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Iatrogenic hypoparathyroidism – not only after thyroid surgery…

Jatrogenna niedoczynność przytarczyc – nie tylko strumektomia...

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Słowa kluczowe

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Summary

The most common causes of hypoparathyroidism are iatrogenic: mostly thyroid or parathyroid surgery. Much less frequently HypoPT is caused by an extensive oncological surgical procedure e.g. because of larynx or upper throat cancer, or external neck radiotherapy, e.g. in the case of lymphoma. In those particular cases, both patients and doctors focus their attention on the oncological nature of the disease itself, which often results in neglect of other health hazards, and potentially poor prognosis, and short survival time in those cases additionally mask the problem. However, in individual patients cured from cancer, unrecognized hypoparathyroidism can significantly affect their health and quality of life. Two such cases are presented. To our knowledge, the cases presented by us are the first cases diagnosed after such a long time after laryngectomy or radiation therapy. This may indicate that other patients undergoing such treatment could be exposed to this rare complication as well, regardless of the time that elapsed after the treatment. This implies the need for systematic monitoring of serum calcium, as well as for enhanced diagnosis in the case of even the slightest clinical suspicion of hypoparathyroidism.

Streszczenie

Najczęstszą przyczynę niedoczynności przytarczyc stanowi leczenie operacyjne chorób tarczycy lub przytarczyc. Znacznie rzadziej niedoczynność przytarczyc jest wynikiem rozległych zabiegów chirurgicznych z przyczyn onkologicznych, np. z powodu raka krtani czy górnej części przełyku, lub radioterapii szyi, np. w przypadku chłoniaka. W tych szczególnych przypadkach onkologiczny charakter samej choroby skupia na sobie większość uwagi zarówno pacjentów, jak i lekarzy, co często prowadzi do zaniedbywania innych zagrożeń dla zdrowia, zaś potencjalnie złe rokowania i krótki czas przeżycia w tych przypadkach dodatkowo maskują problem. Jednak u poszczególnych pacjentów wyleczonych z raka, nierozpoznana niedoczynność przytarczyc może w dłuższej perspektywie wywierać istotny wpływ na zdrowie i jakość życia. Przedstawiamy dwa takie przypadki. Według naszej wiedzy, przedstawione przez nas przypadki są pierwszymi, rozpoznanymi po tak długim czasie po laryngektomii lub radioterapii. Może to oznaczać, że inni pacjenci poddani takiemu leczeniu mogą być podobnie narażeni na to rzadkie powikłanie, bez względu na okres czasu, który upłynął od terapii. Oznacza to konieczność systematycznego monitorowania kalcemii, jak również wykonywania rozszerzonej diagnostyki w przypadku najmniejszego podejrzenia klinicznego niedoczynności przytarczyc.

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INTRODUCTION

Hypoparathyroidism (HypoPT) is a disease of the endocrine system characterized by low serum calcium and inadequately low PTH level. It is a rare disease, entered on the list of orphan diseases by the European Commission in January 2014 (UE/3/13/1210; http://www.ema.europa.eu/ema/index.jsp?curlZpages/medicines/human/orphans/2014/01/human_orphan_001301.jsp&midZWC0b01ac058001d12b) and the only classical hormonal insufficiency, which is not treated by supplementing the missing hormone (PTH) (1-4). Spontaneous HypoPT may be a disease with autoimmune pathogenesis where the cause is a mutation of the autoimmune regulatory gene (AIRE) (5). In addition, there are many other rare genetic diseases that can cause HypoPT: either as part of a larger complex of diseases (e.g., DiGeorge syndrome), or as a single endocrinopathies (6). However, the most common caus-

es of chronic HypoPT are of iatrogenic origin: surgical treatment of thyroid and parathyroid diseases (7, 8).

Much less frequently HypoPT is caused by an extensive oncological surgical procedure e.g. because of larynx or upper throat cancer, or external neck radiotherapy, e.g. in the case of lymphoma. In those particular cases, both patients and doctors focus their attention on the oncological nature of the disease itself, which often results in neglect of other health hazards, and potentially poor prognosis, and short survival time in those cases additionally mask the problem. However, in individual patients cured from cancer, unrecognized hypoparathyroidism can significantly affect their health and quality of life (9). Two such cases are presented.

