Katarzyna Koszałka-Fornal, Dorota Paluszyńska, Barbara Królak-Olejniak

Perinatal hypophosphatasia

Postać okołoporodowa hipofosfatazji

Department of Neonatology, Wrocław Medical University, University Clinical Hospital in Wrocław, Wrocław, Poland

Correspondence: Katarzyna Koszałka-Fornal, MD, Department of Neonatology, University Clinical Hospital in Wrocław, Borowska 213, 50-556 Wrocław, tel.: +48 71 733 15 00, e-mail: animorph@interia.pl

Abstract

Hypophosphatasia, also known as alkaline phosphatase deficiency, is a rare congenital metabolic disorder characterised by early bone and dental defects. First reports on hypophosphatasia date back to 1950s. The prevalence of the disorder in Europe is 1:300,000 births; data on the prevalence in Poland is missing. An abnormal structure of the region coding for the *ALPL* gene, which is responsible for producing tissue-nonspecific alkaline phosphatase, is the main cause of clinical symptoms. Consequently, there is a significant deficiency in the activity or even absence of this enzyme. Due to the heterogeneous clinical expression of hypophosphatasia, multiple clinical forms of the disorder, which vary in their mode of inheritance and prognosis, have been described, including rare and sporadically reported perinatal forms. There are ongoing studies on the aetiology, diagnosis and treatment of different clinical forms of hypophosphatasia. We present a case report of perinatal hypophosphatasia diagnosed in the Department of Neonatology at the University Clinical Hospital in Wrocław, with particular focus on the implemented diagnostic-therapeutic process and possible complications in the affected child during the stay in the neonatal intensive care unit. We also performed a literature review to present a wider picture of the disorder belonging to the group of the so-called rare diseases. We described current diagnostic and treatment possibilities in hypophosphatasia, based on the latest clinical trials, as well as the costs of treatment using Strensiq, the only alkaline phosphatase analogue available on the market.

Keywords: hypophosphatasia, newborn, diagnosis, treatment, rare diseases

Streszczenie

Hipofosfatazja, inaczej niedobór fosfatazy alkalicznej (*hypophosphatasia*), to rzadka wrodzona wada metaboliczna, charakteryzująca się wczesnymi zaburzeniami w budowie kości i zębów. Pierwsze doniesienia na temat jej występowania pojawiły się w latach 50. XX wieku. Hipofosfatazja występuje w Europie z częstością 1:300 000 urodzeń; obecnie brak jest danych na temat jej częstości w populacji polskiej. Główną przyczyną objawów klinicznych w tym schorzeniu jest nieprawidłowa budowa regionu kodującego gen *ALPL*, który odpowiada za produkcję tkankowo niespecyficzną fosfatazy zasadowej. W efekcie dochodzi do znacznych niedoborów aktywności tego enzymu, a nawet do jego braku. Ze względu na heterogenny obraz hipofosfatazji opisano liczne postaci kliniczne tej choroby, o różnym mechanizmie dziedziczenia oraz rokowaniu, w tym również rzadko występujące i sporadycznie opisywane postaci okołoporodowe. Badania nad etiologią, diagnostyką oraz leczeniem różnych postaci klinicznych hipofosfatazji nadal trwają. W pracy przedstawiono opis przypadku okołoporodowej postaci hipofosfatazji, rozpoznanej w Klinice Neonatologii Uniwersyteckiego Szpitala Klinicznego im. Jana Mikulicza-Radeckiego we Wrocławiu, ze szczególnym uwzględnieniem zastosowanego procesu diagnostyczno-leczniczego oraz podkreśleniem możliwych powikłań występujących u chorego dziecka na etapie pobytu na oddziale intensywnej terapii noworodków. Dokonano przeglądu literatury dotyczącej tej choroby w celu przedstawienia szerszego obrazu schorzenia należącego do grupy tzw. chorób rzadkich. Opisano obecne możliwości diagnostyki i leczenia hipofosfatazji, biorąc pod uwagę dane z najnowszych badań klinicznych, jak również koszty terapii jedynym dostępnym na rynku analogiem fosfatazy zasadowej – lekiem Strensiq.

