© Pediatr Med Rodz 2021, 17 (1), p. 47–51
DOI: 10.15557/PiMR.2021.0007

Received: 09.09.2020
Accepted: 19.11.2020
Published: 05.03.2021

Elżbieta Jakubowska-Pietkiewicz[1], Elżbieta Woźniak[1], Dominika Matczak[2]

Diagnosis of secondary osteoporosis – long-term observations in children with myelomeningocele and cerebral palsy

Rozpoznawanie osteoporozy wtórnej – wieloletnie obserwacje dzieci z przepukliną oponowo-rdzeniową i mózgowym porażeniem dziecięcym

[1] Department of Paediatrics, Newborn Pathology and Bone Metabolic Diseases, Medical University of Lodz, Łódź, Poland
[2] Maria Konopnicka Paediatric Centre, Central Teaching Hospital of the Medical University of Lodz, Łódź, Poland
Correspondence: Elżbieta Jakubowska-Pietkiewicz, Department of Paediatrics, Newborn Pathology and Bone Metabolic Diseases, Medical University of Lodz, Sporna 36/50, 91-738 Łódź, Poland, tel.: +48 42 617 77 15, e-mail: elzbieta.jakubowska-pietkiewicz@umed.lodz.pl

Abstract

Background: Cerebral palsy is one of the most common causes of movement disorders in children, whilst myelomeningocele is the most severe form of spina bifida. Both motor dysfunctions result in chronic immobilisation that can lead to secondary low bone mass and even osteoporosis. In this context, risk factors for osteoporosis may also include low calcium and vitamin D intake from diet and long-term use of anticonvulsants or glucocorticosteroids. Long-bone and vertebral fractures in the course of secondary osteoporosis in children with significant motor activity limitation deteriorate their quality of life. **The aim of the study** was to assess the bone mineralisation status and vitamin D concentrations in children and adolescents with motor disabilities in the course of cerebral palsy and myelomeningocele. **Materials and methods:** We analysed data from medical records of 35 children aged 3–18 years, including 20 children with cerebral palsy and 15 children with lumbar myelomeningocele. Selected parameters of calcium and phosphate metabolism, including serum 25-hydroxyvitamin D levels, and the results of a bone densitometry, using dual-energy X-ray absorptiometry in two paediatric measurement programs were assessed. Z-score equal to or lower than −2.0 was considered as criterion of low bone mass diagnosis. In 22/35 children the indications for diagnostics was motor disability (mainly) as well as long-bone and/or vertebral fractures. **Results:** Low bone mass was diagnosed in 27/35 evaluated patients, while osteoporosis in 16/32 patients. Vitamin D concentration not exceeding 30 ng/mL was found in 21/35 (60%) children. **Conclusions:** Measurements of bone mineral density in children with motor disabilities should be included in multidisciplinary medical care. In this group of patients the vitamin D in doses depending on its serum concentration may be used either prophylactically – before bone fracture – or curatively – after being diagnosed with osteoporosis.