CASE 1

A 84-year-old male patient with a tracheotomy after surgical treatment of laryngeal cancer 30 years earlier, was admitted to the internal medicine ward diagnosed with pneumonia. Due to the very long period of time that has elapsed since the surgery, detailed information on the carried out procedure could not be obtained. The patient denied to have the history of radiotherapy. The immediate cause of hospitalization was a loss of consciousness for a few minutes while waiting for the medical appointment with the primary care physician. According to the statement of the patient, similar episodes have occurred many times in the past few years, but he did not report this problem to the doctor. The faints occurred mainly in stressful situations, and they were not connected with the changes in body position, without cardiovascular complaints, convulsions, involuntary urination, with no obvious prodromal symptoms. After combating the infection, the doctors started to diagnose the faints. Laboratory tests have shown the profound hypocalcemia: Ca = 1.31 mmol/l, ionized Ca = 0.73 mmol/l, and hypocalciuria Ca_u = 1.11 mmol/24 h; hyperphosphatemia P = 1.49 mmol/l, and an extremely low concentration of parathyroid hormone intact in the serum (iPTH) = 9.34 pg/ml. Diagnosis: secondary hypoparathyroidism following the laryngectomy. There were no classic signs of tetanic symptoms (Trousseau, Chvostek signs), however there were other clinical features of long hypocalcemia: prolongation of QT interval (QTc = 475 ms) in the electrocardiogram (ECG) and supraventricular and ventricular arrhythmias in 24-hour Holter ECG. A CT scan revealed the presence of massive calcification in the brain and cerebellum (as in Fahr's disease) (fig. 1), but without clinical neurological disorders or pathologies in the electroencephalographic recordings. The examination showed cataract affecting both eyes. An attempt was made to perform a psychological evaluation, but due to significant difficulties in communication with the patient (hearing loss, speech disorders), as well as the advanced age, it was difficult to objectively assess his cognitive abilities. Treatment consisted in administration of calcium carbonate – 1000 mg three times a day, and alfacalcidol – 1 microgram per day. After two months of treatment a satisfactory improvement in the patient's condition was achieved, fainting did not reappear, and the patient observed a significantly better efficiency of movement and improvement of mood. Laboratory studies confirmed improvement of serum calcium level (2.13 mmol/l) and normalization of phosphate level (1.11 mmol/l). ECG showed normalization of QT interval (QTc = 435 ms).

CASE 2

A 54-year-old male, at the age of 26 treated for non-Hodgkin's lymphoma with external irradiation of the neck and mediastinum, was repeatedly hospitalized in the last few years due to attacks of breathlessness with wheezing, resembling asthma. Because the provocation tests showed no evident bronchial hyperresponsiveness, the symptoms were classified as psychosomatic ones, especially that the patient connected the occurrence thereof with emotional stress or physical activity. At the same time, the psychological study revealed personality disorders of depressive and hypochondriacal type – with a serious anxiety and significant social dysfunction, especially in the execution phase. Only the accidental serum calcium level test showed severe hypocalcemia Ca = 1.29 mmol/l. The patient was referred to an endocrinologist. The results of the laboratory tests confirmed the diagnosis – it was radiation-induced hypoparathyroidism: Ca = 1.31 mmol/l; Cau = 0.93 mmol/24 h; iP = 1.61 mmol/l; iPTH = 8.1 pg/ml. The patient was also diagnosed with the concomitant hypothyroidism: TSH = 28.6 uIU/ml; FT4 = 8.75 pmol/l. The presence of calcification in the structures of the brain, particularly in the basal ganglia was also demonstrated in this patient. Application of usual therapy (alfacalcidol 1.25 ug/d + $CaCO_3$ 6 x 1000 mg + L-thyroxine 100 ug/d) restored normal biochemical balance, and the patient's condition significantly improved, symptoms of bronchial smooth muscle contraction did not happen again. Also the patient's mental state and ability to function in society was improved.