Słowa kluczowe: hipofosfatazja, noworodek, diagnostyka, leczenie, choroby rzadkie

INTRODUCTION

Hypophosphatasia (HPP), also known as alkaline phosphatase deficiency, is a congenital metabolic disorder classified into the group of rare diseases and characterised by early-onset abnormalities in the structure of bones and teeth. The disorder was first described in 1948 by John Campbell Rathbun⁽¹⁾, while first cases of familial HPP were reported in the 1950s^(2,3). In Europe, the prevalence of severe and mild HPP is estimated at 1:300,000 and 1:6,300 births, respectively⁽⁴⁾. Data on the prevalence of HPP in Poland is missing. The HypoGenek foundation, which supports families with congenital HPP and promotes knowledge about this disease, has been operating since 2016 in Poland. Currently, the foundation looks after 9 patients, including 6 children, most of whom were diagnosed in early childhood⁽⁵⁾.

HPP is a disease with a variable mode of inheritance and an unknown degree of penetration. An abnormal structure of the region coding for the *ALPL* gene, which triggers a range of disorders, from deficiency in the activity of tissue-nonspecific alkaline phosphatase to a complete absence of the enzyme, is the main cause of HPP⁽⁶⁾. Leading centres conducting research on the genetic structure of various forms of HPP are mainly located in France and they contribute *ALPL* mutations, previously described only in literature, to the database coordinated by the Université de Versailles-Saint-Quentin-en-Yvelines. The database is updated based on ongoing research. Up to the time of writing this paper, a total of 388 *ALPL* mutations have been identified⁽⁷⁾.

Hypophosphatasia has been classified into clinical subtypes based on the time of symptom onset and their severity. Severe forms, such as perinatal and childhood HPP, which are inherited in an autosomal recessive manner, and mild forms, which occur mainly in adults and are primarily inherited in an autosomal dominant fashion, have been distinguished⁽⁸⁾. The present paper discusses childhood forms of HPP with a particular focus on perinatal hypophosphatasia, with 70 cases described in worldwide literature so far⁽⁹⁾. Clinical cases diagnosed prenatally have also been reported⁽¹⁰⁾.

Severe forms of HPP often manifest already in the prenatal period. Symptoms that may raise a suspicion of congenital HPP in pregnancy include difficulty visualising foetal bones (skull, pelvis, ribs) on ultrasound, bone shortening, deformation or abnormal structure, as well as, in rare cases, prenatal fractures⁽⁸⁾. Similar symptoms are observed postnatally, but in addition to bone changes in newborns, generalised hypotension and convulsions can also occur as the deficiency in tissue alkaline phosphatase impairs vitamin B₆ metabolism and synthesis of gamma-aminobutyric acid (GABA), leading to changes in the metabolism of nervous tissue due to altered penetration through the blood-brain barrier⁽¹¹⁾. Increased respiratory failure is also quite common as abnormal

structure of thoracic bones, reduced AP size in particular, may cause pulmonary hypoplasia. Laryngeal stridor causes high-pitched cry in the newborn. In the mild perinatal form, the ultrasonographic symptoms observed at the initial stages of pregnancy have a tendency to resolve in the third trimester⁽⁸⁾.

Milder forms also include infantile (first symptoms before 6 months of age) and childhood HPP. They are characterised by disturbances in the child's development, such as problems with reaching the subsequent stages of development (sitting, standing up, walking), which is due to the dominant muscle and joint abnormalities⁽¹²⁾. Furthermore, dental (loss of deciduous teeth) and osseous (e.g. craniosynostosis) problems as well as recurrent upper respiratory tract infections occur. Problems with feeding infants and electrolyte disturbances, which generate vomiting, dehydration and constipation, may also occur⁽¹³⁾.

Laboratory diagnosis of HPP is primarily based on the measurement of alkaline phosphatase (ALP) activity in blood serum or plasma. Elevated calcium or phosphorus levels may also be important additional diagnostic information⁽¹⁴⁾. Disturbances in bone structure are also confirmed by imaging techniques: radiography (X-ray), ultrasound, and computed tomography (CT). First of all, symptoms of mineralisation disorders, abnormal structure and irregular surfaces of the metaphyses as well as abnormal bone shape, e.g. thinning, are sought⁽¹⁵⁾.

As in all rare diseases, the diagnosis of HPP, its infantile form in particular, is difficult and requires differentiation from other diseases related to bone metabolism.

CASE REPORT

A child whose prenatal ultrasound image suggested congenital bone fragility (osteogenesis imperfecta) or camptomelic dysplasia, accompanied by polyhydramnios, intrauterine growth restriction (IUGR) and possible lung hypoplasia, was staying under perinatal palliative care at the University Clinical Hospital in Wrocław. No extended prenatal diagnosis was performed during pregnancy due to the lack of parental consent for amniocentesis. Medical case conference, including a neonatologist, clinical geneticist and obstetrician-gynaecologist, was set up and a decision was made to terminate the pregnancy via elective caesarean section at term. The decision was fully accepted by the parents.

