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Secondary Hyperparathyroidisme

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Summary: *Secondary hyper parathyroidisme (SHP) is defined by a compensatory elevation of the parathormone (PTH) habitualy associated with normal or hypocalcemia. This situation is frequently in multiple pathologies. Chronic renal insufficiency and vitamine D insufficiency are the most common causes. When the diagnosis is established, additional tests are performed to rule out differential diagnoses and institute effective treatment. In fact, the absence of correction of secondary hyperparathyroidism can lead to serious complications.*
The objective of this study was to report the causes of SHP encountered in our practice and to specify their clinical and evolutionary characteristics.
Keywords: *Secondary hyper parathyroidisme, hypocalcemia, Chronic renal insufficiency, vitamine D insufficiency PTH*

I. Introduction

Secondary hyperparathyroidisme (SHP) is defined by a compensatory elevation of the parathormone (PTH) habitualy associated with normal or hypocalcemia. This situation is frequently encountered in general population and in multiple pathologies. Chronic renal insufficiency; vitamine D insufficiency and potent anti-resorbers (oral and parenteral bisphosphonates ...) are the most common causes (1).When the diagnosis is established, additional tests are performed to rule out differential diagnoses and institute effective treatment. In fact, the absence of correction of secondary hyperparathyroidism can lead to serious complications(2). The objective of this study was to report the causes of SHP encountered in our practice and to specify their clinical and evolutionary characteristics.

II. Population,methodology

This is a retrospective study of the records of patients presenting SHP hospitalized and monitored in the department of endocrinology of Bab el oued teaching hospital during the period from 2006 to 2015.
For each patient, were collected; the clinical and paraclinical parameters established during the initial management and / or the rehospitalizations, Particularly concerning personal medical history (nephropathy, hepatopathy, malabsorption, menopause, hypertension, rickets, osteomalacia, iatrogenic intake, etc.); famililal medical history (similar case). Reason for consultation, age at onset of symptomatology, age at diagnosis, and time to diagnosis.

Exploration indicated the symptomatic or asymptomatic caracter of SHP by searching General signs : weight, height, BMI, weight loss, general condition, osteo-articular signs : bone pain, fractures, tumefaction, arthralgia, walking troubles,

Renal signs: nephritic colic, emission of computation, hematuria, dysuria,

Digestive signs: anorexia, nausea/vomiting, epigastralgia, transit disorders,

Cardiovascular signs: BP cycle, dyspnea, palpitation, heart failure,

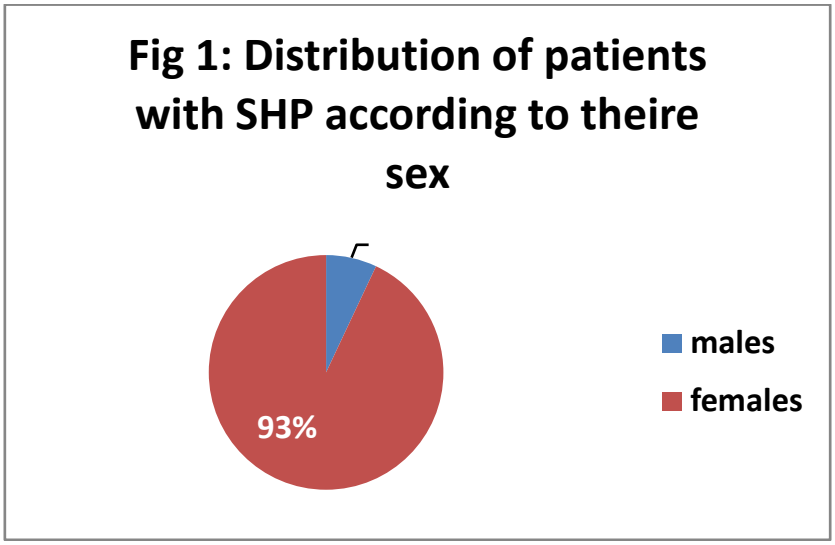
Neuromuscular signs: paresthesias of the extremities, osteotendinous hyper reflexivity, myalgia/cramps, amyotrophy, dermatological signs: pruritus and specific signs of hypocalcaemia: Trousseau's sign, Chvostek's sign.

