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Sagliker syndrome in patients with secondary hyperparathyroidism and chronic renal failure: Case report

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ABSTRACT

INTRODUCTION: Sagliker described craniofacial, skeletal, neurologic and soft tissue abnormalities in patients with secondary hyperparathyroidism with end-stage chronic renal disease. This unique entity has been attributed to delay in treatment of renal insufficiency. As of 2012 sixty cases have been reported. The aim of the study is to report this entity in five patients and to propose this condition as an indication for parathyroidectomy.

METHODS: We report five patients. All patients had chronic renal failure (CRF) and secondary hyperparathyroidism that fulfilled the criteria for Sagliker syndrome and underwent parathyroid surgery. We collected detailed information, including clinical history, laboratory data, and old/current photographs for comparison.

RESULTS: The five patients, four women and one man mean age 21 years, had severe secondary hyperparathyroidism (mean serum preoperative PTH = 3779.6 pg/ml, mean preoperative Ca^{2+} = 8.83 mg/dl and P^{3-} = 5.66 mg/dl); maxillary and mandibular bone changes; teeth/dental abnormalities; and soft and benign tumors in the mouth. Three had severe uglifying facial appearance. All patients underwent total parathyroidectomy without postoperative complications. After surgery mean serum PTH was 17.16 pg/ml ($p = 0.006$), P^{3-} = 3.38 mg/dl ($p = 0.0068$) and Ca^{2+} = 6.97 mg/dl ($p = 0.345$). At surgery, average height was 149.8 cm, a mean of 6 cm ($p = 0.003$) less than at the beginning of CRF. Preoperative Beck Depression Inventory test mean score was 37 (severe depression); 6 months after surgery mean score was 15.8 (mild mood disturbance)($p = 0.0001$). Clinical follow-up was satisfactory with a mean follow up time of 14 months.

CONCLUSION: We consider that Sagliker syndrome should be added to current surgical indications for parathyroidectomy.

1. Introduction

Sagliker syndrome (SS) was described by Sagliker et al. in 2004. Patients with chronic renal failure (CRF) have elevated levels of serum phosphorus (P^{3-}), parathyroid hormone (PTH) and alkaline phosphatase with low levels of calcium (Ca^{2+}). All these changes occur as a result of renal function decline with a drop of 1,25-dihydroxyvitamin D3 [1,25-(OH) 2 D3] levels and hypocalcemia secondary to impaired intestinal and renal Ca^{2+} absorption. PTH secretion, regulated by serum Ca^{2+} levels, rises in response to hypocalcemia. In early stages of CRF elevated circulating PTH levels enhance P^{3-} excretion and may result in decreased serum P^{3-} levels. In advanced stages of CRF, P^{3-} excretion becomes impaired, and hyperphosphatemia suppresses 1a-hydroxylase activity further decreasing 1,25-(OH) 2 D3 production and directly stimulating PTH release. A special subgroup of patients with CRF develop multiple changes that include "uglifying" facial appearance, short stature, extremely severe maxillary and mandibular changes, soft tissues in the mouth, teeth-dental abnormalities, finger tip changes and severe psychological problems [1]. The expression of all of these changes has been described as Sagliker syndrome.

This unique entity has been attributed to delay in treatment of renal insufficiency because of poverty and limited access to health care [2].

