneumonia during hospital stay. A series of univariate and one multivariate logistic regression models were built to determine the risk factors for ICU admission.

A group of 42 newborns who received pamidronate were assessed separately. The drug was administered under control of calcium and phosphate metabolism, which was assessed in accordance with generally accepted standards. Changes in biochemical calcium and phosphate metabolism parameters were assessed before and after the first bisphosphonate cycle. Blood levels of ionised calcium were measured after each dose of the drug.

Statistical analysis

The distribution of variables was analysed by assessing histograms and interpreting the Shapiro–Wilk test. Qualitative variables were described using frequencies and percentages of occurrence. Differences between variables were tested using the following tests: Chi^2, Fisher and Fisher–Freeman–Halton tests. Continuous variables were described using the median and the first and third quartiles. The Mann–Whitney *U* test was used for differences between independent variables, and the Wilcoxon test was utilised for dependent variables. Analysis of variance was performed using the Friedman test. Variables showing a statistically significant impact on the risk of ICU admission in univariate models were included in the multivariate logistic regression model. The variable "week of gestation" was excluded due to its collinear relationship with the Apgar score, and the variable "birth weight" was excluded due to its negligible impact. The analyses were performed using IBM SPSS Statistics version 28.0 (IBM Co., Armonk, NY, USA). A $p < 0.05$ was considered statistically significant.

RESULTS

Detailed characteristics of patients are presented in Tab. 1. Based on the interview with the parents, it was noted that in 33/49 cases (67.3%; 4 – missing data), the mother was informed that she would give birth to a sick child before delivery (based on foetal ultrasound – US). Prenatal US most often described shortened, deformed limbs and ribs, and intrauterine

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fractures – bone dysplasia and achondroplasia were suspected. In 50/53 (94.3%) patients, no OI was diagnosed in the immediate family. Positive family history was found in 3/53 (5.7%) patients, i.e. the mother of 1 newborn was diagnosed with OI; in another case, the mother's previous pregnancy ended in the child's death due to OI (type II); and the father of 1 child experienced frequent bone fractures in childhood.

The general condition of the newborns on admission was moderately severe to severe in 23/53 (43.4%) cases, requiring intensive medical care due to breathing difficulties and severe general condition; moderate clinical condition was observed in 17/44 (32.1%) children, with limited spontaneous motor activity, tearfulness and severe pain. Relatively good and good general condition was observed in 13/53 (24.5%) patients.

On physical examination, 52/53 (98.1%) newborns had abnormal body proportions related to past fractures, including long bones of the limbs. Skeletal symptoms included shortening of the lower and upper limbs, saber-shaped thighs and lower legs, soft skull bones, large anterior and posterior fontanel, narrow chest, wide cranial sutures and blue discoloration of the sclera. Most children required treatment for perinatal fractures (fractures during transport, daily activity, care procedures, spontaneous fractures). Fresh bone fractures manifested with limited mobility, oedema of the limbs, pain, deterioration of the child's general condition and required the use of analgesics and immobilisation.

Throughout the hospital stay, ≥10 and <10 fresh bone fractures were diagnosed in 18/53 (34%) and 35/53 (66%) newborns, respectively. Fresh fractures mainly occurred in the humerus, femur and forearm. All patients suffered multiple prenatal bone fractures, as confirmed by radiological imaging.

More than half of the newborns, i.e. 32/53 (60.4%), were fed with a bottle or maternal milk. Eleven (20.7%) patients periodically required mixed feeding (nasogastric

