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Analysis of Prior Medical Histories of Patients Operated on for Primary Hyperparathyroidism

Analiza przeszłości chorobowej chorych operowanych z powodu pierwotnej nadczynności przytarczyc

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Abstract

Objectives. Selecting those symptoms and signs associated with primary hyperparathyroidism that most frequently masked their main cause and had been treated as separate disease entities.
Material and Methods. The prospective study comprised 54 patients (48 women and 6 men) aged 47.4 ± 15.7 years who underwent surgery for primary hyperparathyroidism from 1999 to 2004. Patients with MEN syndromes were excluded. The following data from problem-oriented history and previous discharge summaries were analyzed: 1) previously reported symptoms and treatment of such diseases as osteoporosis, rheumatoid arthritis, nephrolithiasis, peptic ulcer, pruritus, pancreatitis, diabetes, arrhythmia, bone tumors, decreased muscle strength, and lowered psychomotor drive or intellectual fitness and 2) time from the first symptoms to the final diagnosis by an endocrinologist and the operation.
Results. The occurrence of different clinical masks of P-HPT was irregular. Most frequently the patients had previously been diagnosed as having osteoporosis inappropriate to age, non-specific bone and joint pains, nephrolithiasis, moderate peptic ulcer, and low psychomotor drive or intellectual fitness. The longest period of treatment before the diagnosis of P-HPT was due to nephrolithiasis (up to 17 years, including more than a dozen operations, PCNLs and ESWLs), peptic ulcer, and arthritic pains. Early-onset osteoporosis led to a quick diagnosis of P-HPT (usually within 1 year), but in elderly patients it would be underestimated by GPs. Two patients had been operated on for suspected bone tumors, and the nature of the disease was elucidated by the histological diagnosis of a brown tumor. Non-specific neurological symptoms did not usually make the patients seek medical advice.
Conclusions. The symptoms and signs that build up the clinical picture of primary hyperparathyroidism are still usually treated by GPs and various specialists as separate disease entities, while their main cause remains undiagnosed for a long time. It is advisable that all patients who present with the symptoms and signs described above have blood tests for calcium level and be referred to an endocrinologist for consultation, which could direct the diagnostics in the right way (**Adv Clin Exp Med 2007, 16, 2, 257–262**).

Key words: primary hyperparathyroidism, parathyroidectomy, symptoms and signs.

Streszczenie

Cel pracy. Wyodrębnienie dolegliwości i objawów w przebiegu pierwotnej nadczynności przytarczyc, które najczęściej maskowały swoją główną przyczynę i były leczone jako samodzielne jednostki chorobowe.
Materiał i metody. Badaniami prospektywnymi objęto 54 chorych (48 kobiet i 6 mężczyzn) w wieku 47,4 ± 15,7 lat, operowanych w latach 1999–2004 z powodu pierwotnej nadczynności przytarczyc (P-HPT). Z badań wyłączono chorych z zespołami MEN. Na podstawie danych z ukierunkowanego wywiadu i dokumentacji leczenia zanalizowano: 1) dotychczasowe objawy i leczenie takich chorób, jak: osteoporoza, choroba zwyrodnieniowa stawów, kamica moczowa, choroba wrzodowa, świąd skóry, zapalenie trzustki, cukrzyca, zaburzenia rytmu serca, guzy kości, osłabienie siły mięśniowej, a także obniżenie napędu psychomotorycznego i sprawności intelektualnej; 2) czas, jaki upłynął od wystąpienia pierwszych objawów do ustalenia rozpoznania przez endokrynologa i operacji.
Wyniki. Maski P-HPT występowały z różną częstością. U operowanych chorych najczęściej rozpoznawano uprzednio nieadekwatną do wieku osteoporozę, nieswoiste dolegliwości stawowe, kamicę moczową, chorobę wrzodową o umiarkowanym nasileniu oraz obniżenie sprawności intelektualnej lub napędu. Przez najdłuższy czas przed rozpoznaniem P-HPT pacjenci byli leczeni, nieskutecznie, z powodu kamicy moczowej (nawet przez 17 lat, także za