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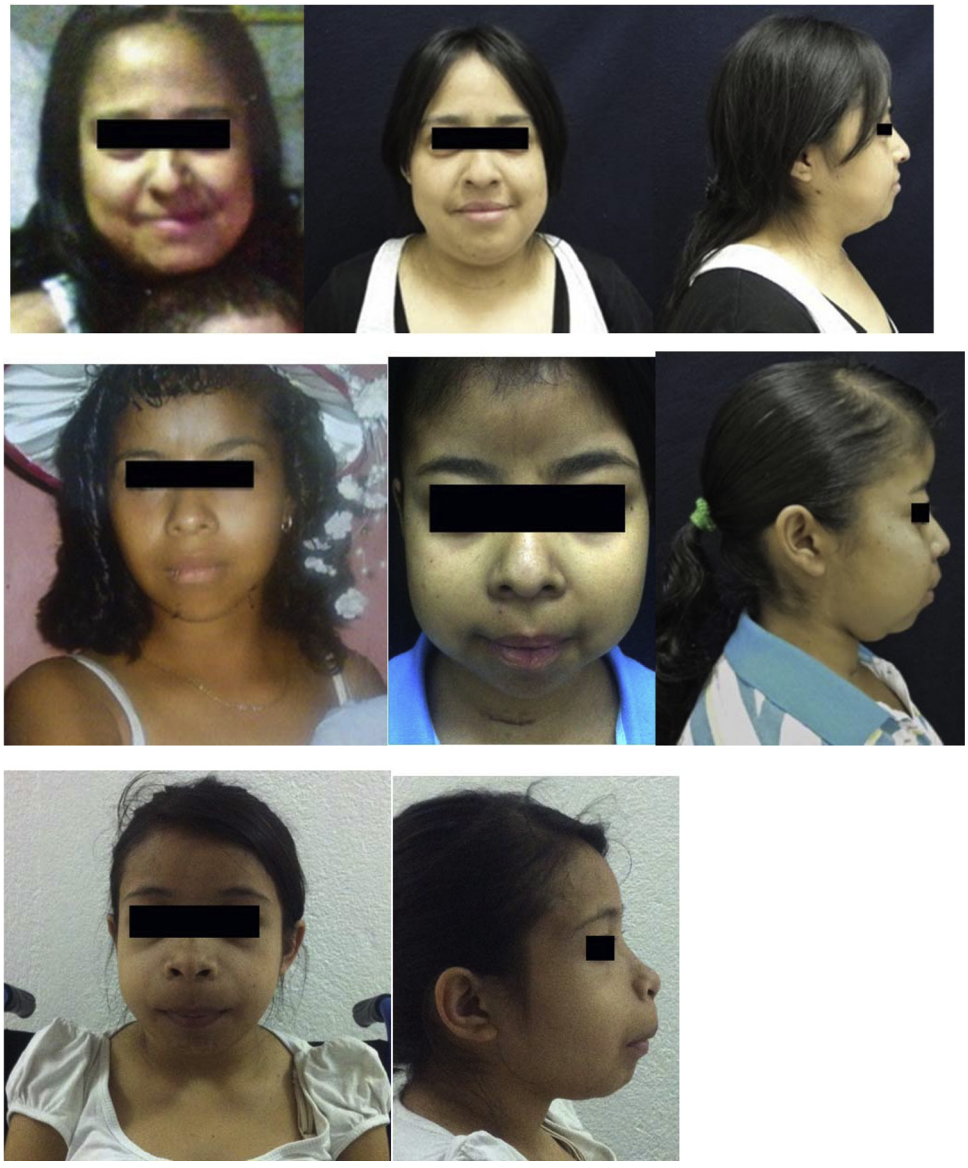

Fig. 1. Left showing previously normal face (first two patients), center and right showing current uglifying humanface appearances.

As of 2012, sixty cases had been reported in literature. The aim of the study is to report this entity in five patients with end-stage renal disease and to propose this condition as an indication for parathyroidectomy.

2. Methods

In our study, we report five patients who were evaluated from March of 2012 to October 2013.

All patients had CRF and secondary hyperparathyroidism (sHPT), fulfilled the criteria for Sagliker syndrome, and underwent parathyroid surgery. We collected detailed information, including clinical history, physical exam and laboratory data.

We took face and body pictures and requested copies of previous pictures and family photo albums, which included pictures of other family members. Informed consent was received from patients and institutional review board approval was obtained. To evaluate depression we performed Beck Depression Inventory test [3] before and six months after surgery.

Descriptive statistics were used to analyze baseline characteristics. Changes over time were analyzed with the use of paired-samples Student's *t* test. All statistical analyses were performed with the use of STATA 12.