A female newborn from third pregnancy and third delivery was born via caesarean section at completed 38 weeks gestation with an Apgar score of 6/6/6/8 at 1/3/5/10 minutes and with a birth weight of 2,750 g (10–25 percentiles). After birth, the child required supportive adaptation followed by non-invasive ventilation using nasal continuous positive airway pressure (n-CPAP) with FiO₂ 0.5. Analgesic treatment and parenteral nutrition were initiated. Blood was collected for laboratory tests, with particular focus on calcium and phosphate metabolism parameters.

Parameter	Value	Reference
Inorganic phosphorus	10.5 mg/dL	4.5–9 mg/dL
Total calcium	10.8 mg/dL	8–11 mg/dL

Tab. 1. Laboratory tests of blood serum, 1 day of life

Fig. 1. X-ray (babygram) after birth

Fig. 2. X-ray (babygram) in the following days of life

In the perinatal physical examination, abnormal, narrow chest with reduced A-P size, arched long bones with the presence of calluses and bruises, and no accompanying signs of dysmorphia were particularly noticeable.

Due to the deterioration of the child's clinical condition and increasing respiratory failure, the girl was intubated and mechanically ventilated using the Dräger ventilator in the PC-AC (pressure control – assist control) mode with FiO_2 0.5 two hours after delivery. In the following days, the child's condition was severe, but stable.

Preliminary blood tests excluded the presence of infectious agents, but the parameters of bone metabolism were in the upper limit of normal (Tab. 1).

Whole body radiograph (babygram) confirmed prenatal diagnosis of bone anomaly; radiologist's description: "The bones of the forearm are bilaterally arched – a state after previous/fresh fracture? The left femoral bone and the right lower leg bones are arched – as above. Metaphyses of long bones in the lower limbs with irregular outlines" (Fig. 1).

Ultrasonography showed no abdominal abnormalities. Although no structural abnormalities of the central nervous system were observed in transfontanellar ultrasound, impaired cerebral blood flow was noted. Echocardiography (ECHO) performed on day 1 of life excluded structural defects of the heart and vessels; signs of pulmonary hypertension were noted.

As the girl's condition stabilised, the diagnostic process was continued – pathological mobility of the left forearm as well as the left and right lower leg was found. Due to the persistent pathological mobility of the left lower leg with internal rotation, the newborn was fitted with a foot-femur plaster half-cast during the following days for immobilisation. The following findings were reported in another radiography (babygram): "The visible bones of both upper limbs are shortened and deformed – angular deformity of both forearm bones in both upper limbs is noticeable. Correct number of metacarpal bones of both hands. Finger bones are impossible to discern. Deformation and shortening of the bones of both lower limbs. Left femur significantly deformed, arched. The remaining bones of the left lower limb are obscured by the plaster half-cast. The bones of the right lower limb are also deformed and shortened. The fibula in the right lower limb is missing. Most likely the number of metatarsal bones in the right foot is correct (bone shadows overlap). It is impossible to discern the right ankle" (Fig. 2). In view of the abnormalities found, the diagnosis of calcium-phosphate metabolism was extended, and further evaluation of laboratory parameters and their follow-up were ordered (Tabs. 2–4).

Laboratory tests were consulted by phone with a specialist in clinical genetics and metabolic diseases in children. Type 2 osteogenesis imperfecta and thanatophoric dysplasia were initially excluded. A suspicion of HPP was raised due to persistent low ALP levels.

At 4 days of life, the child developed increasing hypercalcaemia; NaCl 0.9% plus furosemide infusion was initiated. Additionally, calcium and Vitalipid were discontinued from parenteral nutrition, phosphate supplementation was gradually reduced in favour of breast milk.

At 7 days of life, after a telephone consultation with the Department of Metabolic Bone Diseases of the Central Teaching Hospital in Łódź, the girl was qualified for ALP analogue therapy and arrangements for her hospital stay in the Department were made.