Category	Number of patients $n = 53$	Postnatal fractures			ICU admission		
		<10 $n = 18$	≥10 $n = 35$	*p*	Yes $n = 23$	No $n = 30$	*p*
Gender: • female • male	 24 (45.3%) 29 (54.7%)	 10 (55.6%) 8 (44.4%)	 14 (40.0%) 21 (60.0%)	>0.05^{Chi2}	 8 (34.8%) 15 (65.2%)	 16 (53.5%) 14 (46.7%)	>0.05^{Chi2}
Pregnancy: • 1 • 2 • >2	 22 (41.5%) 18 (34%) 13 (24.5%)	 9 (50.0%) 5 (27.8%) 4 (22.2%)	 13 (37.1%) 13 (37.1%) 9 (25.8%)	>0.05^{FFH}	 13 (56.6%) 5 (21.7%) 5 (21.7%)	 9 (30.0%) 13 (43.3%) 8 (26.7%)	>0.05^{Chi2}
Childbirth: • 1 • 2 • >2	 25 (47.2%) 19 (35.8%) 9 (17.0%)	 9 (50.0%) 5 (27.8%) 4 (22.2%)	 16 (45.7%) 14 (40.0%) 5 (14.3%)	>0.05^{FFH}	 13 (56.5%) 6 (26.1%) 4 (17.4%)	 12 (40.0%) 13 (43.3%) 5 (16.7%)	>0.05^{FFH}
Delivery mode: • vaginal • C-section *Missing data*	 7 (13.2%) 41 (77.4%) 5 (9.4%)	 4 (22.2%) 12 (66.7%) 2 (11.1%)	 3 (8.57%) 29 (82.86%) 3 (8.57%)	>0.05^{F}	 1 (4.3%) 20 (87.0) 2 (8.7%)	 6 (20.0%) 21 (70.0%) 3 (10%)	>0.05^{F}
Week of gestation	38 (37–39)	38 (37–39)	38 (36–39)	>0.05^{UMW}	38 (36–38)	38 (37.75–39)	**<0.05^{UMW}**
Birth weight [g] *Missing data*	2,805 (2,362–3,120) 1	2,822 (2,402–3,327)	2,800 (2,347–3,066) 1	>0.05^{UMW}	2,592 (2,245–3,020) 1	2,847 (2,465–3,252)	>0.05^{UMW}
Apgar score	8 (7–9)	9 (9–10)	8 (7–8)	**<0.001^{UMW}**	7 (6–8)	9 (8–10)	**<0.001^{UMW}**
Prenatal screening: • normal • abnormal *Missing data*	 15 (28.3%) 33 (62.3%) 5 (9.4%)	 10 (55.5%) 7 (39.0%) 1 (5.5%)	 5 (14.3%) 26 (74.3%) 4 (11.4%)	**<0.01^{Chi2}**	 5 (21.7%) 15 (65.2%) 3 (13.1%)	 10 (33.3%) 18 (60.0%) 2 (6.7%)	>0,05^{Chi2}
Length of postnatal hospital stay [days]	12 (9–22)	11 (9–19)	15 (9–36)	>0.05^{UMW}	22 (10–60)	11 (9–17,5)	**<0.01^{UMW}**
Number of postnatal fractures: • <10 • ≥10	 18 (34.0%) 35 (66.0%)	 –	 –	 –	 5 (21.7) 18 (78.3)	 13 (43.3) 17 (56.7)	>0.05^{Chi2}
Feeding method: • breastfeeding or bottle • nasopharyngeal tube	 39 (73.6%) 14 (26.4%)	 17 (94.4%) 1 (5.6%)	 22 (62.9%) 13 (37.1%)	**<0.05^{F}**	 10 (43.5%) 13 (56.5%)	 29 (96.7%) 1 (3.3%)	**<0.001^{F}**
Anaemia: • yes • no	 27 (50.9%) 26 (49.1%)	 13 (72.2) 5 (27.8)	 14 (40.0) 21 (60.0)	**<0.05^{Chi2}**	 8 (34.8) 15 (65.2)	 19 (63.3) 11 (36.7)	>0.05^{Chi2}
Pneumonia: • yes • no	 31 (58.5%) 22 (41.5%)	 16 (88.9%) 2 (11.1%)	 15 (42.9%) 20 (57.1%)	**<0.01^{Chi2}**	 7 (30.4%) 16 (69.6%)	 24 (80.0%) 6 (20.0%)	**<0.001^{Chi2}**

Data are presented in percentages (%), medians and quartiles (Q1–Q3).
Chi2 – Chi^2 test; **MNU** – Mann–Whitney *U* test; **F** – Fisher's *F* test; **FFH** –Fisher–Freeman–Halton test.

