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Bone fractures in children and adolescents: a frequent problem with a diverse aetiology

Złamania kości u dzieci i młodzieży – częsty problem, zróżnicowana etiologia

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Abstract

Bone fractures in children and adolescents are primarily an orthopaedic problem; however, frequent fractures or multiple fractures at a time require a more extensive diagnostic investigation performed by a paediatrician, endocrinologist and even a geneticist. It is estimated that one in three children aged up to 17 years will experience a bone fracture. The frequency of fractures rises with age, peaking at 11–14 years. The majority of fractures happen as a result of trauma; however, some of them are a sign of genetic diseases (osteogenesis imperfecta, osteopetrosis) or mineral imbalance (metabolic bone disease of prematurity, rickets, osteoporosis). Bone fractures in small children require particular attention, since they may be a sign of not only systemic disorders, but also of battered child syndrome. Not only fractures of long bones, but also fractures of the vertebrae are an underappreciated problem in young patients. They may be spontaneous or associated with inflammatory, autoimmune or neoplastic diseases. Glucocorticoids that are used to treat these diseases are considered to be the main risk factor for the development of steroid-related osteoporosis, regardless of the patient's age. Due to the diverse aetiology of bone fractures in children and adolescents, the cooperation of multiple specialists in the diagnostic investigation of calcium and phosphate imbalance and disorders of bone mineralisation is important.

Keywords: children, bone fractures, osteogenesis imperfecta, osteoporosis

Streszczenie

Złamania kości u dzieci i młodzieży są problemem przede wszystkim ortopedycznym, ale złamania wielokrotne i mnogie mogą wymagać poszerzenia diagnostyki z udziałem pediatry, endokrynologa, a nawet genetyka. Szacuje się, że co trzecie dziecko w wieku do 17. roku życia dozna złamania kości, a częstość złamań rośnie wraz z wiekiem i osiąga swoje maksimum w wieku 11–14 lat. Większość złamań ma charakter pourazowy, część jest jednak objawem chorób genetycznie uwarunkowanych (wrodzona łamliwość kości, osteopetroza) lub zaburzeń gospodarki mineralnej (choroba metaboliczna kości wcześniaków, krzywice, osteoporoza). Szczególnej uwagi wymagają złamania kości u małych dzieci, ponieważ mogą być objawem nie tylko zaburzeń ogólnoustrojowych, ale także zespołu dziecka maltretowanego. Problemem niedocenianym u pacjentów w wieku rozwojowym są nie tylko złamania kości długich, ale również złamania kręgów, które mogą mieć charakter samoistny lub wtórny do przebiegu chorób zapalnych, autoimmunologicznych i nowotworowych. Stosowane w ich leczeniu glikokortykosteroidy uważane są za główny czynnik ryzyka rozwoju osteoporozy posteroidowej, niezależnie od wieku pacjenta. Ze względu na różnorodną etiologię złamań kości u dzieci i młodzieży ważna jest wielospecjalistyczna współpraca w zakresie diagnostyki zaburzeń gospodarki wapniowo-fosforanowej i mineralizacji kośćca.

Słowa kluczowe: dzieci, złamania kości, wrodzona łamliwość kości, osteoporoza

INTRODUCTION

Bone fractures in children and adolescents are usually trauma-related. The risk of fracture at a young age is 10–25%. It is higher in boys (42%) than in girls (27%) and rises with age. Fractures occurring in the first year of life account for 1% of all fractures; bone fractures in children aged 7–10 years constitute as much as 25%, while for children aged 11–14 years, the percentage is over 30%. Fractures occur more often in the bones of the upper extremities (50% of all bone fractures) than in those of the lower extremities[1–4]. In children and adolescents, fractures are a seasonal phenomenon: most happen from May to August, while the lowest number of them occur in November and December. This is mainly associated with children's outdoor physical activity. Bone fractures in children and adolescents account for 18% of all injuries; 12% of bone fractures are the result of transport injuries, with half of them being bicycle accidents[3]. Post-traumatic fractures include the following mechanisms: slipped epiphysis (in the region of the growth plate, with either complete or partial separation of the epiphysis; 15–20% of all bone fractures), subperiosteal fracture (greenstick fracture), avulsion (the whole epiphysis or its part being torn off) and plastic (elastic) deformity[3]. However, bone fractures are not always associated with trauma. They may also result from a genetic disease, a metabolic disorder or a deficiency. A diverse aetiology of fractures is found particularly in the youngest children.