As part of the preparation of the child for transport to the Department of Metabolic Bone Diseases in Łódź, a Broviac

Parameter	Value	Reference
Parathyroid hormone	4.6 pg/mL	18.5–88 pg/mL
Vitamin 25(OH)D ₃	19.19 ng/mL	<15 – deficiency 15–20 – insufficiency >20 – sufficiency
Alkaline phosphatase	<5 U/L	48–406 U/L
Inorganic phosphorus	4.8 mg/dL	4.5–9 mg/dL
Total calcium	13.3 mg/dL	8–11 mg/dL

Tab. 2. Laboratory tests of blood serum, day 3 of life

Parameter	Value	Reference
First morning urine: calcium	17.5 mg/dL	0–250 mg/dL
First morning urine: inorganic phosphorus	15.04 mg/dL	–

Tab. 3. First morning urine test, day 3 of life

Parameter	Value	Reference
Alkaline phosphatase	8 U/L	0–500 U/L
Inorganic phosphorus	3.1 mg/dL	2.3–4.7 mg/dL
Corrected calcium	15.7 mg/dL	–

Tab. 4. Laboratory tests of blood serum, day 5 of life

Parameter	Value	Reference
C-reactive protein	76 mg/L	0–5 mg/L
Procalcitonin	25.48 ng/mL	0–0.05 ng/mL
WBC	8.34 thousand/ μ L	4–20 thousand/ μ L
Ferritin	4,386.4 μ g/L	6–400 μ g/L

Tab. 5. Laboratory tests of blood serum, day 12 of life

central line was placed (in the Department of Paediatric Surgery of the University Clinical Hospital in Wrocław). At the same time, laboratory findings showed increased levels of C-reactive protein (CRP); blood culture for aerobic bacteria (BacT/ALERT) as well as urine culture and catheter tip culture were conducted. After obtaining positive urine culture (*Enterococcus*), targeted antibiotic therapy was initiated. Physical examination revealed a gradual increase in oedema. On day 11 of life, fresh bleeding from the urinary tract occurred; second-line antibiotic therapy (vancomycin and meropenem) was used. The child required transfusion of blood components and intensified respiratory treatment.

Inflammatory parameters on day 12 are shown in Tab. 5. Blood culture was positive for *Staphylococcus hominis* (methicillin-resistant strain) and *Staphylococcus epidermidis*. Vancomycin therapy was continued according to the antibiogram.

Once patient's condition stabilised, further follow-up imaging tests were performed before the child was transferred to the centre where there was a possibility of treatment. Abdominal ultrasound findings were as follows: "Liver enlarged up to 6 cm in the CC direction in the MCL, with increased homogeneous echogenicity, with no foal lesions [...]." Other organs were unremarkable on ultrasound.

Central nervous system ultrasound showed a symmetrical ventricular system with no structural cerebral changes. Detected abnormalities included small cysts measuring up to 3 × 4 mm and 5 × 6 mm in the projection of the germinal zone.

Cardiological evaluation showed no signs of pulmonary hypertension. Coagulation tests and blood count were performed, yielding normal results.

Cardiac ultrasound interpretation was as follows: "RV 8.7, LV 19.7/11.3, IVS 3, LVPW 2.6, FS 42%, EF 76%. Correct position of the heart. Compliant venoatrial, atrioventricular and ventricular-vascular connections. Heart chambers not enlarged, normal myocardial contractility. Atrial septum: trace left-to-right shunt through the PFO. Continuous interventricular septum with normal movement during systole. MV – normal morphology and function. TV – normal morphology, trace TVI with a gradient of up to 27–32 mm Hg. AoV – normal morphology and function; flow velocity of about 1.4 m/s. PV – normal morphology and function; flow velocity of about 0.8 m/s (pulMAT 62 ms). Closed DA. Left-sided aortic arch with normal isthmus flow. Pulsatile flow in the abdominal aorta. No evident signs of pulmonary hypertension, trace PFO."

Urine culture at 30 days of hospital stay was positive for bacilli (*Klebsiella oxytoca*, *Morganella morganii*); Tazocin was included.

At 31 days of life, the child was transferred in a neonatal ambulance to the Department of Paediatric Intensive Care of the Central Teaching Hospital in Łódź, where tracheostomy was performed and mechanical ventilation was continued. HPP therapy was started at 5 months of age.

Next generation sequencing (NGS) showed the presence of pathogenic and potentially pathogenic *ALPL* variant in the neonate; since cytogenetic evaluation failed to confirm whether these variants are located in one or both copies of the gene, the diagnosis was extended to include testing in the girl's parents.