Tab. 1. General characteristics of the study group

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Category	Unadjusted OR	95% CI	*p*	Adjusted OR	95% CI	*p*
Gender: • female • male	 ref. 2.143	 0.700–6.557	 >0.05	–	–	–
Pregnancy: • 1 • 2 • >2	 ref. 0.266 0.433	 0.070–1.013 0.106–1.761	 >0.05 >0.05	–	–	–
Childbirth: • 1 • 2 • >2	 ref. 0.426 0.738	 0.123–1.480 0.160–3.414	 >0.05 >0.05	–	–	–
Delivery mode: • vaginal • C-section	 ref. 5.714	 0.631–51.767	 >0.05	–	–	–
Week of gestation	0.668	0.478–0.934	**<0.05**	–	–	–
Birth weight [g]	0.999	0.998–1.000	**<0.05**	–	–	–
Apgar score	0.552	0.366–0.833	**<0.01**	0.629	0.425–0.932	**<0.05**
Prenatal screening: • normal • abnormal	 ref. 1.667	 0.466–5.956	 >0.05	–	–	–
Number of postnatal fractures: • <10 • ≥10	 ref. 2.753	 0.808–9.381	 >0.05	–	–	–
Anaemia: • yes • no	 ref. 3.239	 1.041–10.074	 **<0.05**	 ref. 2.223	 0.532–9.292	 >0.05
Pneumonia: • yes • no	 ref. 9.143	 2.592–32.253	 **<0.001**	 ref. 5.147	 1.255–21.117	 **<0.05**

OR – odds ratio; **95% CI** – 95% confidence interval; **ref.** – reference.

Tab. 2. Univariate and multivariate logistic regression models of the explanatory variable – hospitalisation in the intensive care unit

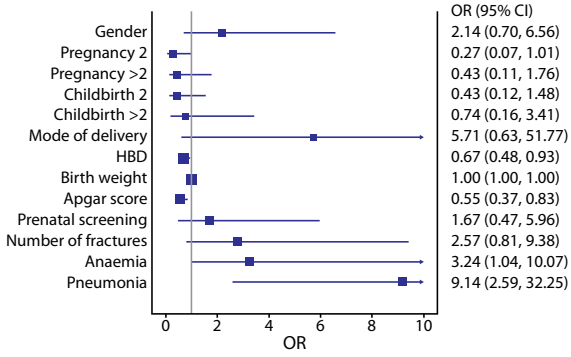

Fig. 1. Univariate binary logistic regression model of the explanatory variable. Hospitalisation in an intensive care unit

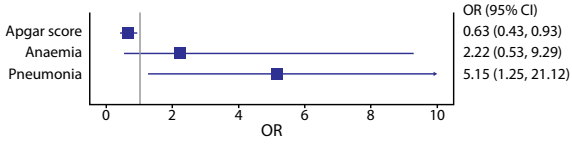

Fig. 2. Multivariate binary logistic regression model of the explanatory variable. Hospitalisation in an intensive care unit

tube and a bottle) due to temporary breathing problems. However, a permanent gastric tube was the only method of feeding in 10 (18.9%) patients who were in the most severe general condition (depending on the accompanying infections).

Pneumonia was diagnosed in 22/53 (41.5%) patients and was treated with intravenous antibiotics. These patients periodically required oxygen therapy due to respiratory effort and saturation drops below 95%.

Anaemia was diagnosed in 26/53 (49.1%) newborns, of which 14/26 (53.8%) required transfusion of irradiated leukocyte-poor packed red blood cells; the other patients received hematopoietic preparations.

Agenesis of the corpus callosum, hydrocephalus, multiple organ defects, atrial septal defect, and liver failure (cholestasis) were additionally detected in 6 patients.

