

# Saglikier syndrome: a new entity, an old problem. Report of a series of cases.

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## Abstract


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**Introduction:** Saglikier syndrome, described by Dr. Yahya Saglikier in 2004, constitutes the most advanced state of secondary hyperparathyroidism in chronic kidney disease. Deforming and disabling clinical syndrome that reduces the quality of life and adds psychological disorders to the patient with chronic kidney disease. This study aims to report on a series of eight cases in Mexico and warn about the correct management and follow-up of secondary hyperparathyroidism.

**Cases:** Eight cases presented with ages between 17 and 35 years, serum parathyroid hormone levels between 1583 and 4715 pg/ml, and alkaline phosphatase levels between 146 and 2065 IU/L. All cases had brown tumors in the maxilla and mandible characteristic of Saglikier syndrome.

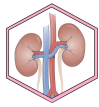
**Evolution:** All patients were ingesting calcium and vitamin D analogs at diagnosis or in the last three months.

**Conclusion:** Saglikier syndrome is the most severe and chronic complication of secondary hyperparathyroidism and chronic kidney disease. The significant bone involvement of this syndrome generates a disabling facial and prolonged bone deformity that impacts morbidity, mortality, and mental health. Concomitant with bone alterations, vascular and cardiac calcifications add a crucial cardiovascular risk, so any surgery constitutes a high risk

## Keywords:

**MeSH:** Hyperparathyroidism, Secondary; Hyperostosis Frontalis Interna; Kidney Diseases; Renal Insufficiency, Chronic; Case Reports.

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Chronic kidney disease in advanced stages frequently presents bone mineral alterations and exceptionally high bone turnover, such as secondary hyperparathyroidism in almost all patients with chronic kidney failure on replacement therapy. Sagliker syndrome (SS) was described by Dr. Yahya Sagliker in 2004 when he found two cases with similar characteristics [1]. Although an approximate incidence of 0.5% has been reported [2], of all cases of chronic kidney disease, only 60 cases have been reported in the literature, considering the presence of a more significant number of cases in developing countries [3]. This syndrome occurs in patients with severe and late hyperparathyroidism refractory to medical treatment with a disfiguring and catastrophic evolution [3]. Characteristically, a presentation in childhood and adolescence with short stature due to growth retardation has been associated with effects on the centers of bone growth [3, 4]. The phenotype corresponds to a facial deformity with maxillary and mandibular lesions described as a disfigured appearance or "squirrel face," severe dental abnormalities, benign tumors in the oral cavity, chest deformity, hearing loss, tumors in bone tissues, affection of the fingertips and the presence of psychological disorders or depression due to the condition of physical appearance [5-9]. The most frequent is the natural history of hyperparathyroidism with hyperphosphatemia, hypocalcemia, increased alkaline phosphatase, and parathyroid hormone. In genetic studies, four nonsense mutations have been detected in the exons of the *GNAS1* gene in 40% of patients with SS. This mutation would be triggered in the context of severe hyperparathyroidism and could be responsible for abnormal bone growth [8, 10]. Another study determined that 73.9% of patients had a combination of bone dysplasia or hereditary dystrophies with chronic kidney disease, and genetic alterations pointed to mutations of the *GNAS1*, *FGF23*, and *FGFR3* genes [10].

The objective of the present study was to report a series of cases with SS in a national referral center in Mexico.

## Materials and methods

From March 2016 to February 2018, patients who entered the nephrology service at the Centro Médico Nacional Siglo XXI diagnosed with severe hyperparathyroidism were registered, of which 8 had the Sagliker syndrome phenotype. A detailed medical history, physical examination, complementary radiological or biochemical studies, and analysis of the previously received treatment were performed.

## Results

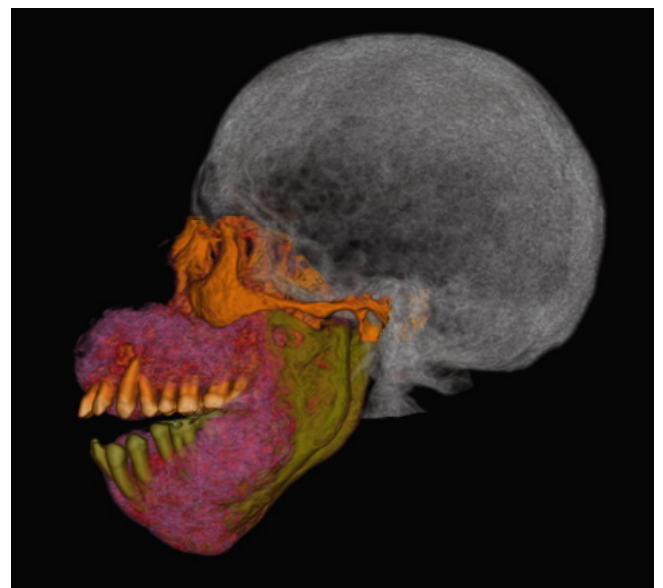
Eight patients with the characteristic phenotype of Sagliker syndrome were detected in the study period. Two women and six men with ages ranging from 15 to 35 years. The cause of the kidney disease was mainly undetermined, and two had reflux nephropathy. A total of 12.5% (one patient) presented hypocalcemia at diagnosis, one more presented hypercalcemia, and 75% showed normocalcemia (Table 1). A total of 62.5% (five patients) had hyperphosphatemia, 25% (two