Paraclinically, a biological and radiological assessment completed clinical exploration:
Calcium phosphate assessment: PTH, calcemia and phosphatemia over 3 days, calciuria of 24h, total proteins, albuminemia, 25OHD, complete blood count (CBC),

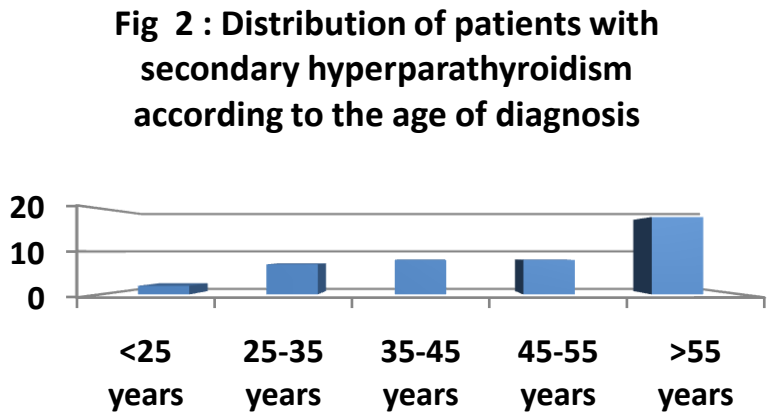
Renal assessment: blood urea, blood creatinine, clearance of creatinine, 24h proteinuria, microalbuminuria of 24 h. Hepatic assessment: transaminase: (ASAT, ALAT), ALP, GGT and prothrombin level,Renal ultrasound, CT, BMD (T and Z score of the lumbar spine and left femur), bone radiography, cervical ultrasound +/- Fine needle aspiration, parathyroid scan with Tc^{99m} MIBI. The etiological assessment was guided by the context of the patients. After intiation of treatment, patients were reviewed and re-evaluated regularly.

III. Results

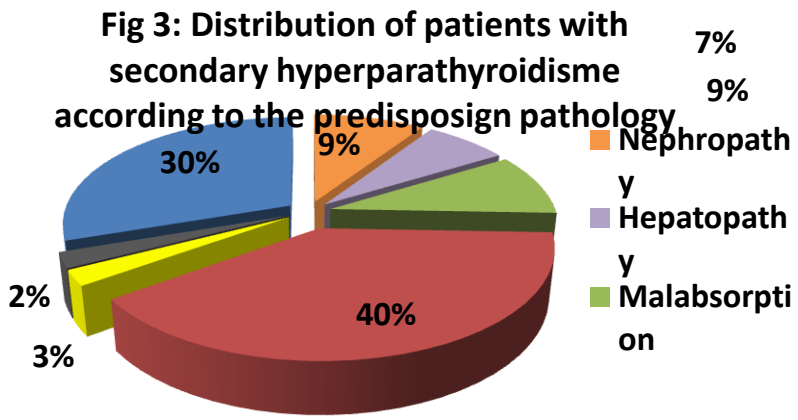
47 cases of SHP have been reported. They represent 25.7% of all hyperparathyroidismes (primary, secondary and tertiary), totaling 183 in all, with an average of 4 hospitalizations per year. Secondary hyperparathyroidism concerns mainly women, with a sex ratio of 13 women to 1 man (Fig 1).



Half of SHP were observed after 55 years (n: 22/47). Secondary hyperparathyroidism affects the 25-35, 35-45 and 45-55 age groups equally (Fig2).



We noticed a clear feminine predominance. The mean age of women was 50 ± 0.2 years. The mean age of men was 42 ± 0.4 years. Etiologically, complicated high blood pressure was the most common cause. It was found in 40% of the cases (Fig3).