Keywords: osteoporosis, bone mineral density, cerebral palsy, myelomeningocele

Streszczenie

Wstęp: Mózgowe porażenie dziecięce jest jedną z najczęstszych przyczyn zaburzeń ruchowych u dzieci, a przepuklina oponowo-rdzeniowa stanowi najcięższą formę rozszczepu kręgosłupa. Obie dysfunkcje ruchowe są powodem przewlekłego unieruchomienia, które może prowadzić do wtórnej niskiej masy kostnej, a nawet osteoporozy. W ich kontekście czynnikami ryzyka osteoporozy mogą być także niedobór wapnia i witaminy D w diecie, długotrwałe stosowanie leków przeciwdrgawkowych czy glikokortykosteroidów. Złamania kości długich i kręgów w przebiegu osteoporozy wtórnej u dzieci ze znacznym ograniczeniem aktywności ruchowej skutkują natomiast pogorszeniem jakości ich życia. **Celem pracy** była ocena stanu mineralizacji kości oraz stężeń witaminy D u dzieci i młodzieży z niepełnosprawnością ruchową w przebiegu mózgowego porażenia dziecięcego i przepukliny oponowo-rdzeniowej. **Materiał i metody:** Analizie poddano dokumentację 35 dzieci w wieku 3–18 lat – 20 z mózgowym porażeniem dziecięcym i 15 z przepukliną oponowo-rdzeniową odcinka lędźwiowego kręgosłupa. Oceniano parametry gospodarki wapniowo-fosforanowej, w tym stężenie 25-hydroksywitaminy D, oraz wyniki badania densytometrycznego wykonywanego metodą dwuwiązkowej absorpcjometrii promieniowania rentgenowskiego w dwóch programach pediatrycznych. Z-score równe lub mniejsze niż −2,0 było podstawą rozpoznania małej masy kostnej. Wskazanie do przeprowadzenia diagnostyki stanowiły niepełnosprawność ruchowa (przede wszystkim), a także złamania kości długich i/lub kręgów u 22/35 dzieci. **Wyniki:** Małą masę kostną rozpoznano u 27/35 badanych, osteoporozę natomiast u 16/32 pacjentów. Stężenie witaminy D nieprzekraczające 30 ng/ml stwierdzono u 21/35 (60%) dzieci. **Wnioski:** Pomiary gęstości mineralnej kości u dzieci niepełnosprawnych ruchowo powinny być włączone do wielospecjalistycznej opieki medycznej. Stosowanie witaminy D w dawkach zależnych od jej stężenia w surowicy może mieć w tej grupie pacjentów charakter profilaktyczny – przed wystąpieniem złamania kości – lub leczniczy – w rozpoznanej osteoporozie.

Słowa kluczowe: osteoporoza, gęstość mineralna kości, mózgowe porażenie dziecięce, przepuklina oponowo-rdzeniowa

INTRODUCTION

Chronic immobilisation is a consequence of complex neuromuscular abnormalities during childhood and adolescence. In addition, it is also one of the risk factors for secondary mineralisation disorders, including osteoporosis or low bone mass. It is often accompanied by malnutrition that increases the risk of skeletal complications[1–3]. Children and adolescents with cerebral palsy (CP) and a significant decrease in motor activity secondary to neurodevelopmental disorders are physically disabled and at a particular risk of bone mass loss[3,4]. In addition, chronic diseases during child's development that require long-term treatment, hospital stays and limitations of children's own activity may affect the skeletal system and therefore it is recommended to perform bone densitometry in this group[1,5]. A diagnosis of low bone mass density (BMD) may indicate an increased risk of clinically significant bone fractures and the need for use vitamin D and calcium supplements, and even bisphosphonates[6,7].

AIM OF THE STUDY

The aim of presented study was to assess bone mineralisation status and vitamin D levels in children and adolescents with motor disabilities in the course of CP and myelomeningocele (MMC).

MATERIALS AND METHODS

The study included the data from medical records of 35 children aged 3–18 years hospitalised at the Department of Paediatrics, Newborn Pathology and Bone Metabolic Diseases, Medical University of Lodz between 2005 and 2018. Retrospective analyses included the first medical history and physical examination related to the time period in which osteoporosis/low bone mass was diagnosed. CP was diagnosed in 20 children, and 15 children with lumbar MMC underwent neurosurgery with the implantation of a ventriculoperitoneal (VP) shunt due to accompanying hydrocephalus. The patients were referred from outpatient specialist care to the Department of the authors in order to assess the bone mineral metabolism.

The inclusion criteria for the evaluation included: a significant reduction in patient's own activity in the course of the underlying disease, already performed densitometry and the patient's history of no vitamin D intake during the 3 months before hospitalisation. The data from children with total parenteral nutrition and endocrine disorders were not analysed.

All children with MMC and 8/20 children with CP used wheelchairs. Antiepileptic drugs were administered to 7/20 patients with CP. In some children (11/35) with osteoporosis diagnosed in the authors' Department, therapy with bisphosphonates (sodium pamidronate) was initiated after receiving parents' informed consent.

In each individual, anthropometric measurements of body weight and height were performed, in accordance with generally accepted principles, and the results were evaluated on growth charts[8]. Basic parameters of calcium-phosphate metabolism were assessed in all children, including serum of 25-hydroxyvitamin D [25(OH)D] levels by enzyme-linked immunosorbent assay (ELISA)[9]. According to the guidelines developed for the Polish population, low vitamin D concentration was considered at values below 30 ng/mL[9,10]. Parathyroid hormone (PTH) concentration was measured by a chemiluminescent microparticle immunoassay (CMIA) method.