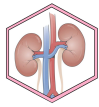
patients) had hypophosphatemia, and one had average serum phosphorus. The serum alkaline phosphatase level was high in 87.5% of the cases (seven patients), with values from 233 to 2065 IU/L. Serum parathyroid hormone ranged from 1500 to 4715 pg/mL (Table 1).

**Figure 1.** Tomography with bone window, sagittal projection: maxillary and mandibular prominence due to tumor lesion with blastic appearance. Case 1.



**Figure 2.** Three-dimensional reconstruction in sagittal projection, same tumor with involvement in the entire maxilla and mandible (2016). Case 1.





All patients had a mandibular deformity, and six had a concomitant maxillary deformity (Figures 1 and 2). Brown tumors were present in seven of the eight patients, short stature was constant in the patients, bone resorption in salt and pepper (Figures 3 and 4), vascular calcifications were present in four of the eight patients, and a history of pathological fracture was present in five. Dental alterations and oral cavity involvement were present in six patients. A diagnosis of major depression was established in three patients. All patients were ingesting calcium as effervescent calcium or calcium carbonate at the time of diagnosis or in the last three months, as well as vitamin D analogs, particularly calcitriol. None of the patients were treated with aluminum, phosphorus binders, or cinacalcet.

## Discussion

Secondary hyperparathyroidism is a frequent complication of chronic kidney disease; however, the incidence of Sagliker syndrome is still being studied, which characteristically causes facial deformity conditioned by mandibular and maxillary affection and short stature. These irreversible changes, as in the case series reported [1, 3]. A higher incidence in adolescence is also noted; however, in our cases, the highest incidence was reported in adulthood between the third and fourth decades of life [9]. In this series of cases, the serum PTH level was extremely high, up to twelve times the recommended level for stage 5 kidney disease, suggesting a slow and slow evolution of hyperparathyroidism. The use of calcium and calcium chelators was constant in all patients. However, a significant proportion already had vascular calcifications that could translate into an increased risk of cardiovascular complications and mortality. Still, phosphorus binders or calcium-sensitive receptor inhibitors were not used.

The most frequent is the presence of hypocalcemia and hyperphosphatemia. In this series of cases, severe hypercalcemia occurred in one case and hypophosphatemia in two cases, correlated with hyperfunctional or ectopic tissue in parathyroid scintigraphy and probable tertiary hyperparathyroidism.

Delayed or inadequate treatment reflects the significant bone disease and facial deformity that generates psychological disorders and depression in the patient, the latter present in six of the eight patients, similar to that reported in the first studies that describe this syndrome [3-5].

The use of surgical treatment is still controversial since new medical treatments are available; however, most of those that could be effective are outside the reach of the health sector in Mexico, which is related to the severity of the evolution [3, 11]. No studies analyze the development of patients with Sagliker Syndrome who undergo subtotal parathyroidectomy or their outcome or mortality, considering their high cardiovascular risk.

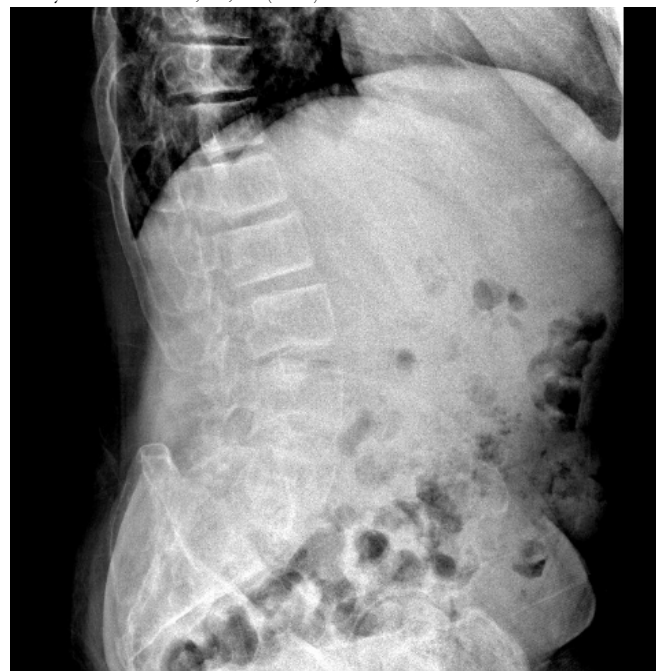
Regarding the possible etiology of Sagliker syndrome, it is known that genetic studies have identified different types of mutations in the GNAS1, FGF23 and FGFR3 genes [10], mutations that, without renal failure, explain the presence of bone dysplasias and hereditary osteodystrophies, and in the context of chronic kidney disease,