Metabolic bone disease of prematurity (osteopaenia of prematurity, rickets of prematurity) occurs in more than 50% of newborns with a birth weight of <1,000 g and in 16–40% of children with a weight of <1,500 g. Risk factors also include the consequences of prematurity such as prolonged parenteral nutrition (over 14 days) and delayed start of enteral nutrition, the use of glucocorticoids and diuretics, bronchopulmonary dysplasia, infections (sepsis), necrotising enterocolitis and low physical activity. Osteopaenia of prematurity occurs between week 6 and 12 of the corrected age. It is diagnosed using clinical chemistry tests, including serum calcium and phosphorus and their excretion with urine, and alkaline phosphatase activity (>500 U/L). Radiographic studies are also performed. Long bone and rib fractures are grade 3 radiographic findings associated with osteopaenia of prematurity (Fig. 1). The primary causal factor of this disease is shortened pregnancy, since as much as 80% of mineral substance accumulation occurs in the third trimester. For this reason, the recommended prevention and treatment primarily involve the supplementation of phosphorus, calcium and vitamin D[4,5].

GENETIC DISEASES

Bone fractures associated with genetic diseases can occur at any stage of development. This is because the course of the disease, possibilities of treatment (replacement therapy, symptomatic treatment) and the consequences of the evolution of the genetic disease itself and its modification by therapy all play a role in the occurrence of bone fractures. Fractures of long bones in the neonatal period indicate a severe form of disease which may lead to progressive deformations in the skeletal system and constitute a serious threat to the health and life of the newborn[5,6].

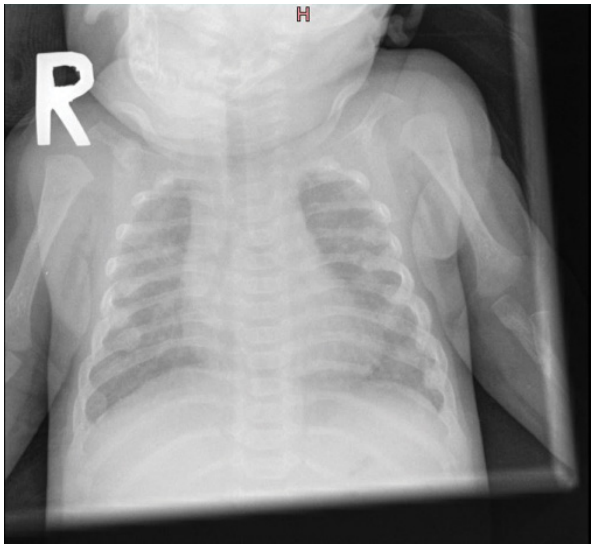

Fig. 1. Rib fractures associated with metabolic bone disease of prematurity in a 4-month-old child (first pregnancy, triplet pregnancy, triplet baby 3, week 24, birth weight 680 g, Apgar score 6/7/7; history of necrotising enterocolitis, short bowel syndrome, retinopathy of prematurity, intraventricular bleeding, bronchopulmonary dysplasia, sepsis). The child also had right radial and ulnar fractures

Osteogenesis imperfecta (OI; brittle bone disease) is a clinically and genetically heterogeneous increased susceptibility of bones to fractures which lead to the shortening and deformation of long bones and ribs and to impaired body proportions (ORPHA666). Type II (lethal) and type III (progressive deforming) according to the Sillence classification are the most severe clinical forms of OI diagnosed already during pregnancy. Fractures of long bones of the limbs and fractures of the ribs occur in the antenatal and perinatal periods. This results in the need to put the newborn in the frog position after birth. The child develops skeletal deformities and pain. This compromises the general condition of the neonate and can lead to respiratory failure[7,8]. OI aetiology mainly involves mutations in type 1 collagen genes *COL1A1* and *COL1A2* and in many other genes as well: *BMP1*, *WNT1*, *SERPINF1*, *IFITM5*, *MBTPS2*, *CRTAP*, *LEPRE1*[5,6,8]. The diagnosis of OI is based on clinical examination, a babygram and genetic testing (Fig. 1). The current classification of OI includes 20 types of the condition[9]. Apart from long bone, rib and vertebral fractures, the clinical presentation also includes blue sclerae, soft cranial bones, triangular face, dentinogenesis imperfecta features, ligament laxity, hearing loss and decreased bone mineral density[7–9]. However,