DISCUSSION

As a rare metabolic disorder, HPP requires particular perinatal vigilance from doctors. Not all cases of HPP are diagnosed prenatally, but literature data recommend repeated ultrasound scans during pregnancy. Severe HPP cases are usually detected in the first trimester, whereas the mild form is more difficult to diagnose – the symptoms are undetectable until the second trimester, and clinical improvement is observed in the following weeks in some cases (it is suspected that an increase in bone mineralisation occurs due to maternal ALP passing through the placenta)⁽⁷⁾. Neonatologists may suspect skeletal abnormality already during the first physical examination after birth.

The diagnosis of HPP is primarily based on ALP measurements in the serum or plasma. Elevated calcium and phosphorus in young children are important information when

making a diagnosis⁽¹⁴⁾. Basic tests of calcium and phosphate metabolism can be performed in centres of all reference levels; however, due to possible complications and the need for extensive diagnostic and therapeutic procedures, tertiary centres with an intensive care unit, preferably in consultation with centres specialising in bone diseases or metabolic disorders, are the preferred place of birth and further hospitalisation of newborns with HPP⁽¹⁶⁾. The 5-year mortality rate for perinatal and infantile cases of HPP with respiratory failure is estimated at 73%⁽¹⁷⁾. A study summarising the issue of HPP based on a 25-year experience of the Center for Metabolic Bone Disease and Molecular Research in St. Louis failed to confirm any cases of long-term survival among patients with perinatal HPP⁽¹⁸⁾.

All families with HPP should receive specialist genetic care. The chances of a couple who had one child with perinatal HPP to have another child affected is 25%⁽¹⁴⁾. In addition to the foundations for families affected by rare diseases, there is also an international registry of HPP patients, which collects medical and statistical data to help better understand the mechanism and treatment of the disease⁽¹⁹⁾. Available statistics estimate that the correct diagnosis of HPP can be made within a week if the first symptoms occur before the age of 1 year compared to 8.5 months for children who develop symptoms later in life⁽²⁰⁾.

Strensiq is currently the only drug used globally to treat childhood HPP. In 2008, it was authorised in the European Union and classified as an orphan drug (used for the treatment of rare diseases) by the European Medicines Agency (EMA)⁽²¹⁾. In Poland, it was approved for use in 2015⁽²²⁾. Currently, the therapy with Strensiq is implemented only by highly specialised departments dealing with metabolic bone diseases. Strensiq is a glycoprotein analogous to the ALP fusion protein, asphotase alpha, which almost doubles the prognosis of patients with HPP⁽²³⁾. The drug is given as a subcutaneous injection at a dose of 2 mg/kg 3 times a week or 1 mg/kg 6 times a week (a total of 6 mg/kg per the week)⁽²⁴⁾. Among other things, asphotase alpha improves bone mineralisation⁽²⁵⁾. Adverse effects of the drug include, among other things, hypersensitivity reactions, lipodystrophy (in the form of local adipose tissue atrophy or hypertrophy) and local reactions caused by subcutaneous injections. In rare cases, hypocalcaemia, decreased vitamin B₆ levels, kidney stones and hepatitis have been reported. No relationship between the drug and ectopic calcifications found in some of the patients has been identified⁽²⁴⁾. HPP therapy is free of charge for patients in the UK and Germany⁽²⁶⁾. In 2017, the cost of one-year treatment with Strensiq was estimated from about \$ 286,416 for patients with body weight <10 kg to \$ 2,545,920 for patients with body weight >40 kg⁽²⁷⁾.

Conflict of interest

Authors do not report any financial or personal connections with other persons or organizations, which might negatively affect the contents of this publication and/or claim authorship rights to this publication.

Acknowledgements

We would like to thank the Department of General, Interventional Radiology and Neuroradiology of the Medical University in Wrocław, headed by Professor Marek Szaśadek, MD, PhD. The imaging data made available to the Department of Neonatology in the form of radiographic images (babygrams) and their descriptions by Jagoda Jacków, MD, as well as repeated ultrasound imaging significantly contributed to the diagnosis in the described clinical case, guiding the diagnostic process towards congenital hypophosphatasia as well as allowed initiation of appropriate early treatment.