COMMENTS

Thyroid operations are associated with hypokalemia, mainly due to temporary or permanent impairment or damage to the parathyroid vascularisation (8). Transient hypocalcemia is observed in 16-55% of cases following thyroidectomy. In a recently published study, from out of 50% of patients in whom postoperative hypocalcemia was observed, 38% suffered from hypoparathyroidism for over a month (10). In another retrospective study, transient hypocalcemia was observed in 35% of patients after total thyroidectomy, 3% had persistent hypocalcemia for 6 months after the surgery, and in 1.4% permanent hypoparathyroidism was diagnosed two years after the surgery (11). The

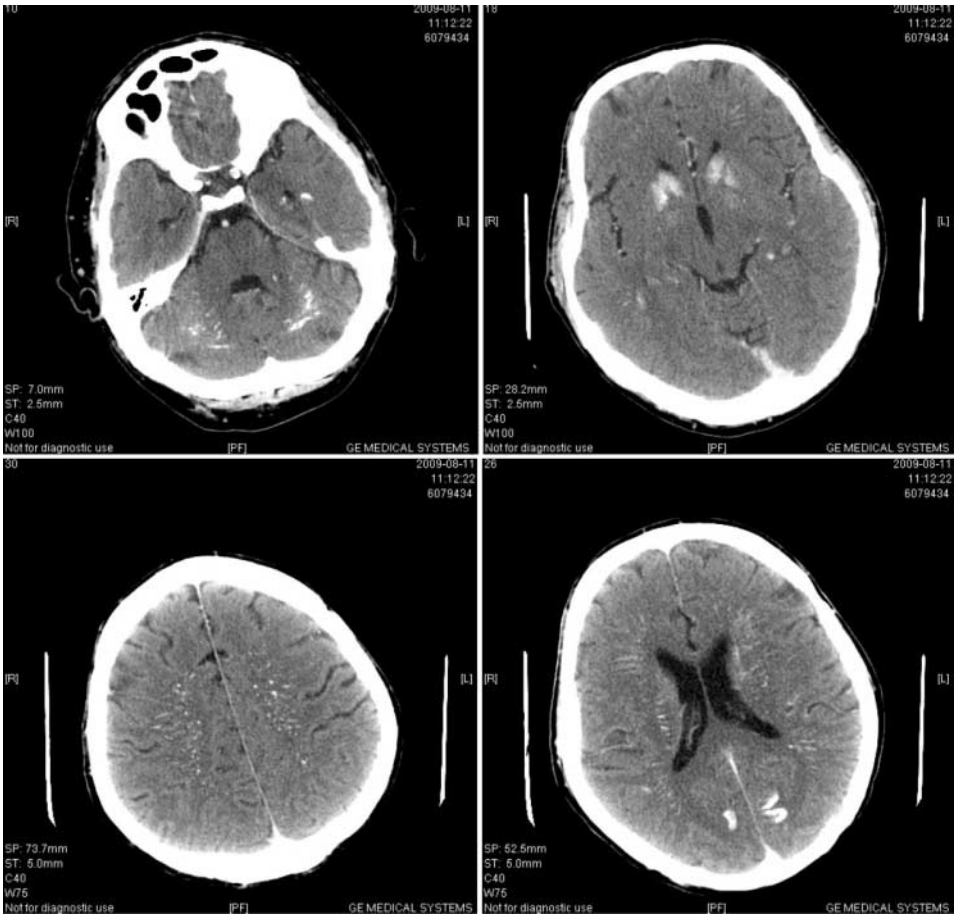

Fig. 1. Massive calcification of the brain with hypoparathyroidism.

type and extent of the surgery is associated with a risk of hypocalcemia: it is the highest after total thyroidectomy including excision of the lymph nodes (8, 12). Transient hypocalcemia was observed more frequently after thyroidectomy in patients with the Graves-Basedow disease, than in those with a non-toxic goiter, however the incidence of permanent hypoparathyroidism did not differ between the groups (13).

In patients undergoing resection of the larynx or pharyngectomy and laryngectomy due to cancer of the larynx, complete or partial resection of the thyroid gland is often necessary. Even in the case of the less advanced cancer, at least mobilization of the thyroid gland is necessary, with accompanying damage to the vasculature, in general also inferior thyroid arteries ligation or at least their branches is required. This explains why hypocalcemia often occurs as a result of these procedures, however, it is rarely reported and it is not perceived as a major problem. Basheeth et al. described the occurrence of biochemical hypocalcaemia in 43% of patients after laryngectomy within the first week after surgery; however, symptomatic hypocalcemia occurred in 15% of cases only (14). At the same time bilateral excision of the cervical lymph nodes, previous treatment with radiotherapy, and especially the advancement of the T-classification of the tumour were significant predictors of hypocalcemia. Interestingly, there was no correlation between the occurrence of hypocalcemia and the scope of the pharyngectomy, excision or leaving the thyroid gland intact and the presence of the preoperative tracheotomy.