Vitamin D deficiency was found in 24/44 (54.5%) newborns (missing data in 9 children). Osteocalcin was measured in 35/53 patients, with values falling within the normal range in all patients. Parathyroid hormone was decreased in 3/39 (7.7%) and increased in 7/39 (17.9%) children; the data was missing in the medical history of 14 newborns. Calcium

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Category	*n* = 42		Δ	$p_{Wilcoxon}$
	Before first bisphosphonate cycle	After first bisphosphonate cycle		
Parathyroid hormone [pmol/L] *Missing data*	35.30 (23.27–59.41) 11	107.95 (68.45–126.40) 30	70.40 (32.00–83.90) 31	**<0,01**
Alkaline phosphatase [U/L] *Missing data*	230.0 (149.7–347.2) 6	251.0 (177.0–317.0) 23	−9.00 (−59.00 to 49.00) 23	>0.05
Calcium [mg/dL] *Missing data*	10.20 (9.81–10.69) 2	9.00 (7.90–9.60) 11	−1.25 (−2.40 to −0.28) 12	**<0.001**
Phosphorus [mg/dL] *Missing data*	6.03 (5.57–6.41) 4	4.21 (3.62–4.90) 14	−1.55 (−2.36 to −0.58) 16	**<0.001**
Magnesium [mg/dL] *Missing data*	2.02 (1.85–2.17) 4	2.01 (1.80–2.12) 16	0.08 (−0.16 to 0.21) 17	>0.05
Urinary calcium/creatinine ratio [mg/dL] *Missing data*	0.29 (0.15–0.46) 11	0.09 (0.03–0.16) 19	−0.21 (−0.44 to −0.03) 22	**<0.001**
Urinary phosphorus/creatinine ratio [mg/dL] *Missing data*	1.37 (0.57–1.80) 12	0.92 (0.44–1. 85) 20	0.00 (−0.84 to 0.74) 21	>0.05
Urinary magnesium/creatinine ratio [mg/dL] *Missing data*	0.18 (0.08–0.26) 20	0.18 (0.10–0.28) 25	−0.03 (−0.12 to 0.08) 27	>0.05
Pyrilinks-D (urinary deoxypyridinoline (DPD) [nmol]/creatinine [mmol] ratio) *Missing data*	47.34 (33.28–48.11) 27	49.6 (40.09–72.94) 27	−0.03 (−8.25 to 27.50) 31	>0.05
Osteocalcin [ng/mL] *Missing data*	21.22 (13.77–39.90) 18	26.19 (14.86–36.19) 25	0.45 (−9.43 to 4.46) 29	>0.05
Data are presented as medians and quartiles (Q1–Q3). **Δ** – difference before and after the administration of bisphosphonates; $p_{Wilcoxon}$ – *p*-value for Wilcoxon.				

Tab. 3. Biochemical parameters of calcium and phosphate metabolism before and after the administration of the first pamidronate cycle

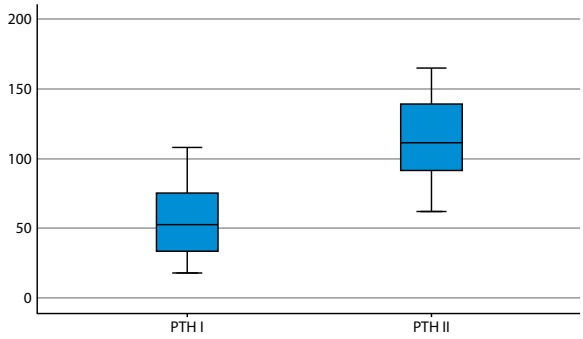

Fig. 3. Parathormone concentration [pmol/L] before and after administration of the 1st cycle of sodium pamidronate at 1 month of age

deficiency was diagnosed before treatment in 4/50 (8.0%) (missing data in 3 patients).