In each patient, DXA (dual-energy X-ray absorptiometry) bone density examination was performed in the total body less head (TBLH) and/or the lumbar spine in anterior-posterior (AP SPINE) projection measurement program with use of Lunar Prodigy Advance device (GE Healthcare). The duration of the DXA study was 4 minutes for TBLH and 30 seconds for the AP SPINE program. The radiation doses were 0.37 μGy and 37 μGy, respectively, and the measurement error was less than 1% for both programs (coefficient of variation, CV <1%).

The Infant option was used in 2/35 children under 5 years of age. Low BMD was diagnosed when Z-scores were equal to or lower than –2.0, and in the case of accompanying long-bone and/or vertebral fractures, osteoporosis was diagnosed[1]. In patients with weight or height deficiency (respective values below the 3rd percentile), bone densitometry results were corrected for the child's biological age[1,5].

The study was approved by the Bioethics Committee of the Medical University of Lodz (RNN/144/03/KE 2003).

RESULTS

Tab. 1 presents data on prior bone and/or vertebral fractures in both groups of children and an assessment of their somatic development. In 3 patients, there was no documented history of bone fractures. All children had a total of 43 long-bone and vertebral fractures. Bone fractures were reported more frequently in patients with MMC (10/13, 77%). 12 children with CP (60%) experienced more than one bone and vertebral fractures (31 in total). Weight and height deficiencies were more common in patients with CP (9/20, 45%), and in 4/15 children (33%) with MMC body length and weight deficiency was scored below the 10th percentile.

The results of laboratory tests assessing calcium-phosphate metabolism, e.g. PTH, calcium (Ca), inorganic phosphorus (Pi) and magnesium (Mg) concentration in both groups are presented in Tab. 2. In all children, Ca and Mg concentrations were within the reference range. Pi levels were elevated in 44% of CP patients and 60% of MMC patients.

DOI: 10.15557/PiMR.2021.0007

Clinical data	Cerebral palsy $n = 20$	Myelomeningocele $n = 15$
Bone/vertebral fractures	12 (60%)*	10 (77%)**
Body weight		
<10 percentile	9 (45%)	4 (27%)
10–90 percentile	11 (55%)	11 (73%)
>90 percentile	–	–
Body height		
<10 percentile	8 (40%)	7 (47%)
10–90 percentile	12 (60%)	8 (53%)
>90 percentile	–	–
* Missing data in 1 patient. ** Missing data in 2 patients.		

Tab. 1. Body weight, height and number of bone/vertebral fractures in the study group

		PTH $n = 20$	Ca $n = 18$*	Pi $n = 18$*	Mg $n = 18$*
Cerebral palsy	↑	1 (5%)	0	**8 (44%)**	0
	N	17 (85%)	18 (100%)	9 (50%)	17 (94%)
	↓	2 (10%)	0	1 (6%)	1 (6%)
		PTH $n = 15$	**Ca $n = 15$**	**Pi $n = 15$**	**Mg $n = 15$**
Myelomeningocele	↑	1 (7%)	0	**9 (60%)**	0
	N	14 (93%)	15 (100%)	6 (40%)	15 (100%)
	↓	0	0	0	0
* Missing test result in the medical records for 2 children.					

Tab. 2. Results of laboratory tests of selected parameters of calcium-phosphate metabolism

The 25(OH)D levels in both groups of children are presented in Tab. 3. The mean concentration of 25(OH)D in both groups was 26.19 ng/mL [standard deviation (*SD*) 13.55], which was below the optimal level[10]. Overall, 21/35 (60%) of patients were found to have low serum 25(OH)D levels (suboptimal, deficient and severely deficient). However, in 4/35 (11%) 25(OH)D concentration was lower than 10 ng/mL. In 67% of children with MMC, the 25(OH)D concentration did not exceed 30 ng/mL. The lowest concentration of the hepatic vitamin D metabolite (3.4 ng/mL), indicating severe deficiency, was found in a patient with CP and significant malnutrition.

Tab. 4 shows densitometry findings (mean values and their statistics) in both studied groups. Lower mean Z-scores were obtained in the AP SPINE program and in children with CP.