pomocą kilkunastu zabiegów operacyjnych, PCNL i ESWL), choroby wrzodowej i dolegliwości wiązanych z chorobą zwyrodnieniową stawów. Osteoporoza w młodym wieku doprowadzała do szybkiego rozpoznania P-HPT (zwykle w ciągu 1 roku), a w wieku starszym bywała bagatelizowana przez lekarzy pierwszego kontaktu. 2 pacjentki z podejrzeniem nowotworu kości były leczone ortopedycznie, dopiero rozpoznanie histopatologiczne guza brunatnego wyjaśniło przyczynę choroby. Nieswoiste objawy neurologiczne najczęściej nie skłaniały do zasięgania porady lekarza.

Wnioski. Objawy składające się na obraz chorobowy pierwotnej nadczynności przytarczyc są bardzo często leczone przez lekarzy podstawowej opieki zdrowotnej i specjalistów poszczególnych dziedzin jako samodzielne jednostki chorobowe, podczas gdy ich główna przyczyna pozostaje przez dłuższy czas nierozpoznana. U wszystkich pacjentów z opisanymi dolegliwościami powinno być wskazane rutynowe oznaczanie stężenia wapnia i konsultowanie się z endokrynologiem, co ułatwiłoby wczesne skierowanie diagnostyki we właściwym kierunku (**Adv Clin Exp Med 2007, 16, 2, 257–262**).

Słowa kluczowe: pierwotna nadczynność przytarczyc, paratyreoidektomia, objawy.

In Western Europe and the USA, i.e. in countries where blood tests for serum calcium and phosphates are a part of routine practice, primary hyperparathyroidism (P-HPT) is currently diagnosed in 1–3‰ of the population [1–3]. In Poland the correct diagnosis of this disease is still made much less frequently; its incidence in our country is estimated as 10–30/100,000 [1, 2, 4]. This may be explained by the very irregular pattern of the clinical picture of primary hyperparathyroidism and by the fact that its course is masked by a number of other, more common diseases, which are therefore treated inadequately with poor result. The clinical masks of primary hyperparathyroidism, both primary and secondary, include nephrolithiasis, peptic ulcer, osteoporosis, rheumatoid arthritis, bone tumors, pancreatitis, hypertension and arrhythmia, diabetes, pruritus, decreased muscle strength, lowered psychomotor drive or intellectual fitness, and even psychic disorders. The full set of symptoms and signs is exceptionally rare. The disease usually takes a single-organ course, most frequently involving the kidneys or bones; less often, two or more clinical masks appear together [1–8]. In its early phase, P-HPT may also be asymptomatic for a long time, presenting as moderate hypercalcemia; in Western countries this form of P-HPT is nowadays found in as many as about 50% cases [3, 9].

Bone tissue is one of the main targets of parathormone (PTH), as are the kidneys and the gastrointestinal tract. Hyperparathyroidism brings about decalcification of the bones. In its early stage the disease presents on X-ray as subperiosteal resorption, best visible particularly within the phalangae of the hands. Generalized osteoporosis with nonspecific long bone pains develops later. In the advanced stage it takes on the form of osteitis fibrosa cystica generalisata, bone deformities, pathological fractures, bone cysts, and brown tumors. Calcium deposits may imitate the symptoms of gout, arthritis, or other joint diseases [1–4, 7, 10]. Pain and deformities of bones and joints are commonly attributed to other causes, typically treated by rheumatologists and orthopedic surgeons. Bone tumors and cysts, on the other hand, are primarily suspected of malignancy; they also require differentiation from fibrous dysplasia of the bone and Paget's disease. Osteoporotic changes should be differentiated from primary or secondary osteoporosis.

The renal pathology of P-HPT includes nephrolithiasis, renal diabetes insipidus, or even nephrocalcinosis, due to high concentration of calcium and phosphates in the urine. Nephrolithiasis occurs in about 2/3 of patients with P-HPT. It usually presents with frequent attacks of renal colic, though it may have the form of staghorn calculi with no significant pain. Renal stones are recurrent despite medical and surgical treatment; in time this may lead to pyelonephritis and renal insufficiency. In some patients, renal diabetes insipidus may develop due to decreased sensitivity of tubular receptors to antidiuretic hormone induced by hypercalcemia [1, 2, 4, 6, 11–13].