3. Results

Five patients, four females and one male with a median age of 21 years, had chronic renal failure with a median interval of four years between diagnosis of CRF and our evaluation. All presented with severe secondary hyperparathyroidism, with mean serum preoperative PTH = 3779.6 pg/ml, mean preoperative Ca^{2+} = 8.83 mg/dl and P^{3-} = 5.66 mg/dl.

Three patients had severe uglifying facial features; the difference in facial appearance in two cases is shown in current photographs compared with those taken several years earlier (Fig. 1). The other two patients had mild uglifying facial features.

In all five cases teeth were irregularly shaped and located; three of them had soft, large, tumor-like tissue accumulations particularly in the upper side of the oral cavity (Fig. 2). All had difficulty standing, but none had fingertip changes, scapula deformity, or hearing problems (Table 1). Average height at the beginning of CRF was 155.8 cm.

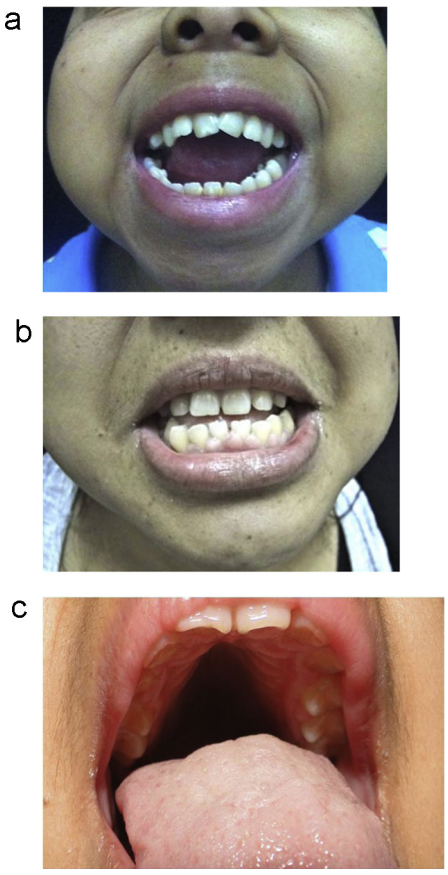

Fig. 2. (a) Showing maxillary and mandibular bone changes, dental malocclusion (b and c) soft and benign tumors in the mouth.

Table 1
Clinical characteristics.

	Age	Sex	Dental abnormalities	Mandibular abnormalities	Finger tips abnormalities	Height differences (cm)
1	21	F	Yes	Yes	No	10
2	27	F	Yes	Yes	No	5
3	19	F	Yes	Yes	No	5
4	21	F	Yes	Yes	No	5
5	29	M	Yes	Yes	No	5
	21[a]					6 cm[b] ($p = 0.003$)

[a] Median.
[b] Mean.

Table 2
Laboratory and test results.

	Preoperative	Postoperative	*P*
PTH (pg/ml)	3779.6	17.16[a]	0.006
Ca^{+2}(mg/dl)	8.83	6.97[a]	0.345
P^{-3} (mg/dl)	5.66	3.38[a]	0.0068
Beck test score	37	15.8[b]	0.0001

[a] After one week.
[b] After six months.

All patients underwent total parathyroidectomy without thymectomy. Parathyroid glands were easily identified because of their enlarged size and in each case the four glands were removed. There were not postoperative complications. After surgery mean serum PTH was 17.16 pg/ml ($p = 0.006$), $P^{3-} = 3.38$ mg/dl ($p = 0.0068$) and $Ca^{2+} = 6.97$ mg/dl ($p = 0.345$) (Table 2).

At surgery, average height was 149.8 cm, a decrease of 6 cm ($p = 0.003$) from the beginning of CRF (Fig. 3).

Fig. 3. Picture shows differences height between one patient and her mother (left picture 12 years-old and right 21 years-old).

The Beck Depression Inventory test yielded a mean score of 37 (severe depression) preoperatively; 6 months after surgery the mean score was 15.8 (mild mood disturbance); the difference was statistically significant ($P = 0.0001$).