Whole-body infant densitometry using dual X-ray absorptiometry (DXA) was performed in 30/53 (56.6%) newborns, with results ranging between 0.109 and 0.361 g/cm^2.

Based on our experience in treating OI patients, the newborns were classified into two groups: <10 bone fractures and ≥10 bone fractures. It was observed that more than 10 fractures of long bones and/or ribs significantly worsen the patient's general condition. Differences were found between patients with <10 fractures on the babygram and those with more fractures. Children with a higher number of fractures presented with abnormalities in somatic development already in foetal life (83.8% vs. 41.2%, $p < 0.01$) and received a lower Apgar score (8 vs. 9, $p < 0.001$). These patients were more likely to require gastric tube feeding (37% vs. 6%, $p < 0.05$) and to develop anaemia (60% vs. 28%, $p < 0.05$) and pneumonia (57.1% vs. 11.1%, $p < 0.01$). There was no statistically significant relationship between the number of fractures and the type of delivery, birth weight, or length of postnatal hospital stay.

We also analysed differences between patients who required ICU admission and those who did not (Tab. 2). Patients requiring intensive care had lower postnatal Apgar scores (7 vs. 9, $p < 0.001$), and a twofold longer postnatal hospital stay (22 vs. 11 days, $p < 0.01$). They were more likely to be fed using an intragastric tube (56.5% vs. 3.3%, $p < 0.001$) and to develop pneumonia (70% vs. 20%, $p < 0.001$). Neither the type of delivery nor the number of fractures detected after delivery had a statistically significant impact on the need for ICU admission.

The analysis of univariate logistic regression models revealed several factors that influenced the need for ICU admission, which were then included in the multivariate model (Figs. 1, 2). The multivariate model showed a statistically significant impact for the assessment of the newborn's general condition after delivery and pneumonia.

Each Apgar score reduced the risk of ICU admission by 37% [odds ratio, OR: 0.629, 95% confidence interval (95% CI): 0.425–0.932]. However, pneumonia increased this risk more than 5 times (OR: 5.147, 95% CI: 1.255–21.117). Anaemia had no significant impact on the risk of ICU admission (OR: 2.223, 95% CI: 0.532–9.292).

Analysis of medical records showed that all children received analgesics: tramadol hydrochloride, paracetamol,

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$n = 42$	Day 1	Day 2	Day 3	Δ	$p_{Friedman} < 0.001$
Ionised calcium [mmol/L] *Missing data*	1.20 (1.13–1.26) 5	1.18 (1.09–1.22) 2	1.07 (0.98–1.20) 2	1 vs. 2 – 0.02 (–0.14 to 0.10) 1 vs. 3 – 0.11 (–0.21 to –0.01) 2 vs. 3 – 0.09 (–0.16 to 0.00)	1 vs. 2 – $p > 0.05$ 1 vs. 3 – $\mathbf{p < 0.001}$ 2 vs. 3 – $\mathbf{p < 0.01}$
Data are presented as medians and quartiles (Q1–Q3). **Δ** – difference between treatment days; $p_{Friedman}$ – *p*-value for Friedman.					

Tab. 4. Ionised calcium levels 4 hours after pamidronate administration

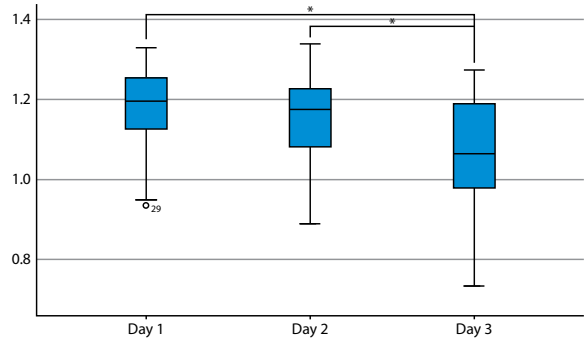

Fig. 4. Blood concentration of ionised calcium [mmol/L] 4 hours after administration of pamidronate sodium dose

and ibuprofen. Patients in the most severe general condition were put on morphine. The vast majority of newborns required treatment with at least two analgesics.