References

- Rathbun JC: Hypophosphatasia; a new developmental anomaly. *Am J Dis Child* 1948; 75: 822–831.
- Schneider RW, Corcoran AC: Familial nephrogenic osteopathy due to excessive tubular reabsorption of inorganic phosphate; a new syndrome and a novel mode of relief. *J Lab Clin Med* 1950; 36: 985–986.
- Rathbun JC, MacDonald JW, Robinson HMC et al.: Hypophosphatasia: a genetic study. *Arch Dis Child* 1961; 36: 540–542.
- Mornet E, Yvard A, Taillandier A et al.: A molecular-based estimation of the prevalence of hypophosphatasia in the European population. *Ann Hum Genet* 2011; 75: 439–445.
- <http://www.hypogenek.pl/spolecznosc.html>.
- Whyte MP: Hypophosphatasia: an overview for 2017. *Bone* 2017; 102: 15–25.
- http://www.sesep.uvsq.fr/03_hypo_mutations.php.
- Baujat G, Michot C, Le Quan Sang KH et al.: Perinatal and infantile hypophosphatasia: clinical features and treatment. *Arch Pediatr* 2017; 24 (5S2): 5S61–5S65.
- Castells L, Cassanello P, Muñoz F et al.: Neonatal lethal hypophosphatasia: a case report and review of literature. *Medicine (Baltimore)* 2018; 97: e13269.
- Warren RC, McKenzie CF, Rodeck CH et al.: First trimester diagnosis of hypophosphatasia with a monoclonal antibody to the liver/bone/kidney isoenzyme of alkaline phosphatase. *Lancet* 1985; 2: 856–858.
- Belachew D, Kazmerski T, Libman I et al.: Infantile hypophosphatasia secondary to a novel compound heterozygous mutation presenting with pyridoxine-responsive seizures. *JIMD Rep* 2013; 11: 17–24.
- Rothenbuhler A, Linglart A: Hypophosphatasia in children and adolescents: clinical features and treatment. *Arch Pediatr* 2017; 24 (5S2): 5S66–5S70.
- Mornet E: Hypophosphatasia. *Orphanet J Rare Dis* 2007; 2: 40.
- Gennero I, Conte-Auriol F, Salles JP: Laboratory diagnosis of hypophosphatasia. *Arch Pediatr* 2017; 24 (5S2): 5S57–5S60.
- Whyte M: Hypophosphatasia: enzyme replacement therapy brings new opportunities and new challenges. *J Bone Miner Res* 2017; 32: 667–675.
- Daniel AB, Saraff V, Shawn NJ et al.: Healthcare resource utilization in the management of hypophosphatasia in three patients displaying a spectrum of manifestations. *Orphanet J Rare Dis*. 2018; 13: 142.
- Whyte MP: Hypophosphatasia – aetiology, nosology, pathogenesis, diagnosis and treatment. *Nat Rev Endocrinol* 2016; 12: 233–246.
- Whyte MP, Zhang F, Wenkert D et al.: Hypophosphatasia: validation and expansion of the clinical nosology for children from 25 years experience with 173 pediatric patients. *Bone* 2015; 75: 229–239.
- <http://www.hppregistry.com/>.
- Högler W, Langman C, Gomes da Silva H et al.: Diagnostic delay is common among patients with hypophosphatasia: initial findings from a longitudinal, prospective, global registry. *BMC Musculoskelet Disord* 2019; 20: 80.
- European Medicines Agency: Strensiq. Available from: <https://www.ema.europa.eu/en/medicines/human/EPAR/strensiq>.

22. Charakterystyka Produktu Leczniczego Strensiq. Available from: https://www.ema.europa.eu/documents/product-information/strensiq-epar-product-information_pl.pdf.
23. Whyte MP, Rockman-Greenberg C, Ozono K et al.: Asfotase alfa treatment improves survival for perinatal and infantile hypophosphatasia. *J Clin Endocrinol Metab* 2016; 101: 334–342.
24. STRENSIQ® (asfotase alfa) injection, for subcutaneous use. Initial U.S. Approval: 2015. Available from: https://alexion.com/Documents/Strensiq_USPI.aspx.
25. Whyte MP, Greenberg CR, Salman NJ et al.: Enzyme-replacement therapy in life-threatening hypophosphatasia. *N Engl J Med* 2012; 366: 904–913.
26. Libura M, Władusiuk M, Małowicka M et al.: Choroby rzadkie w Polsce. Stan obecny i perspektywy. Uczelnia Łazarskiego, Warszawa 2016. Available from: https://www.lazarski.pl/fileadmin/user_upload/dokumenty/instytutu/Choroby_rzadkie_w_Polsce_Stan_obecny_i_perspektywy.pdf.
27. Asfotase alfa (Strensiq). Canadian Agency for Drugs and Technologies in Health, Ottawa (ON) 2017. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK476055/>.