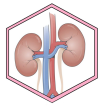
produce activating mutations that increase PTH levels > 1500 ng/ml, tissue calcifications, brown tumors and calcification of the soft tissues around the mouth.

**Figure 3.** Left lateral radiograph with bone resorption of the skull in salt and pepper image (2016). Case 3.



**Figure 4.** Lumbar lateral radiograph with decreased intervertebral space and lytic lesions at L5, S1, S2 (2016).





The exact cause of perioral calcification in Sagliker syndrome is not known. Elevated calcium levels in the soft tissues around the mouth may contribute to perioral calcification in Sagliker syndrome. The tissues with the most calcium are bone tissue, teeth, blood vessels, muscles, and the nervous system. In the mouth and the perioral area, there is a confluence of all these tissues, making it more susceptible to deforming calcifications in individuals with chronic kidney disease and genetically predisposed to develop secondary hyperparathyroidism.

The idea that the syndrome is due to chronic underdialysis and affects underdeveloped countries is rejected by the genetic findings described, and alterations of the GNAS1 gene explain hyperparathyroidism. The low prevalence of SS could be explained by most patients with specific genetic osteodystrophies who develop chronic kidney disease. New studies should determine the genetic context of the psychological disorders of these patients.

**Table 1.** Demographic and biochemical characteristics of patients with Sagliker syndrome.

Patient	Sex	Age (years)	Etiology of kidney disease	Serum calcium (mg/dL)	Phosphorus (mg/dL)	PTH (pg/mL)	Falkalin (IU/L)
1	M	23	Vesicoureteral-renal reflux	9.3	4.8	1583	349
2	M	32	Not determined	12.5	1.6	3500	2065
3	H	26	Not determined	7.1	1.6	3591	233
4	H	23	Not determined	8.3	5.4	3173	1065
5	H	21	Vesicoureteral-renal reflux	9.9	9.1	4715	1623
6	H	25	Not determined	9.8	4.3	4233	1790
7	H	17	Not determined	9.7	10	1500	714
8	H	35	Not determined	9.4	5.4	3741	146

## Conclusion

Sagliker syndrome is the most severe and chronic complication of secondary hyperparathyroidism and chronic kidney disease. The critical bone condition of this syndrome generates a disabling facial and long bone deformity that affects the morbidity and mortality of those suffering from it. Concomitant with bone alterations, the presence of vascular and cardiac calcifications adds a crucial cardiovascular risk, so any scheduled or elective surgery should be considered high risk, in addition to the risk of difficult intubation due to the presence of tumors in the oral cavity. Adequate and early treatment could prevent the evolution to this advanced state of hyperparathyroidism; however, it is not readily available in health services, so parathyroidectomy is the final resource. Managing psychological disorders is essential, given the catastrophic changes caused by Sagliker syndrome.

### Abbreviations

SS: Sagliker syndrome.

### Supplementary information

Supplementary materials have not been declared.

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Does not apply.

### Authors' contributions

Annel Ortiz Vilorio: Data curation, Formal analysis, Fund acquisition, Research, Project management, Resources, Software, Writing - original draft.

Dominga Jiménez Guzmán: Conceptualization, supervision, validation, visualization, methodology, writing: revision and edition.

Pedro Trinidad Ramos: Supervision, Validation, Visualization, Methodology, Writing: review and edition.

All the authors have read and approved the final version of the manuscript.

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### Availability of data or materials

The datasets generated and analyzed during the current study are not publicly available due to the confidentiality of the participants.

### Declarations

#### Ethics committee approval and consent to participate

Informed consent was signed for patient participation in this case report.

#### Consent for publication

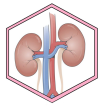
The authors have permission for publication by the patients of the present study.

#### Conflicts of interest

The authors report no conflicts of interest.

#### Author information

Not declared.



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