DISCUSSION

The diagnosis of osteoporosis in children and adolescents is based on the International Society for Clinical Densitometry (ISCD) criteria. They take into account the result of the densitometry, i.e. Z-score (with reference to sex- and age-matched group), equal to or lower than

25(OH)D concentration [ng/mL]	Cerebral palsy $n = 20$	Myelomeningocele $n = 15$
<10 – severe deficiency	4	0
10–20 – deficiency	3	5
20–30 – suboptimal level	4	5
Total	**11 (55%)**	**10 (67%)**
>30 – norm	**9 (45%)**	**(33%)**
Mean concentration	26.22	26.16
Minimum concentration	3.4	10.01
Maximum concentration	50.8	58

Tab. 3. 25(OH)D concentration in children with cerebral palsy and myelomeningocele

Densitometry	Cerebral palsy	Myelomeningocele
Spine Z-score		
$\bar{x}$	–3.56	–3.46
SD	1.9	1.5
Min.	–7.7	–5.75
Max.	0.6	–1.03
TBLH Z-score		
$\bar{x}$	–2.05	–1.6
SD	1.7	1.2
Min.	–5.4	–4.1
Max.	0.6	0.1

Tab. 4. The result of densitometry in children with cerebral palsy and myelomeningocele

–2.0 and prior clinically significant fractures. According to the definition, these are at least: one spine fracture or two or more long-bone fractures until the age of 10 or three fractures until the age of 19[1,5].

In the study group of children and adolescents, secondary osteoporosis was diagnosed in 16/32 (50%) of patients with bone fractures in medical history. When making the diagnosis, the lower BMD value was also considered: TBLH or spine Z-score. In some patients, the examination was performed only in the AP SPINE option, because the measurement site was adjusted to the possibility of performing and interpreting the result, depending on the deformities of the skeletal system and the patient's clinical condition during examination.

The current literature emphasizes that bone densitometry is part of a comprehensive assessment of skeletal system in children and adolescents with an increased risk of bone fractures[1,6,11,12]. The increased risk of bone fracture concerns mainly patients receiving long-term glucocorticosteroids and anticonvulsants[1,5]. In the presented group, none of the children received glucocorticosteroids, while 7 children with CP were treated with anticonvulsants. Important risk factors also include chronic inflammatory diseases, malnutrition and significantly reduced motor activity, e.g. in CP and MMC[13–15]. Early diagnosis of low bone mass in children with

 DOI: 10.15557/PiMR.2021.0007

these diseases reduces the risk of osteoporosis in adulthood[4,13–15]. Therefore, densitometry was performed in patients with CP and MMC. As already mentioned, bone and/or vertebral fractures are necessary for the diagnosis of osteoporosis. In the analysed medical records, a total of 43 fractures in 32 patients were documented. Vertebral fractures occurred in 3 boys with CP, while femoral fractures were most often in MMC patients.

Henderson et al. assessed 619 children with muscular dystrophy and CP and showed that the risk of bone fractures increases with BMD Z-score decline. Each decrease in the Z-score increased the risk of bone fractures from 6% to 15%[2], which is difficult to demonstrate in the described patients, because this study does not present continuous observations.

Vitamin D level were also measured in the presented group of children and adolescents, with low values found in 60%. Other authors made similar observations and therefore, similarly to our previous report, they recommend the assessment of vitamin D levels in these patients[6,16–18].

Possible explanations for vitamin D deficiency in the studied children and adolescents include: home-based "lifestyle" (the children did not walk independently, rarely left the house), coexisting gastrointestinal motility disorders, nutritional deficiencies and therapy with anticonvulsants[1,16,19]. On the other hand, Toopchizadeh et al. found no significant differences in 25(OH)D levels in children with different types of CP receiving antiepileptic drugs[17].

Low vitamin D levels in disabled children may also be consistent with the general trend of vitamin D deficiency in the healthy population[20–22]. Therefore, in this group, as in healthy children, vitamin D should be used in prophylactic doses, and in the case of a fracture or documented deficiency, increased to therapeutic doses[9,10].

In some of presented patients, hyperphosphatemia was observed, which may be diet-related (due to consumption of heavily processed products). The results of other biochemical tests did not differ from the reference values, which indicates a certain balance in the calcium-phosphate metabolism.