Therapy with antiresorptive agents from the group of bisphosphonates (pamidronate disodium) was initiated in 42/53 hospitalised neonates, and was used for 3 consecutive days, as in accordance with literature data[7]. The first dose of the drug was 0.125–0.250 mg/kg body weight. A lower dose (0.125 mg/kg body weight) was used in patients with chest deformities resulting from rib fractures and increased respiratory effort. A dose of 0.250 mg/kg body weight was used in children with extrathoracic fractures and bone deformations, who were respiratory and circulatory efficient. On cycle days 2 and 3, the dose was increased to 0.250–0.500 mg/kg body weight, respectively[12–15]. Pamidronate was administered intravenously as a 4-hour physiological saline infusion, followed by ionised blood calcium measurement 4 hours after the end of the infusion[16–20].

An analysis of biochemical calcium and phosphate metabolism parameters in newborns revealed significant changes after the first pamidronate cycle (Tab. 3). After bisphosphonate administration, parathyroid hormone increased by an average of 70 pmol/L ($p < 0.01$), total calcium dropped by 1.25 mg/dL ($p < 0.001$), and phosphorus dropped by 1.55 mg/dL ($p < 0.001$) (Fig. 3). The calcium/creatinine ratio dropped by 0.21 after treatment ($p < 0.001$). The change in the calcium/creatinine ratio and osteocalcin levels was not statistically significant.

Comparing the measurements of ionised blood calcium 4 hours after the end of each dose of pamidronate, it was observed that the lowest levels were achieved after the third dose and were lower by an average of 0.11 mmol/L vs. treatment day 1 ($p < 0.001$) and by 0.09 mmol/L vs. treatment day 2 ($p < 0.01$) (Tab. 4, Fig. 4).

After administering the drug, most patients (67.4%) developed transient hypocalcaemia. Six newborns developed increased body temperature on days 1–3, and required symptomatic treatment (calcium preparations, antipyretics) until normal serum calcium levels were achieved and the child's clinical condition improved. Patients' vital signs (heart rate, saturation, respiratory rate) were monitored throughout the treatment cycle and no reduction in respiratory rate below 30/min or bradycardia were observed. One newborn developed oedema of the lower limbs and lower abdomen, as well as a decrease in serum protein after the administration of pamidronate, which was managed with albumin transfusion. Another newborn experienced short-term whole-body convulsions due to hypocalcaemia; in this case, intravenous calcium supplementation was initiated, which resulted in resolution of symptoms and normalisation of calcium levels.

Pamidronate treatment was not initiated in the first month of life in 11 patients due to severe general condition (intensive care), airway infection, low number of fractures, and lack of parental informed consent to non-standard treatment.

OI was confirmed by genetic testing later in life in 25/53 (47.2%) children, with *COL1A1* mutation in 19 and *COL1A2* mutation in 7 patients (1 patient had both mutations). Genetic tests have not been performed or are underway in the remaining respondents (22/44).

Complications due to bone fractures occurred in 9/53 newborns. These were brachial plexus paralysis, radial nerve damage, upper limb paresis, and subperiosteal haematoma of the parietal area. Muscle and ligament laxity led to inguinal, umbilical or scrotal hernia in 4/53 patients.

DISCUSSION

The paper summarised 20 years of experience of one clinical centre specialising in the treatment of metabolic bone diseases in children. We presented patients with OI types II and III. The diagnosis was confirmed by radiological imaging, with all babygrams showing both fresh and past bone fractures at various stages of healing[21,22]. According to the literature, an X-ray may be sufficient to confirm the clinical diagnosis[8,21,23,24].

OI types II and III can be diagnosed based on a prenatal US. Shikhrakar et al. pointed out that, unlike OI type II, which can be detected as early as 24 weeks gestation, type III is usually detected after 18 weeks of pregnancy, manifesting with significant shortening of long bones, underdeveloped

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thorax, and marked femoral deformation or fracture, or altered femur length/abdominal circumference ratio (less than 0.16). However, the assessment of the skeletal system may be omitted during prenatal US[23].