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the phenotypical presentation can be much more diverse; for example, in Bruck syndrome, bone fractures are accompanied by arthrogryposis, while in Cole–Carpenter syndrome, affected individuals develop craniosynostosis, hydrocephalus and ocular proptosis[6,8].

It is important to emphasise the fact that depending on the type of disorder, bone fractures can occur at any stage of development. OI is a rare disease; it occurs in one in 15,000–20,000 births[8]. Osteogenesis imperfecta has been treated symptomatically for over 30 years with pharmacotherapy including mainly bisphosphonates (administered from as early as the neonatal period), and with orthopaedic treatment and rehabilitation[5–9].

Another cause of bone fractures occurring already in the neonatal period is **hypophosphatasia** (HPP), which results from a mutation in the *TNSALP* gene for tissue non-specific alkaline phosphatase (ORPHA436). The condition leads to a reduced activity of alkaline phosphatase, decreased mineralisation of the skeleton and dental changes. HPP occurs in Europe in 1 out of 300,000 births. Its course can be very severe: the perinatal type, which is usually lethal, is characterised by the most severe presentation. There are also perinatal/infantile type, childhood type and adult type, in which only dental changes are observed. Bone fractures occur as early as in the perinatal period; they are accompanied by soft cranial bones, shortened and deformed long bones and bones of the chest cavity, vitamin B_6 deficiency, hypercalcaemia, and, in the most severe form of the disorder, seizures and respiratory failure. Replacement therapy is used: asfotase alfa (brand name Strensiq) is administered subcutaneously[5,10].

Bone fractures, chest abnormalities associated with rickets, radiological findings of periosteal demineralisation and elevation, and hypercalcaemia with a high level of parathormone are characteristic features of **neonatal severe hyperparathyroidism**[5]. Symptomatic treatment involves the administration of bisphosphonates.

Other genetic diseases which may be associated with long bone fractures (primary fractures that are part of the clinical presentation or fractures that are secondary to decreased skeletal mineralisation) are described below.

1. **Neurofibromatosis type 1** (NF1; von Recklinghausen's disease) is a rare disease (ORPHA636), a phakomatosis resulting from a mutation in the neurofibromin gene. Clinical signs of NF1 include café au lait spots, intraneural neurofibromas and optic nerve glioma, among other manifestations. Apart from fractures, the following abnormalities are observed in the skeletal systems of individuals affected with NF1: long bone dysplasia, pseudoarthrosis, musculoskeletal pain, scoliosis and decreased bone mineral density[11].
2. **Alagille syndrome** is the result of a mutation in the *JAGGED1* gene (ORPHA52). The characteristic manifestations of the disease include cholestasis (yellow skin and pruritus), facial defects, cardiovascular abnormalities (90% of which affect pulmonary arteries), posterior embryotoxon on ophthalmological examination and bone changes. These include, alongside pathological fractures, butterfly vertebrae, hemivertebrae, absence of the 12th rib, presence of connective tissue membranes between the ribs, radius and ulna fusion and spina bifida[12].
3. **Gaucher disease** (GD) is a sphingolipidosis caused by glucocerebrosidase deficiency (*GBA1* mutation; ORPHA355). GD is described as a disorder of the blood (thrombocytopaenia, anaemia, hepatomegaly and/or splenomegaly) and of the bones. Chronic bone pain (including pseudo-osteomyelitis), particularly of the pelvis and femora, deformities, joint hypermobility and osteoporosis with bone and vertebral fractures are typical for Gaucher disease. Infiltrations with focal osteosclerosis and osteonecrosis are observed in the bone marrow[13]. Substrate reduction or enzyme replacement therapy is used.
4. **Osteopetrosis** (ORPHA2781) is a rare heterogeneous syndrome caused by abnormal differentiation and function of osteoclasts. *TSFSF11*, *CLCN7*, *OSTMT* and *TCIRG1* gene mutations lead to increased bone mineralisation, bone pain, inflammatory lesions in the bones and bone marrow, periodontal lesions and compression neuropathy. Other manifestations include hepatosplenomegaly, pancytopaenia, hypocalcaemia and renal tubular acidosis. Delayed somatic and intellectual development is observed in affected children. Symptomatic treatment is used in the form of bone marrow transplantation[14].