Preoperatively all patients were treated with supplements of mean oral calcium (600 mg/d), alfacalcidol (1–2 μg/d), iron sucrose injection (200 mg/week), erythropoietin injection (50 UI/kg/week) Two patient were treated with amlodipine (10 mg/d), atenolol (50 mg/d), enalapril (20 mg/d) and another patient was given losartan (50 mg/d). Postoperatively all dosages remained the same except for mean oral calcium which was increased to 1200 mg/TID. Clinical follow-up was satisfactory with a mean follow up time of 14 months.

4. Discussion

Sagliker syndrome is assumed to result from insufficient treatment of sHPT in early stages of CRF. This syndrome can be observed in developing countries where people lack access to necessary medical treatment and do not receive timely treatment for renal insufficiency [4]. Our country, is an economically distressed, has the disadvantages that could lead to the appearance of SS.

Our patients had CRF onset a median of 4 years prior to our evaluation, but none of them reported having delayed treatment, according to the medical history interview. Although these patients are economically disadvantaged and have scarce resources, we could not determine by interview that treatment (such as oral calcium, alfacalcidol, erythropoietin injection and anti-hypertensive medication) had been recommended but not received.

Patients were referred for parathyroidectomy for secondary hyperparathyroidism. None had the possibility of a renal transplant because they could not afford surgery and/or long-term immunosuppression, so we made the decision to perform a total parathyroidectomy without thymectomy. We consider that to perform a thymectomy augments the morbidity of these already frail patients, specially considering that by definition patients with renal failure have coagulation problems [5].

We chose total parathyroidectomy instead of subtotal parathyroidectomy because our goal is to avoid persistence and recurrence of disease. The largest study published by Schneider et al. [6] reports

rates of 4.1% of persistence and 6.1% of recurrence with subtotal parathyroidectomy with thymectomy compared to 0% persistence and recurrence with total parathyroidectomy without thymectomy. In our study we have a 0% persistence or recurrence of hyperparathyroidism.

The other surgical alternative is total parathyroidectomy with thymectomy with autotransplant. This option has 0.4% of persistence and 5.4% of recurrence [6]. We did not consider that option for the reasons given above.

All of the referred patients were clinically suited for surgery and none had postoperative complications. Because we have followed up these patients a mean of just 14 months, we are not surprised not to have observed any changes in facial bone structure or other bone deformities; whether such changes will develop later, as some authors allege, is unknown.

This descriptive report respond to our effort to understand why certain patients with CRF develop SS and what the optimal therapy of SS is. Major limitations of this study are that our experience is limited to five cases; we had no control group, either of CRF patients without SS or SS patients given treatment other than parathyroidectomy; and we gathered information only retrospectively about the onset of CRF so we cannot determine cause-effect relationships. It is still uncertain why a subgroup of patients with sHPT develops SS. Genetic associations, and in particular, mutations on the GNAS1 gene exons have been described and are seen only in some of the SS patients [7]. In our patients we were not able to perform molecular and genetic studies because of economic restrictions.

Psychiatric problems have also been described. Depression and anxiety disorder coexist with other SS symptoms [8]. Our interviews revealed that our patients had severe depression before surgery, with improvement after surgery. Whether the improvement was a direct effect of parathyroidectomy or had another cause could not be determined.

When pharmacological treatment of sHPT does not lead to adequate regulation of parathyroid function, parathyroidectomy should be performed and not delayed. We suggest that SS should be considered an indication for parathyroidectomy.

In the meanwhile we need to continue gathering information to determine why a subgroup of patients with sHPT develops SS.

5. Conclusion

Sagliker syndrome is a complication of secondary hyperparathyroidism in a subgroup of patients with CRF. We consider that Sagliker Syndrome should be added to current surgical indications for parathyroidectomy.

Conflicts of interest

None of authors have conflicts of interest.

Sources of funding

None.

Ethical Approval

Ethical approval was granted by Universidad Francisco Marroquín IRB.

Author contribution

All authors contributed to the paper: study design, data collections, data analysis and writing.

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