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Disturbances of calcium phosphate metabolism in childhood endocrinopathies – diagnostic problems

Zaburzenia przemiany wapniowo-fosforanowej w endokrynopatiach wieku rozwojowego – problemy diagnostyczne

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The availability of densitometry, determinations of concentration levels of vitamin D, bone turnover markers, and FGF23, combined with progress in genetic diagnostic management allow for an increasingly precise evaluation of developmental-age calcium phosphate metabolism disturbances. It should be remembered that 90% of the peak bone mass is formed by the end of puberty; thus, a proper diagnosis and treatment of disturbances of the calcium phosphorus metabolism in children are a decisive factor affecting the risk of fractures and comfort of life in adults. Attention has recently been focused on the necessity of vitamin D supplementation and on monitoring vitamin D concentration levels, and an increasing number of reports address the association between the VDR gene polymorphism and numerous diseases, but a thorough analysis of the calcium phosphate metabolism is still performed too rarely. Proof may be found in the delayed diagnosis of hyperparathyroidism in children; in spite of the fact that the condition is markedly less common in children as compared to adults, in the former patients its course is highly dramatic. The incidence of primary hyperparathyroidism in children is 2–5/100,000, while other authors report 1/200–300,000, whereas in adults the incidence rate is 1/1000 individuals [1–3]. Contrary to adults, in the majority of children – as many as 79–99% – the course of the disease is fully symptomatic, which may result from a higher dynamics of metabolic processes and faster bone turnover in the growth period. Numerous authors emphasize the role of erroneous and markedly delayed diagnostic management of hypercalcaemia symptoms, with the time lapse from the appearance of the initial symptoms to establishing the diagnosis ranging from several months to 2–3 years, which was also confirmed by our observations [2–4]. Children demonstrating weakness and body mass loss, polyuria, polydipsia, bone deformities, and fractures are not subjected to calcium and phosphate level determinations for many months [1, 2]. Prolonged hypercalcaemia may result in secondary complications that are seen in as many as 44% of children with primary hyperparathyroidism; such complications include nephrocalcinosis, peptic ulcers, arterial hypertension, and osteoporosis and they persist in spite of the primary condition having been cured. In this group of patients, an important diagnostic element is a genetic analysis that rules out genetic mutations of the following genes: *MEN 1* (the MEN1 syndrome), *RET* (MEN 2A), *CDC73* (hyperparathyroidism, jaw tumour syndrome), and *GCM2* (familial isolated hyperparathyroidism) [1, 4, 5].

Neonatal severe hyperparathyroidism (NSHPT) is associated with a homozygotic mutation that inactivates the *CASR* calcium receptor; its course involves dramatic hypercalcaemia, extreme PTH concentration levels, and parathyroid hyperplasia. The condition requires treatment to be introduced in the first hours of life; thanks to genetic testing the condition is increasingly properly diagnosed and treated. On the other hand, heterozygotic mutations of *CASR*, as well as *GNA11* and *AP2S1*, result in mild familial hypocalciuric hypercalcemia (FHH) that is often diagnosed only in an adult [5].

Due to attacks of manifest tetany, the diagnostic management of hypoparathyroidism (HP) is usually more efficient. Nevertheless, diagnostic problems continue to emerge; they involve patients with positive tetany test results in the case of normocalcaemic tetany and are also encountered in the case of establishing a differential diagnosis discerning between epilepsy, which is often a complication of chronic hypocalcaemia, and tetany in hypoparathyroidism. In the neonatal period and infancy, congenital hypoparathyroidism is more frequently detected as an element of syndromes and less commonly as an

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isolated condition. The most frequent condition seen in older children and adults is acquired hypoparathyroidism: postoperative hypoparathyroidism (0.5–6.6% of permanent HP following total strumectomy) and autoimmune HP, either isolated or as an element of polyendocrinopathy. Congenital isolated hypoparathyroidism may be caused by a sporadic or a familial mutation (genetic inheritance of AD, AR, XR) which leads to parathyroid agenesis (mutation of the genes responsible for parathyroid development, i.e. *GCM2-6p24.2* and *SOX3-2p25.3 Xq27.1*) or by a mutation resulting in disturbances of PTH synthesis and secretion (*prepro PTH -11p15* gene mutation) [6]. Congenital HP is more often seen as an element of congenital conditions: Di George syndrome (*del.22q11.2*); HDR syndrome (AD, hypoparathyroidism, sensorineural hearing loss, renal dysplasia), Kenny-Caffey and Sanjad-Sakati syndromes (*TBC 1q42-q43*), or mitochondrial DNA disorders (Kearn-Sayre syndrome, MELAS, MTPDS) [6].