Bone fractures can also be associated with other rare genetic syndromes such as, for example, **osteoporosis pseudoglioma syndrome** (**OPGG**), in which an *LRP5* mutation results in severe osteoporosis, its clinical symptoms and vision loss, Hajdu–Cheney syndrome (acro-dento-dysplasia) and Menkes disease, a copper metabolism disorder leading to neurodegeneration[15,16].

Battered (abused) child syndrome may be an underestimated cause of bone fractures in small children. The term "child abuse" refers to maltreatment and neglect of a child leading to compromised health, cognitive processes and self-esteem, and to loss of trust[17]. The diagnosis of the syndrome is difficult and requires the knowledge of risk factors and clinical signs. Apart from skin lesions, behavioural disorders and systemic symptoms, physical violence can lead to characteristic bone fractures:

- partial fractures of metaphyses and diaphyses of long bones;
- fractures of posterior rib segments;
- fractures of small fingers in non-ambulatory children;
- scapular, sternal, spinous process and cranial fractures.

They are found in children up to 3 years of age and are often at various stages of healing[16].

Infants with bone fractures which may suggest shaken baby syndrome (SBS) require particular attention. Comprehensive diagnostic investigation demonstrates the presence of subdural haematomas and retinal, vitreous or intraocular bleeding in such infants[16–18].

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In infants and older children, bone fractures may be the result of a **metabolic disease**. An example of such a disease is **deficiency rickets**, which occurs in the periods of rapid growth, particularly in infancy and the peripubertal period. The aetiology of the disease is related to vitamin D and, in Asian countries, calcium deficiency[16,19]. Skeletal findings include, among other signs, thickening of costochondral joints (rachitic rosary), thickening of metaphyses of long bones, frontal bossing (caput quadratum) and delayed closure of the fontanelles. In advanced bone changes (Fraser stage 2 and 3), X-ray shows laboratory flask-like distended metaphyses with ragged edges, and transverse and/or metaphyseal fractures of long bones and anterolateral fractures of the ribs[16,19]. Treatment involves supplementation for deficiencies.

Osteoporosis is another metabolic bone disorder which can occur at a young age. It is characterised by low bone mass and compromised microarchitecture of the bones, which results in an increased susceptibility to fractures. According to the International Society for Clinical Densitometry (ISCD) criteria, osteoporosis is diagnosed in children and adolescents based on bone densitometry and clinically relevant long bone and/or vertebral fractures. Clinically relevant bone fractures include:

- two or more long bone fractures in children up to 10 years of age
- or three or more long bone fractures in children and adolescents up to 19 years of age;
- at least one non-traumatic vertebral fracture[20,21].

Fractures which are clinically irrelevant for the diagnosis of osteoporosis are recurrent fractures of finger and toe bones, high-energy trauma fractures (transport injuries, sports injuries, blunt trauma) and those resulting from falls from a height of more than 3 metres[20].

In the paediatric population, densitometry is performed using dual-energy X-ray absorptiometry (DXA) at two sites: anterior-posterior lumbar spine (SPINE) and total body less head (TBLH). Areal bone mineral density (aBMD; g/cm^2) and bone mineral content (BMC; g) are assessed. The result is assessed with regard to calendar age, sex and body size (Z-score). According to densitometry criteria, children aged over 5 years, and adolescents and young adults aged up to 20 years have normal bone mineral density if their Z-score falls between –1.0 and +1.0. A Z-score of –2.0 to <–1.0 is interpreted as decreased bone mineral density (too low for age), while osteoporosis can be diagnosed with a **Z-score of ≤–2.0**[21,22].