4.6% of patients have a similar family history of SHP. The most common reasons for consultation were bone pain (37.2%) and nephritic colic (27.9%) (Table I). Incidentally discovered SHP account for only 11.6% of the total population studied. The majority of them are symptomatic (88,4%). Despite this, the delay in diagnosis is delayed: 8.6 ± 0,16 years (6 months - 10 years).

Tableau I: Distribution of patients with SHP according to the reason of consultation:

Reason of consultation	Number of patients	Percentage (%)
Diffuse bone pain	16	37 ,2
Recidivant nephritic colic	12	27,9
Cervicale pain	2	4,6
Systematic screening	6	13,9
Brown tumor	1	2,3
Pathological fractures	1	2,3
Signs of hypocalcemia (tetany crise/paresthesy)	2	4,6
Demineralisating osteopathy	1	2,3
Salivary lithiasis	1	2,3
Suspicion of Fahr syndrom	1	2 ,3

Clinical manifestations are dominated by osteoarticular signs (77,3 %) and renal signs (32%) (Table II)

Table II: Distribution of patients with SHP according to the presented clinical signs

Clinic	Symptoms	Nbre	Percentage%
1.Osteoarticular signs	Bone pain	29	67,4
	Pathological fractures	3	7
	Tumefaction	0	0
	Walking troubles	5	11 ,6
	Articular pain	12	28
	Osseus deformation	2	4,6
2.Urinary signs	Nephretic colics	11	26
	Emission of calcul	4	9,3
	Hematuria	3	7
	Dysuria	4	9,3
3.Digestive signs	Anorexia	1	2,3
	Nauseas/vomiting	3	7
	Epigastralgia	8	18,6
	Transit troubles	11	26
4.Cardiovascular signs	Dyspnea	9	21
	Palpitation	10	23,2
	Heart failure	0	0
5.neuromuscular signs	Paresthesies of the extremities	12	28
	Osteo-tendineous Hyporeflexivity	2	4,6
	Myalgies	7	16,3
	Amyotrophy	0	0
6.cutaneous signs	Pruritus	1	2,3

On the paraclinical way; bilogical aspect of SHP was classical with mean PTH levels at 135.34 pg/ml (106,46 – 144,4) (Fig 4), mean value of calcemia at 85,08 mg/l (70 – 82,6) and a mean value of phosphoremia at 48,27 mg/l ± 0,1 (38- 56).

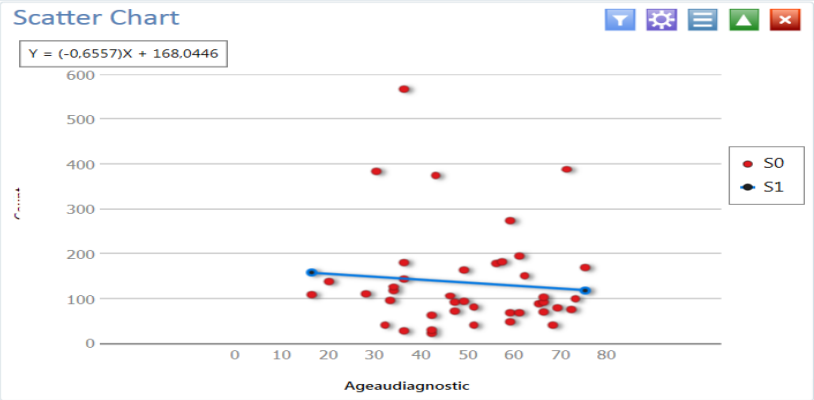


Fig 4 : Mean value of PTH of patients

On the radiological aspect; 67.4% of patients had caracteristic signs. Conventional x-rays showed diffuse sub-periosteal bone hyper-resorption signs especially in the cranium, long bones, phalanges and joints, and lytic lesions (cysts or brown tumors) in 25% of cases. Densitometric examination of the skeleton revealed a decrease in bone mineral density in all patients, with an average T-score of - 2.8 SD (- 2, - 3.8).