According to the literature and our own observations, it can be concluded that the most important factor leading to low BMD is low or absent spontaneous motor activity due to the underlying disease (CP, history of MMC surgery), which increases the risk of fractures[2,3,6,18,19,23]. It is worth noting that in the studied population, low BMD was not always associated with bone fractures, and vertebral fractures occurred in only 3 patients. Children may have reported early enough to implement post-densitometry preventive measures (calcium and vitamin D supplementation) and thus prevent bone fractures.

Supplementation of calcium and vitamin D in prophylactic doses under serum concentrations monitoring is recommended in disabled patients with an increased risk of osteoporosis. In the case of fractures, it is recommended to extend the diagnosis to include laboratory, radiological and densitometric tests, and even treatment with bisphosphonates[4,6,7,12].

The diagnosis of secondary osteoporosis in children significantly affects their quality of life, therefore it is necessary to use calcium, vitamin D and bisphosphonate[5,24,25]. These forms of therapy increase BMD, and hence reduce the risk of fractures. Beneficial effects of bisphosphonates have been reported in patients with CP, although these drugs are mainly used in disabled patients with previous bone fractures, treated with glucocorticoids, and with congenital brittle bone disease (osteogenesis imperfecta)[7]. Children with CP and osteoporosis can also be effectively and safely treated with zoledronic acid[26].

SUMMARY

Based on a retrospective analysis, it was found that skeletal mineralisation disorders and vitamin D deficiency constitute significant health problems in children with disabilities. BMD reduction and low 25(OH)D serum levels were reported in over 75% (27/35) and 60% of examined children, respectively. In children with MMC, biochemical abnormalities were more frequent as compared to the CP group, more fractures were observed, osteoporosis was diagnosed more often, as well as treatment was initiated in more children. However, as they are single-centre observations, a further studies with a larger sample sizes are warranted.

CONCLUSIONS

1. Measurements of bone mineral density in children with motor disabilities should be included in multidisciplinary medical care.
2. In this group of patients the vitamin D in doses depending on its serum concentration may be used either prophylactically – before bone fracture – or curatively – after being diagnosed with osteoporosis.

Conflict of interest

The authors declare no financial or personal relationships with other persons or organisations that could adversely affect the content of the publication and claim the right to this publication.

Funding/Support and role of the sponsor

The work is financed by the Medical University of Lodz (503/1-090-02/503-11-001).