The elevated plasma calcium concentration stimulates gastrin secretion, which leads to peptic ulcer resistant to treatment [1–3]. Additionally, nausea and vomiting may also occur as well as loss of appetite. High calcium level may inhibit peristalsis, which presents as constipation; single cases of ileus have even been reported [1–3].

High calcium level promotes pancreatic stones and acute pancreatitis [1–3].

The influence of hypercalcemia on the central nervous system presents with lowered psychomotor drive and intellectual fitness, headache, difficulty in concentration, apathy, and depression to various degrees. In some rare cases, psychosis may even occur. There are also noticeable peripheral neuromuscular disorders, such as decreased muscle strength, adynamia, and fatigability [1–3, 14, 15].

Progressive calcification of the arterial wall due to high hypercalcemia leads to hypertension. In time, cardiac valves also become calcified and

the myocardium is involved. Electrolyte imbalance with a prevalence of calcium ions may result in bradycardia, requiring implantation of a pacemaker in the most severe cases [1, 2, 16].

A higher incidence of diabetes mellitus or glucose intolerance has been reported among patients with P-HPT compared with the general population [3, 4, 12].

In some patients, deposits of calcium phosphates crystallize in soft tissues, particularly the skin, which is the cause of itching [2–4].

The aim of this study was to select those symptoms and signs associated with primary hyperparathyroidism that most frequently masked their main cause in our patients and had been initially treated as separate disease entities.

Material and Methods

Fifty-four patients were included in the prospective study, 48 women and 6 men (female to male ratio: 8:1) who underwent surgery for primary hyperparathyroidism (P-HPT) from 1999 to 2004. The average age at operation was 47.4 ± 15.7 years. Sporadic patients with MEN syndromes were excluded from the study. Taking into account the data from problem-oriented history and any previous discharge summaries, the symptoms and treatment of the following diseases were analyzed: osteoporosis, rheumatoid arthritis or similar problems, nephrolithiasis, peptic ulcer, pruritus, pancreatitis, diabetes, bone tumors, decreased muscle strength, and lowered psychomotor drive or intellectual fitness. The time that elapsed from the onset of the first symptoms to the final diagnosis by an endocrinologist and the operation was also evaluated.

Table 1. Incidence of particular symptoms and signs of primary hyperparathyroidism

Tabela 1. Częstość występowania poszczególnych objawów pierwotnej nadczynności przytarczyc

Symptoms and signs of primary hyperparathyroidism (Objaw pierwotnej nadczynności przytarczyc)	No. of patients (Liczba chorych) n (%)
Osteoporosis – inappropriate to age Osteoporoza – nieadekwatna do wieku)	36 (67)
Non-specific bone and/or joint pains (Nieswoiste dolegliwości kostno--stawowe)	31 (57)
Nephrolithiasis (Kamica moczowa)	28 (52)
Peptic ulcer (Choroba wrzodowa)	15 (28)
Pruritus (Świąd skóry)	1 (2)
Pancreatitis (Zapalenie trzustki)	2 (4)
Bone tumors (histologically – brown tumor) (Guzy kości (histologicznie – guz brunatny))	2 (4)
Decreased muscle strength (Osłabienie siły mięśniowej)	13 (24)
Lowered psychomotor drive or intellectual fitness (Obniżenie napędu psychomotorycznego lub sprawności intelektualnej)	24 (44)
Arrhythmia (Zaburzenia rytmu serca)	0
Diabetes (Cukrzyca)	0
All the above occurring simultaneously (Wszystkie ww. objawy jednocześnie)	0