Osteoporosis is usually diagnosed as a secondary condition associated with other chronic diseases and their treatment (mainly with glucocorticoids: glucocorticoid-induced osteoporosis, GIOP). Osteoporosis can also be primary in nature: spontaneous, idiopathic osteoporosis or be associated with genetic diseases. Regardless of aetiology, osteoporosis is treated with vitamin D and calcium supplements, and with bisphosphonates. In severe osteoporosis with vertebral fractures, orthopaedic devices and rehabilitation are used[20–22].

In the context of aetiology of fractures in children and adolescents, it is important to mention **fibrous dysplasia**. It is a benign genetic tumour of the bone forming as a result of abnormal growth, development and differentiation of bone tissue[23]. Pathological fractures are multifocal and are a late sign of dysplasia in McCune–Albright syndrome. Unifocal disease can remain asymptomatic for a long time. Characteristic features of fibrous dysplasia include bone pain, gait disturbances and bone deformities. McCune–Albright syndrome additionally includes café au lait skin pigmentation and endocrinological disorders, including premature puberty. Treatment is symptomatic and depends on the course of dysplasia (pharmacotherapy, orthopaedic procedures)[23].

The non-traumatic causes of bone fractures discussed above do not represent a complete set of clinical possibilities; therefore, it is worth knowing the risk factors for increased susceptibility to bone fractures in children and adolescents. According to Huh and Gordon, these include:

- osteogenesis imperfecta described above;
- a history of three or more fractures, which are necessary to diagnose osteoporosis;
- low bone mass on DXA;
- physical disability lasting more than 6 months;
- cerebral palsy or myelodysplasia;
- congenital heart disease;
- underweight and/or short stature, eating disorder;
- parenteral nutrition or tube feeding, prematurity: risk factors for metabolic bone disease of prematurity;
- the use of glucocorticoids and other medicines affecting the bones: secondary osteoporosis;
- radiotherapy, chemotherapy or organ transplantation;
- renal failure and seizure disorder[24].

Considering the often complex aetiology of bone fractures at a young age, it is worth planning a diagnostic process that would make it possible to determine the cause of this alarming problem. Some tests and examinations can be performed by the primary care physician, while other investigations and subsequent treatment require the cooperation of specialists (Tab. 1). This is particularly important in children aged up to 3 years[16].

CONCLUSION

Frequent fractures in children and adolescents require not only immediate orthopaedic care, but also appropriate diagnostic investigation, from the assessment of basic calcium and phosphate balance through imaging studies to molecular testing. This is of particular importance in children up to 3 years of age, since the aetiology of fractures in this group may be associated with genetic diseases and bone mineralisation disorders. Early diagnosis of these abnormalities allows young patients to receive proper treatment and rehabilitation, improving their quality of life.

Conflict of interest

The author does not report any financial or personal affiliations to persons or organisations that could adversely affect the content of or claim to have rights to this publication.

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Test/examination	Assessed element	Possible diagnosis
Physical	Underweight, short stature	Neglect
	Skin: substantial bruising	Maltreatment, vitamin C deficiency
	Eyes: retinal haemorrhage	Shaken baby syndrome
	Hair: twisted, fragile, fair	Menkes disease
	Teeth: dentinogenesis imperfecta	Osteogenesis imperfecta
Neurological	Muscle tone, reflexes	Cerebral palsy, neuromuscular diseases
Biochemical imbalance of calcium and phosphates	Serum and urine levels of calcium and phosphorus; vitamin D, parathormone and alkaline phosphatase activity levels	Metabolic bone disease of prematurity, rickets, hypophosphatasia
Trace elements and other	Copper and ceruloplasmin levels Vitamin C level	Menkes disease Scurvy
Molecular	*COL1A1* and *COL1A2* mutations *LRP5* mutation and other	Osteogenesis imperfecta Osteoporosis pseudoglioma syndrome
Imaging	X-ray, ultrasound, densitometry	Osteoporosis, bone dysplasia
Other	Urinalysis, liver function tests; lipase, amylase and lactate dehydrogenase activity levels, other	Inflammatory, autoimmune, neoplastic diseases

Tab. 1. Proposed tests and examinations and their possible interpretation in children with bone fractures