In some patients with diagnosed idiopathic hypoparathyroidism the cause of hypocalcaemia is a mutation activating the Ca-SR-ADHH calcium receptor (*CASR;* AD *3q13*), which results in constitutive activation of the calcium receptor in the parathyroids and kidneys; consequently, no PTH ejection occurs in spite of low serum calcium levels and hypercalciuria. Familial hypocalcaemia and hypercalciuria may be asymptomatic; nevertheless, some patients require supplementation treatment starting in the very first days of life due to recurrent tetany attacks. The availability of genetic testing addressing the calcium receptor-activating mutation allows for precise modification of treatment that should be individually planned based on the calcium phosphate product (Ca x P) and 24-h calciuria monitoring in view of the high risk of nephrocalcinosis seen in these patients.

Diagnostic problems are seen in patients with pseudohypoparathyroidism (PHP). Due to TSH resistance that is manifested early in life, many patients continue for years to be diagnosed with congenital hypothyroidism and, in spite of their demonstrating phenotypic traits of Albricht syndrome, are treated solely with thyroxin [7, 8]. Chronic hypocalcaemia may result in contractures of the Achilles tendons, epilepsy, and Fahr's syndrome. Taking into consideration the clinical and molecular overlapping of various PHP subtypes and following the discovery of acrodysostosis-accompanied defects in such genes as *PRKAR1A* and *PDE4D,* a new classification of disorders of PTH/PTHrP (iPPSD) signalization and inactivation was proposed in 2016. Clinical and hormonal symptoms characteristic of PHP were defined, and numbering was introduced that would be specific for each molecular alteration, i.e. iPPSD1 – the mutation involving function loss in *PTH1R*, iPPSD2 – the mutation involving function loss in *GNAS*, iPPSD3 – methylation defects in a single or multiple differential methylation regions, iPPSD4 – the *PRKAR1A* mutation, iPPSD5 – the *PDE4D* mutation, iPPSD6 – the *PDE3A* mutation, and iPPSDx – no identified molecular defect present [8].

Parathyroid function disorders are not the only finding that requires evaluation of the calcium phosphate metabolism. Hypercalcaemia may be also present in such acute hormonal disturbances as thyrotoxicosis and adrenal insufficiency, while chronic hormonal disorders reflect the status of skeletal mineralization. Hypercortisolaemia, hypogonadism (especially when the diagnosis is delayed), and uncontrolled diabetes should indicate the necessity of determining bone mineral density [9, 10]. Apart from hypogonadotropic hypogonadism, additional indicators suggesting the same need in female patients with anorexia nervosa are protein-caloric malnutrition and hypercortisolaemia. Substitution treatment with testosterone and many years of oestrogen-progesterone therapy should be monitored by densitometry of the spine. Early detection and treatment of thyrotoxicosis decreases the risk of fractures, but the alterations in the microarchitecture and biomechanical properties render the bones less resistant to fractures [10]. Long-term administration of suppressive doses of thyroxin following the treatment of thyroid cancer results in a decrease in bone mineral density, but to date no recommendations for subjecting children with hormonal disturbances to densitometry have been formulated; the procedure continues to be performed too infrequently, and many of our patients enter adulthood with a decreased bone mass and an increased risk of fractures.

While consulting children with malabsorption disorders, treated with steroids, immobilized for prolonged periods, with paresis involving the extremities, rheumatic diseases, and cancer we – the specialists in endocrinology – should remember about evaluation of the calcium phosphate metabolism, substitution treatment with calcium and vitamin D_3 preparations, as well as densitometry, which must always be interpreted in relation to the bone age of the child.

Summing up, thorough diagnostic management and appropriate treatment of parathyroid diseases in children require diagnostic genetic testing, while patients with other chronic or poorly controlled hormonal disturbances that affect bone mineralization should be monitored by densitometry.

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