Results

The occurrence of different clinical masks of P-HPT was irregular (Tab. 1, Fig. 1). The patients who underwent parathyroidectomy had been most commonly diagnosed as having osteoporosis inappropriate to age (36 of 54, 67%), non-specific bone and/or joint pains (31, 57%), nephrolithiasis (28, 52%), and uncomplicated peptic ulcer (15, 28%). Muscular adynamia, perceived as weakness and fatigability, was also a quite frequent symptom (13, 24%), as well as low psychomotor drive or intellectual fitness (24, 44%). The patients were often unaware of these symptoms until the moment they quickly subsided after the operation. Two female patients (2, 4%) in a very advanced phase of hyperparathyroidism had undergone prior surgery for suspected bone tumors (one of a rib and the other of the maxilla); only the histological diagnosis of a brown tumor explained the cause of the disease. Some manifestations of hyperparathyroidism, i.e. pruritus and pancreatitis, were found in the analyzed group sporadically, in 1–2 individuals (pruritus 1, 2%; pancreatitis 2, 4%). No significant arrhythmias were noted that could be associated with high hypercalcemia. Diabetes mellitus or glucose intolerance was also not demonstrated in any of this group. None of the patients with parathyroidectomy had the full set of the described symptoms and signs.

Hypertension, although quite common among patients who undergo parathyroidectomy, was not included in our analysis of clinical masks of P-HPT as the etiology of hypertension is complex and too difficult to be diagnosed precisely in

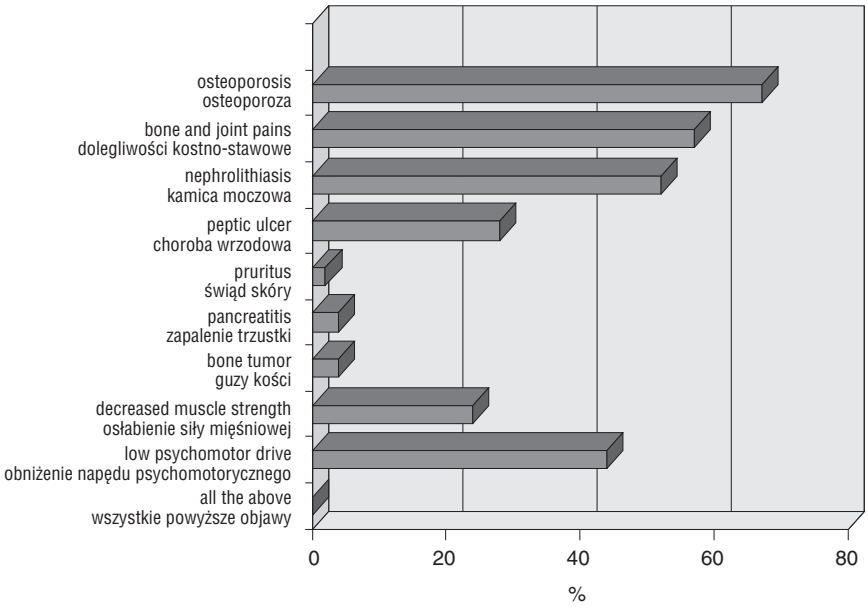

Fig. 1. Incidence of particular symptoms and signs of primary hyperparathyroidism

Ryc. 1. Częstość występowania poszczególnych objawów u operowanych chorych z pierwotną nadczynnością przytarczyc

a surgical department as secondary to P-HPT, while hypertension itself is widespread in the population. It was observed, however, that in the early postoperative period, some patients had relatively lower blood pressure than before while on the same doses of hypotensive drugs. Polyuria was not included in the analysis, either, as none of the patients complained of high urine output and no adequate measurements had been made before.