References

1. Bianchi ML, Leonard MB, Bechtold S et al.; International Society for Clinical Densitometry: Bone health in children and adolescents with chronic diseases that may affect the skeleton: the 2013 ISCD Pediatric Official Positions. J Clin Densitom 2014; 17: 281–294.
2. Henderson RC, Berglund LM, May R et al.: The relationship between fractures and DXA measures of BMD in the distal femur of children and adolescents with cerebral palsy or muscular dystrophy. J Bone Miner Res 2010; 25: 520–526.
3. Okurowska-Zawada B, Konstantynowicz J, Kułak W et al.: Assessment of risk factors for osteoporosis and fractures in children with meningomyelocele. Adv Med Sci 2009; 54: 247–252.
4. Trinh A, Wong P, Fahey MC et al.: Longitudinal changes in bone density in adolescents and young adults with cerebral palsy: a case for early intervention. Clin Endocrinol (Oxf) 2019; 91: 517–524.
5. Bachrach LK, Gordon CM; Section on Endocrinology: Bone densitometry in children and adolescents. Pediatrics 2016; 138: e20162398.
6. Jakubowska-Pietkiewicz E, Orzechowska G, Woźniak E et al.: Bone mineral density and vitamin D status in children with chronic neurological syndromes – clinical observations. Case Rep Clin Med 2018; 7: 315–323.
7. Simm PJ, Biggin A, Zacharin MR et al.; APEG Bone Mineral Working Group: Consensus guidelines on the use of bisphosphonate therapy in children and adolescents. J Paediatr Child Health 2018; 54: 223–233.
8. Kułaga Z, Różdżyńska A, Palczewska I et al.; Grupa Badaczy OLAF: Siatki centylowe wysokości, masy ciała i wskaźnika masy ciała dzieci i młodzieży w Polsce – wyniki badania OLAF. Stand Med Pediatr 2010; 7: 690–700.
9. Płudowski P, Karczmarewicz E, Bayer M et al.: Practical guidelines for the supplementation of vitamin D and the treatment of deficits in Central Europe – recommended vitamin D intakes in the general population and groups at risk of vitamin D deficiency. Endokrynol Pol 2013; 64: 319–327.
10. Rusińska A, Płudowski P, Walczak M et al.: Vitamin D supplementation guidelines for general population and groups at risk of vitamin D deficiency in Poland – recommendations of the Polish Society of Pediatric Endocrinology and Diabetes and the Expert Panel with participation of National Specialist Consultants and Representatives of Scientific Societies – 2018 update. Front Endocrinol (Lausanne) 2018; 9: 246.
11. Jones AR, Zacharin MR, Cameron FJ et al.: Bone density assessment in a tertiary paediatric centre over 13 years: referral patterns and limitations. J Paediatr Child Health 2015; 51: 608–613.
12. Ozel S, Switzer L, Macintosh A et al.: Informing evidence-based clinical practice guidelines for children with cerebral palsy at risk of osteoporosis: an update. Dev Med Child Neurol 2016; 58: 918–923.
13. Duran I, Katzmann J, Martakis K et al.: Individualized evaluation of lumbar bone mineral density in children with cerebral palsy. Arch Osteoporos 2018; 13: 120.
14. Kafadar I, Kilic BA, Yilmaz FK et al.: Bone mineral density in pediatric patients with meningomyelocele. Childs Nerv Syst 2016; 32: 111–119.
15. French ZP, Caird MS, Whitney DG: Osteoporosis epidemiology among adults with cerebral palsy: findings from private and public administrative claims data. JBMR Plus 2019; 3: e10231.
16. Akpinar P: Vitamin D status of children with cerebral palsy: should vitamin D levels be checked in children with cerebral palsy? North Clin Istanb 2018; 5: 341–347.
17. Toopchizadeh V, Barzegar M, Masoumi S et al.: Prevalence of vitamin D deficiency and associated risk factors in cerebral palsy: a study in North-West of Iran. Iran J Child Neurol 2018; 12: 25–32.
18. Finbråten AK, Syversen U, Skranes J et al.: Bone mineral density and vitamin D status in ambulatory and non-ambulatory children with cerebral palsy. Osteoporos Int 2015; 26: 141–150.
19. Bagińska J, Liszewska A, Korzeniecka-Kozerska A: The role of vitamin D replacement therapy in serum FGF23 concentration in children with myelomeningocele compared with healthy children – a preliminary study. J Pediatr Endocrinol Metab 2019; 32: 1259–1264.
20. Chlebna-Sokół D, Konstantynowicz J, Abramowicz P et al.: Evidence of a significant vitamin D deficiency among 9–13-year-old Polish children: results of a multicentre study. Eur J Nutr 2019; 58: 2029–2036.
21. Holick MF: The vitamin D deficiency pandemic: approaches for diagnosis, treatment and prevention. Rev Endocr Metab Disord 2017; 18: 153–165.
22. Smyczyńska J, Smyczyńska U, Stawerska R et al.: Seasonality of vitamin D concentrations and the incidence of vitamin D deficiency in children and adolescents from central Poland. Pediatr Endocrinol Diabetes Metab 2019; 25: 54–59.
23. Martinelli V, Dell'Atti C, Ausili E et al.: Risk of fracture prevention in spina bifida patients: correlation between bone mineral density, vitamin D, and electrolyte values. Childs Nerv Syst 2015; 31: 1361–1365.
24. Iwasaki T, Nonoda Y, Ishii M: Long-term outcomes of children and adolescents who had cerebral palsy with secondary osteoporosis. Curr Med Res Opin 2012; 28: 737–747.
25. Kim MJ, Kim SN, Lee IS et al.: Effects of bisphosphonates to treat osteoporosis in children with cerebral palsy: a meta-analysis. J Pediatr Endocrinol Metab. 2015; 28: 1343–1350.
26. Glorieux FH, Bishop NJ, Plotkin H et al.: Cyclic administration of pamidronate in children with severe osteogenesis imperfecta. N Engl J Med 1998; 339: 947–952.