If bone fractures are detected on ultrasound, the method of delivery remains controversial. Caesarean section is recommended in most cases[14], and was used in more than half of the described patients. On the other hand, Burnei et al. pointed out that caesarean section is not associated with a reduced incidence of fractures in OI newborns[8]. It has been suggested that surgical pregnancy termination should be performed only for other maternal or foetal indications rather than solely for the purpose of preventing fractures in patients[25,26]. Cases of vaginal delivery of a child with OI type III were described by, among others, Shikhrakar et al.[23].

Prenatal diagnosis and genetic counselling should be improved especially in less developed countries since caring for children with OI in low-income countries poses particular challenge[27]. With the development of molecular genetics, the authors have started to emphasize the need to investigate entire families for inheritance and phenotypic variability of OI[4]. Increased awareness of intrauterine fractures allows for appropriate postnatal management and better further development of the child[25]. Screening for gene mutations in the second trimester of pregnancy confirms the diagnosis[28]. Although family history strongly supports the diagnosis of OI, the types of OI may vary between siblings. Between 85 and 90% of cases are inherited in an autosomal dominant manner and are caused by *COL1A1* and *COL1A2* mutations, leading to quantitative or qualitative defects in type 1 collagen[28–31]. The above-mentioned type of mutation was confirmed in patients who underwent genetic screening.

Newborns with OI require special care in the neonatal unit, the most important goal of which is to minimise the risk of new fractures. All nursing and medical procedures should be performed gently and slowly, and even simple medical procedures, such as peripheral line placement, should be done under analgesia to avoid stress, trauma and fracture. All patients hospitalised in the Department received analgesics before intravenous injections and some of the diagnostic tests[13,29].

Symptoms of a fracture include pain and local oedema, as well as deformation of the limb axis and intensification of pain during movement. Such symptoms were observed in our patients. Fresh fractures required immobilisation and administration of analgesics, with paracetamol being the most frequently used drug of first choice, followed by chronic tramadol, which improved the patient's comfort. As a result of multiple fractures, one of the patients was in a serious condition and respiratory disorders in the form of increasing respiratory effort, tachypnoea and cardiac dysfunction, mainly tachycardia, were observed in the course of pain shock[11].

It was reported that children with ≥10 bone fractures received lower Apgar scores after birth, and were more likely to present with abnormalities in their somatic development already in foetal life. Additionally, these patients were more likely to require feeding via a gastric tube and developed anaemia and pneumonia.

Keuning et al. assessed 42 patients with OI type III and showed that their vital lung capacity was reduced compared to those without OI (by 1.57 L on average). Additionally, this was correlated with the degree of scoliosis (multivariate logistic regression model, $\beta - 0.40$, $p = 0.03$), especially in increasing thoracic curvatures. In the study group, pneumonia occurred in 41.5% of the newborns. Impaired alveolar maturation at a later stage of the child's development may be a complication of pneumonia. Authors of many publications emphasise that spirometry to assess lung function should be recommended from an early age in patients with OI[28,30].

It is noteworthy that the majority of neonates with OI were born at term and with normal weight. Also, their condition at birth was considered good based on the Apgar score. It was only the fractures and the associated pain that significantly worsened the child's comfort in the following days of life, and the reduced motor activity was the reason for the increased susceptibility to infections, especially of the airways.

Regardless of the age of patients, IO treatment goals go beyond fracture risk reduction, and include optimising the patient's growth and mobility (maintaining physiological function), increasing bone stability and minimising extra-skeletal complications. Dlesk et al. reviewed and evaluated literature on pain management in children with OI. They identified four valid multimodal analgesia approaches, including bisphosphonate therapy, surgical intervention, physical therapy and psychosocial support. The patients described in this study were treated with pamidronate, analgesics and fracture immobilisation, i.e. three of the four proposed analgesic modalities indicated above[32–35].