Cervical ultrasound performed in patients showed diffuse hyperplasia of all parathyroids in 74%. It was otherwise normal in all other cases.

The tracer used was MIBI-technetium, in 33 cases (38.8%). Wherase (22%) were negative. In the other cases the 4 glands were identified.

Calcimimetics represent a new approach in the management of secondary hyperparathyroidism. They inhibit the secretion of P.T.H by activating the membrane calcium receptors. Their efficacy has been demonstrated in several clinical studies. Their action combined with that of vitamin D suggests a more optimal medical management of secondary hyperparathyroidism.

The association of a normocalcemia or hypocalcaemia with a high PTH should seek calcium deficiency and vitamin D (malabsorption) or renal insufficiency.

Table III : Distribution of patients with SHP according to the etiology

Etiology	Nbre	%
SHP due to vitamine D deficiency	16	34 ,04
SHP due to renal insufficiency	7	14,9
SHP due to digestive malabsorption	24	51,06

Etiological exploration revealed two major causes: digestive malabsorption in half of cases 51.06% and vitamin D deficiency (34.04%). Renal insufficiency is found in 15% of cases (Table III).

Therapeutically, all patients received vitamin-calcium treatment. The post-therapeutic evaluation noted a regression of symptomatology in 80%. And 72% of patients had normalized theire calcium-phosphate. No form of SHP has evolved into the tertiary form.

V. Discussion

Secondary hyperparathyroidism is an endocrinopathy characterized by hypersecretion of parathormone due to a disorder of phosphocalcic metabolism, in particular chronic hypocalcaemia occurring most often in the course of chronic renal insufficiency or deficiency of vitamin D by: insufficient intake , Lack of sunlight in the processes of intestinal malabsorption of vitamin D and during renal insufficiency(1).

The mean age of secondary hyperparathyroidism is 59 years, which is close to the mean age observed in our study. In accordance with the literature, we note a feminine predominance (3). The clinical manifestations of SHP are initially characterized by general symptoms such as asthenia, fatigue or even nervous depression (3).

Later clinical signs are more specific suche as pruritus, osteoarticular pain, muscle pain, polyneuropathy, pancreatitis, renal lithiasis, cardiovascular and soft tissues calcifications, high blood pressure, cardiomyopathy , Heart failure and bone fragility with a significant risk of fracture (Relative risk x 4) (4) . All these alterations expose these patients to a significant increase in the risk of morbidity and cardiovascular mortality.

Conventional x-rays show signs of subperiosteal bone hyper-resorption. There may also be vertebral settlements and spontaneous fractures (5).When SHP is important, there may be brown tumors in the jaws, bones of the face, hands and other sites in the skeleton. Vascular, periarticular, subcutaneous and other soft tissue calcifications are not uncommon (6).

The diagnosis based on clinical and radiological assessements evidences is confirmed by the immunological assay of serum PTH. Further examinations are necessary to discriminate between different differential diagnoses and to ensure its long-term normalization (7).

Imaging will only provide topographic data in the diagnosis of parathyroid hyperfunction. The frequency of seat variation and number of parathyroid glands is a limiting factor, requiring methods exploring the cervical and mediastinal region.

Ultrasound is a very dependent operator's examination which requires the use of high - frequency probe (7.5 to 10 MHz, 5 to 7MHz in case of short neck or presence of a goiter). The hypertrophic glands appear solid, homogeneous, mobile at deglutition, hypoechoic with respect to the thyroid parenchyma. However, ultrasound remains a useful examination for cervical exploration alone. Computed tomography and magnetic resonance imaging, despite their potential for extensive anatomical exploration, represent second-line examinations because of the difficulty of distinguishing parathyroid glands from other neighboring structures (8).