References

1. Larsen AV, Mundbjerg E, Lauritsen JM et al.: Development of the annual incidence rate of fracture in children 1980–2018: a population-based study of 32,375 fractures. Acta Orthop 2020; 91: 593–597.
2. Rusek W, Pop T, Jarochowicz S et al.: Najczęstsze urazy kończyn górnych i dolnych u dzieci. Przegląd Medyczny Uniwersytetu Rzeszowskiego i Narodowego Instytutu Leków w Warszawie 2010; 4: 427–434.
3. Snela S, Inglot G: Epidemiologia urazów kończyny górnej u dzieci i młodzieży. Available from: https://poitr.pl/attachments/article/406/epidemiologia.pdf [cited: 1 February 2023].
4. Angelika D, Ugrasena IDG, Etika R et al.: The incidence of osteopenia of prematurity in preterm infants without phosphate supplementation: a prospective, observational study. Medicine (Baltimore) 2021; 100: e25758.
5. Borg SA, Bishop NJ: New diagnostic modalities and emerging treatments for neonatal bone disease. Early Hum Dev 2018; 126: 32–37.
6. Arshad F, Bishop N: Osteogenesis imperfecta in children. Bone 2021; 148: 115914.
7. Jakubowska-Pietkiewicz E, Siemiątkowska-Stengert W, Chlebna-Sokół D: Wrodzona łamliwość kości typu II – korzystne zmiany w diagnostyce i leczeniu. Opis przypadku. Post N Med 2016; 29: 734–737.
8. Forlino A, Marini JC: Osteogenesis imperfecta. Lancet 2016; 387: 1657–1671.
9. Marom R, Rabenhorst BM, Morello R: Osteogenesis imperfecta: an update on clinical features and therapies. Eur J Endocrinol 2020; 183: R95–R106.
10. Yazici H, Canda E, Kalkan Ucar S et al.: Severe perinatal hypophosphatasia case with a novel mutation. Arch Argent Pediatr 2022;120: e21–e24.
11. Jakubowska-Pietkiewicz E, Woźniak E, Chlebna-Sokól D et al.: Sceletal complications in the course of neurofibromatosis in children. Pediatr Pol 2019; 94: 151–157.
12. Ayoub MD, Kamath BM: Alagille syndrome: diagnostics challenges and advances in management. Diagnostics (Basel) 2020; 10: 907.
13. Stirnemann J, Belmatoug N, Camou F et al.: A review of Gaucher disease pathophysiology, clinical presentation and treatments. Int J Mol Sci 2017; 18: 441.
14. Penna S, Villa A, Capo V: Autosomal recessive osteopetrosis: mechanisms and treatments. Dis Model Mech 2021; 14: dmm048940.
15. Papadopoulos I, Bountouvi E, Attilakos A et al.: Osteoporosis-pseudoglioma syndrome: clinical, genetic, and treatment-response study of 10 new cases in Greece. Eur J Pediatr 2019; 178: 323–329.
16. Servaes S, Brown SD, Choudhary AK et al.: The etiology and significance of fractures in infants and young children: a critical multidisciplinary review. Pediatr Radiol 2016; 46: 591–600.
17. Otto-Buczkowska E: Różne formy maltretowania dzieci – przegląd piśmiennictwa. Nowa Pediatr 2013; 4: 159–163.
18. Turska M, Raban M, Grochowski C et al.: Zespół dziecka maltretowanego. J Educ Health Sport 2017; 7: 1452–1460.
19. Uday S, Högler W: Nutritional rikets & osteomalacia: a practical approach to management. Indian J Med Res 2020; 152: 356–367.
20. Bachrach LK, Gordon CM; Section on Endocrinology: Bone densitometry in children and adolescents. Pediatrics 2016; 138: e20162398.
21. 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.
22. Wasserman H, O'Donnell JM, Gordon CM: Use of dual energy X-ray absorptiometry in pediatric patients. Bone 2017; 104: 84–90.
23. Robinson C, Collins MT, Boyce AM: Fibrous dysplasia/McCune–Albright syndrome: clinical and translational perspectives. Curr Osteoporos Rep 2016; 14: 178–186.
24. Huh SY, Gordon CM: Fractures in hospitalized children. Metabolism 2013; 62: 315–325.