However, very little is known about the persistence of hypokalemia and parathyroid dysfunction in a few or even many years after the surgery. Lo Galbo et al. described the presence of persistent hypocalcaemia in 7.3% of patients who underwent laryngectomy, 24 months after the intervention (15). On the other hand, Thorp et al. identified hypoparathyroidism (with or without symptomatic hypocalcemia) in 60% of patients with cancer of the larynx or pharynx who survived five years after treatment (16). At the same time they claimed that hypoparathyroidism occurred more frequently in patients treated with radiotherapy – alone or in combination with the surgery, than in the group of patients treated surgically only.

Radiation of the neck area is a well-documented factor for delayed hypothyroidism, however the knowledge about the impact of radiation therapy on the parathyroid gland is poor, and hypoparathyroidism seems to be a very rare complication after irradiation. Four parathyroid glands are subjected to radiation during radiotherapy of the head and neck cancer, including lymphoma, Hodgkin's disease, and thyroid cancer. Because of their location, parathyroids are also irra-

diated during the therapy ^{131}I of the thyroid diseases. However, the chief cells of the parathyroid glands show a very high resistance to radiation in terms of loss of function or necrosis (17, 18). Immediate post-radiation destruction of the parathyroid chief cells, causing acute, symptomatic hypoparathyroidism, seems to be extremely rare, in fact it is so poorly documented that its probability is called into question.

Delayed post-radiation hypoparathyroidism also seems to be rare. Eipe et al. described a single patient with low serum calcium and tetany, diagnosed 5 months after the treatment 15.7 MCi ^{131}I (19). Glazbrook described the permanent hypoparathyroidism in seven patients, four of whom received small doses ^{131}I, two underwent a conventional radiotherapy with an external beam and one underwent both forms of treatment (20). Two patients who received external beam therapy, suffered from neck cancer with metastases. All patients who received the treatment with ^{131}I, had earlier undergone thyroidectomy.

Apart from the fact that the probability of an explicit, delayed post-radiation hypoparathyroidism seems to be low, the actual number of patients involved may be even less – due to the natural course of the underlying disease and short survival time.

A significant proportion of patients with hypoparathyroidism in the study of Lo Galbo (15) were characterized by normocalcemia, with inappropriately low concentration of parathyroid hormone – in literature referred to as subclinical or normocalcemic hypoparathyroidism or as hypoparathyroidism with partial PTH deficiency (20). So it seems that, just as in the course of an autoimmune disease, after laryngectomy or radiotherapy, damage to the parathyroid glands may proceed gradually, initially manifesting only as a decrease in the provision of PTH secretion in response to declining calcium levels, and only after some time leading to severe hypocalcemia. Such chronic hypocalcemia is often well tolerated and difficult to identify (4). A typical tetany is rare here, it may more often take atypical forms, also in smooth muscles: colic attack, functional disorders of urination or bronchospasm. Patients complain of constant fatigue, muscle weakness, emotional instability and anxiety (22, 23). Long-term, undiagnosed hypoparathyroidism leads to calcifications in the basal ganglia and other brain structures (24). It can be can be manifested by pyramidal tracts disorders, particularly extrapyramidal, mostly hypo- and hyperkinetic movement disorders, or cause convulsive attacks, which are usually bizarre and do not respond to standard treatment with atypical changes in EEG record (25, 26). Deterioration of intellectual and cognitive abilities, including full dementia – is typical here. Among other psychiatric disorders – pseudo neurotic disorders, anxiety and depression, rarely psychotic disorders – appear frequently. Ectodermic lesions occur: fragility of nails, dry skin and alopecia, a typical ophthalmic complication is a rapidly progressing subcapsular cataract (4, 23).

CONCLUSIONS

Despite the increasing knowledge of the post-radiation and postoperative phenomenon of hypocalcemia, there is still little data on the long-term observation of patients at risk. In the literature there are cases of hypoparathyroidism diagnosed even 40 years after thyroidectomy (27). To our knowledge, the cases presented by us are the first cases diagnosed after such a long time after laryngectomy or radiation therapy. This may indicate that other patients undergoing such treatment could be exposed to this rare complication as well, regardless of the time that elapsed after the treatment. This implies the need for systematic monitoring of serum calcium, as well as for enhanced diagnosis in the case of even the slightest clinical suspicion of hypoparathyroidism.

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