These imaging techniques are especially useful for the ectopic mediastinal localizations of pathological glands (7)(8) (9). Their disadvantages are the high cost of these investigations and the low availability of MRI. Compared to the different techniques of morphological imaging, parathyroid scan has good sensitivity. This depends on several parameters: The weight of the pathological gland which constitutes the most important factor that can influence the positivity of the parathyroid scan. The high level of intact PTH in the blood, the richness of the lesion in mitochondries, a cell proliferation level greater than 5.7% and the G2 + S phase of the cell cycle are factors that increase the sensitivity of the scintigraphy (10)(11)(12).

Compensatory SHP is found mainly in clinical situations which cause a decrease in the concentration of ionized calcium in extracellular fluids or a decrease in 1,25(OH)2 vitamin D or 25 OHD or hyperphosphatemia (2). Several etiologies are responsible of SHP. In chronic renal insufficiency, it appears as soon as the glomerular filtration decreases with a creatinine clearance of less than 60 ml / min, due to the decrease in phosphorus excretion, there is a hyperphosphatemic tendency responsible of the increase in secretion of fibroblast growth factor 23 (FGF23) by osteocytes. This increase in FGF23 is responsible for : a decrease in the proximal reabsorption of phosphates, a decrease in renal synthesis of calcitriol (1.25 (OH) 2D) which results in a decrease in intestinal phosphate absorption. Both of these actions tend to normalize phosphate levels. The decreased renal synthesis of calcitriol decreases the intestinal absorption of calcium, there is a hypocalcemic tendency (13)(14)(15)(16) (17)(18). Inadequate calcium intake may be responsible of SHP in the absence of vitamin D deficiency in particular cases such as during diet, sometimes sectarian, dietary restriction in dairy products or in the elderly because of alterations in calcium absorption and higher kidney elimination due to estrogen deficiency. On the other hand, all the pathologies leading to a disorder of the digestive absorption of calcium, such as celiac disease, cystic fibrosis, short hailstones, are associated with a SHP that is as important as that vitamin D deficiency is associated (19).

On the therapeutic aspect, the treatment consists in correcting the underlying causes of secondary hyperparathyroidism. It is based first on medical means that may be insufficient. Secondary hyperparathyroidism is controlled in the majority of cases by a dietetic adapted with a hypophosphoremic diet and a medical treatment including calcium, phosphorus binders in renal insufficiency and active metabolites of vitamin D. Patients with vitamin D deficiency are treated with vitamin D, or with other measures to correct malabsorption. Patients with cancer are usually treated surgically. In the case of renal insufficiency, the first objective for controlling a high PTH level is to maintain phosphate levels within normal limits. This requires a significant reduction in protein intake (the main source of phosphate inputs). Phosphorus chelators are essential to control phosphoremia in dialysed patients.

Vitamin D, including alfacalcidol, is inexpensive, but its efficacy is limited. The adaptation of certain dialysis parameters, such as calcium concentration in dialysate, duration and / or number of dialysis sessions or The use of synthetic membranes with a large hyperpermeable surface makes it possible to control the concentrations of calcium and phosphorus (20) (21).

A new class of drugs called calcimimetics (cinacalcet) has come to improve the management of SHP. They act by improving the sensitivity of calcium receptors in the parathyroid gland to activation by extracellular calcium. This results in a decrease in the level of parathyroid hormone (PTH) and a subsequent reduction in serum calcium (22)(23).

In the absence of cinacalcet and / or persistence of PTH> 800 ng / L after 6-8 weeks of medical treatment with calcitriol or an of its analogs, most commonly associated with hypercalcemia and / or hyperphosphatemia , Subtotal parathyroidectomy should be considered (9)(24).

IV. Conclusion

Shp is a serious condition that needs to be diagnosed and managed early.Its evolution when not controlled is marked by increased cardiovascular risk and bone morbidity.

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