Children and adolescents with OI experience mild but complex pain, localised in several areas of the body, hence the importance of reducing symptoms to improve the quality of life[34]. Bisphosphonate therapy is the standard of care in paediatric patients[3,20,31,35]. Anti-RANKL antibody and anti-sclerostin antibody remain potential treatment alternatives; clinical trials are still ongoing in this area[14,36,37].

It has been shown that children with severe forms of OI put on pamidronate in specialist centres had a reduced number of fractures and achieved a gradual increase in body length/height[4,12]. The authors observed no worsening of the patients' clinical condition after first dose of pamidronate. Munns et al. noted that 7% of the patients with pre-existing respiratory distress developed respiratory failure after first bisphosphonate cycle[16]. According to other authors, within a week of pamidronate treatment onset, patients presented fewer symptoms of bone pain, as manifested by the lack of crying during handling or care[38]. Due to the inhibition of calcium release from bone, hypocalcaemia is a known potential adverse effect of pamidronate treatment

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and requires close monitoring during and after bisphosphonate therapy. Our experience shows that the lowest hypocalcaemia was observed after the 3rd dose of pamidronate. These patients additionally required calcium supplementation[39]. After intravenous administration, phosphorus and total calcium decrease and parathyroid hormone increases, which is consistent with physiological hormonal regulation. Hypophosphatemia did not require supplementation. Similar treatment outcomes were reported by Rauch et al.[40]. It should be emphasised that the observed biochemical changes did not threaten the health and life of the patients, were transient and quickly normalised after symptomatic management. We therefore consider pamidronate as a safe treatment method in neonates, which is in line with the literature data[6,12,16,17].

The relatively large population of patients with OI types III and II (in light of the rarity of this disease) is the strength of this study. Its limitations, on the other hand, result from inclusion of patients from only one centre on the basis of children's medical history. Laboratory methods and standards, as well as the possibility of assessing certain biochemical parameters have changed throughout the last 20 years, and access to genetic testing has improved.

Although skeletal pathologies are not directly life-threatening, severe skeletal deformities, pain, and immobilisation can progressively impair the quality of life and, in extreme cases, cause complications leading to death. The experience gained in our centre has allowed us to develop a standardised approach that has been successful in optimising the survival of OI neonates. Numerous studies emphasise the role of an early, multidisciplinary approach to a chronically ill child. The treatment team should include physiotherapists, occupational therapists, psychologists and dieticians[24,41]. Our observations may help clinicians to predict possible complications in the neonatal period, as well as changes in laboratory parameters after the first cycle of pamidronate during this period.

SUMMARY

Osteogenesis imperfecta in neonates is a serious clinical problem that requires early diagnosis, treatment and multispecialty care. Neonates with OI types III and II present with fresh bone fractures and prenatal fractures at different stages of healing, which increase the risk of circulatory and respiratory disorders and secondary infections during this period of life. The use of analgesics and antiresorptive agents in the neonatal period is safe: it reduces pain in children and improves their activity. It is also important for further cooperation with the parents. Neonates diagnosed with at least 10 fractures were significantly more likely to be admitted to ICU, received fewer Apgar scores, experienced feeding problems and were more likely to develop anaemia.

CONCLUSIONS

Prenatally diagnosed OI has a severe course (multiple fractures) in the neonatal period. It therefore requires care in a specialist centre, where safe, symptomatic pharmacological treatment (bisphosphonates) can be initiated to reduce pain and the risk of further bone fractures.

Conflict of interest

The authors report no financial or personal relationships with other individuals or organisations that could adversely affect the content of the publication and claim ownership of this publication.

Author contributions

Original concept of study: EJP. Collection, recording and/or compilation of data: EJP, BAG, JN, DCS, EW. Analysis and interpretation of data: EJP, JN, EW. Writing of manuscript: EJP, BAG, JN, EW. Critical review of manuscript: EJP. Final approval of manuscript: EJP.

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