The longest period of ineffective treatment before the eventual diagnosis of P-HPT was due to recurrent nephrolithiasis in one patient for as long as 17 years, whose treatment included more than a dozen operations, PCNLs (percutaneous nephrolithotripsy), and ESWLs (extracorporeal shock wave lithotripsy). Peptic ulcer and bone pains erroneously attributed to arthritis had also been treated for many years (Table 2). Because of their common character, these diseases did not

Table 2. Time from the onset of symptoms to the final diagnosis of primary hyperparathyroidism and operation

Tabela 2. Czas od wystąpienia poszczególnych objawów do rozpoznania pierwotnej nadczynności przytarczyc i operacji

Symptoms and signs of primary hyperparathyroidism (Objaw pierwotnej nadczynności przytarczyc)	Time to diagnosis of P-HPT – years (Czas do rozpoznania P-HPT – w latach)	
	average	maximum
Osteoporosis – inappropriate to age (Osteoporoza – nieadekwatna do wieku)	1	3
Non-specific bone and/or joint pains (Nieswoiste dolegliwości kostno-stawowe)	5	7
Nephrolithiasis (Kamica moczowa)	11	17
Peptic ulcer (Choroba wrzodowa)	6	15
Pruritus (Świąd skóry)	2	2
Pancreatitis (Zapalenie trzustki)	3	5
Bone tumors; histologically – brown tumor (Guzy kości; histologicznie – guz brunatny)	< 1	< 1
Decreased muscle strength (Osłabienie siły mięśniowej)	2	3
Lowered psychomotor drive or intellectual fitness (Obniżenie napędu psychomotorycznego lub sprawności intelektualnej)	2	4

Table 3. Serum concentrations of calcium, phosphates, and PTH found before the operation for primary hyperparathyroidism

Tabela 3. Stężenia wapnia i fosforanów oraz PTH, oznaczane u chorych przed operacją pierwotnej nadczynności przytarczyc

	Mean value (Średnia wartość)	Min. and max. values (Wartość najmniejsza i największa)	Normal range and units (Zakres norm i jednostki)
Calcium (Wapń)	2.91	2.31–3.78	2.0–2.55 mmol/l
Inorganic phosphates (Fosforany nieorganiczne)	0.80	0.58–1.02	0.81–1.45 mmol/l
PTH	440.5	95–1561	11–67 pg/100 ml

raise any suspicions for a long time, until they were associated with other symptoms and blood tests for calcium and phosphates were made. Non-specific neurological symptoms did not usually make the patients seek medical advice. Early onset osteoporosis led to quick diagnosis of P-HPT (usually within 1 year), but in elderly patients it would be underestimated by general practitioners as a diagnostic problem. The correct diagnosis was finally made by an endocrinologist and was based on abnormal serum calcium and phosphate concentrations and elevated parathormone (PTH). It was then confirmed by visualizing enlarged parathyroids by sonography and/or scintigraphy. The preoperative levels of serum calcium, phosphates and PTH are presented in Table 3.

Discussion

Historically, the clinical picture of highly advanced primary hyperparathyroidism consisted mainly of devastating bone disease, presenting as osteoporosis and osteitis fibrosa cystica generalisata, with tormenting bone pains, skeletal deformities, brown tumors, and pathological fractures, accompanied by neurological disorders and nephrolithiasis [1, 2, 5, 8, 12, 13, 17]. Early diagnosis of P-HPT, made possible thanks to the growing understanding of this disease, has consequently brought about a change in its typical clinical picture. Nowadays the disease is usually diagnosed before such complete and typical destruction of the skeletal system develops; analogously, the full set of symptoms from different organs is seldom found in one patient. The differences in the clinical picture of P-HPT described in different regions of the world are mostly due to the possibilities of early diagnosis of the disease before it reaches its fully symptomatic stage. In countries where screening tests for P-HPT have become part of routine clinical practice, it is frequently detected even in its clinically asymptomatic form, which enables effective operative treatment before severe complications arise [3, 9, 11, 18].

As observed above, in this country's setting the symptoms and signs that build up the clinical picture of primary hyperparathyroidism are still usually treated by general practitioners and various specialists as separate disease entities, while their main cause remains undiagnosed for a long time. The low incidence of this rare disease and its diverse, often monosymptomatic clinical course masked by other common complaints may divert the attention of a rheumatologist, urologist, gastrologist, neurologist, and many other medical specialists from the true cause of the illness for many years. It is advisable that all the patients who present with the symptoms and signs described above have blood tests for calcium level and be referred to an endocrinologist for consultation, which could direct the diagnostics in the right way.

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