

Diagnosis and Treatment of Sagliker Syndrome

A Case Series From Iran

Azin Mohebi-Nejad,¹ Seyed Mansour Gatmiri,¹
Seyed-Mohammad Abooturabi,¹ Roya Hemayati,²
Mitra Mahdavi-Mazdeh^{1,3}

¹Nephrology Research Center,
Tehran University of Medical
Sciences, Tehran, Iran

²Division of Nephrology,
Department of Internal
Medicine, Yazd University of
Medical Sciences, Yazd, Iran

³Iranian Tissue Bank Research
and Preparation Center,
Tehran, Iran

Keywords. Sagliker syndrome,
end-stage renal disease,
secondary hyperparathyroidism

Sagliker syndrome was introduced in 2004 in patients with end-stage renal disease and severe secondary hyperparathyroidism. This syndrome describes maxillary and mandibular deformities, dental abnormalities, benign soft tissue tumors in mouth, and various kinds of skeletal changes including short stature and fingertip abnormalities. There are a few reports from different regions of the world. The aim of this study is to report 5 cases of the Sagliker syndrome from Iran.

IJKD 2014;8:76-80
www.ijkd.org

INTRODUCTION

The incidence of end-stage renal disease (ESRD) is on the rise in Iran; its incidence rate has increased from 13.82 pmp in 1997 to 49.9 pmp in 2000 and to 63.8 pmp in 2006.¹ Calcium-phosphorus metabolism imbalance and secondary hyperparathyroidism (SHPT) in ESRD push the patient towards bone and cardiovascular diseases.²⁻⁴ Secondary hyperparathyroidism, especially if occurring in childhood and adolescence, has a devastating effect on many parts of the body including the musculoskeletal system.⁵⁻⁷ It is also associated with higher mortality.⁸⁻¹⁰

Sagliker and colleagues detected a series of symptoms among patients with ESRD developed in young ages. Today, known as *Sagliker syndrome* (SS),¹¹ it includes severe maxillary or mandibular deformities, benign oral tumors, dental abnormalities, fingertip changes, hearing loss, depression and other psychological disorders, short stature, and knee and scapula deformities in the context of SHPT.¹² The prevalence of this syndrome among patients with chronic kidney

disease and SHPT is approximately 0.5%.¹³

Although the exact cause of SS is still unknown, genetic studies have detected 4 missense mutations on the *GNAS1* gene exons among 40% of patients with SS, which might be responsible for pathogenesis of this syndrome.¹³ Since SS is considered to be mainly the skeletal changes associated with SHPT, its pathophysiology is part of SHPT. Conditions associated with chronic kidney disease lead to hyperplasia and hypertrophy of the parathyroid gland cells, and therefore, production of parathyroid hormone (PTH) increases progressively.^{6,14,15} While decreased clearance of phosphorus resulting in hyperphosphatemia is known to be the main cause of SHPT,¹⁶ many other mechanisms including the deficiency of active vitamin D, anemia, and hypocalcemia contribute to it.^{6,14,17}

Skeletal abnormalities in SS are similar to thalassemic patients and include changes in the facial appearance, leading to a resemblance to the characteristic thalassemic "chipmunk face." Like thalassemia, the skull and facial bones are usually abnormal in SS. Since the patients with

SS develop an appearance similar to thalassemic patients, misdiagnosis may be made.

Although the process of musculoskeletal changes stops with kidney transplantation, deformities occurred due to SS are not reversible and this leads to a poor quality of life for the affected patients.^{13,18} There is a certain need to raise professional awareness of the symptoms of SS especially in countries with lack of facilities to start dialysis soon or offer dialysis with optimal doses. The aim of this study is to report 5 cases of the Saglikler syndrome from Iran. We reviewed the registry of 220 hemodialysis patients in Imam Khomeini Hospital, Tehran, and 166 patients in Shahid Sadoughi Hospital and Rahnemoon Hospital, Yazd, Iran, in order to identify patients with the features compatible with SS.

CASE REPORTS

Case 1

Case 1 was a 26-year-old man under hemodialysis since the age of 11. He had severe facial bone and dental deformities and benign oral tumors (Figure 1). He also had two surgeries for parathyroidectomy without optimal control of hyperparathyroidism and a surgery on the oral cavity for removing a benign tumor in the hard palate. His serum PTH level was 492 pg/mL. He had short stature (152 cm) and was unable to walk due to the deformities in his lower extremities. His fingertips showed upward curve in the third phalanges (Figure 1). He was receiving 0.25 µg/d of oral calcitriol. Sevelamer, 1600 mg, was administered, three times a day, but because the patient could not afford the

medication, he received 800 mg of the medication, three times a day.

Case 2

Case 2 was a 28-year-old woman, on hemodialysis for 3.5 years starting at the age of 24 years old. She received a kidney transplant at the age of 27 years, but changes in her appearance did not regress, although her serum PTH level decreased to normal. She had short stature (146 cm) and suffered from leg deformities such as genovarium. She also had dental abnormalities (Figure 2). Her PTH level was 615 pg/mL. She received calcitriol, 0.25 µg/d, and sevelamer, 800 mg, three times a day.

Case 3

Case 3 was a 23-year-old man with a history of sickle cell anemia who was on hemodialysis for 5 years. He had chipmunk face appearance



Figure 2. Oral soft tissue swelling and dental abnormalities.



Figure 1. Left, Oral soft tissue swelling and dental abnormalities. Right, Deformities of the fingers.

due to maxillary hyperplasia and frontal bossing. Hemoglobin electrophoresis was performed for him and major thalassemia was ruled out. He suffered from hearing loss, short stature (154 cm), and waddling gait due to deformity and pain in both knees. He had a serum PTH level of 156 pg/mL. He received calcitriol, 0.25 µg/d, and a total daily dose of 3000 mg of oral calcium carbonate.

Case 4

Case 4 was a 33-year-old man who was on hemodialysis for 21 years (Figure 3). His height was 150 cm. He had mandibular and teeth deformities (Figure 3) and suffered from depression. His serum PTH level was 714 pg/mL and he received a total daily dose of 1500 mg of oral calcium carbonate, 0.5 µg/d of oral calcitriol, and 2400 mg of oral sevelamer.

Case 5

Case 5 was a 37-year-old woman undergoing hemodialysis for 20 years. She had short stature (100 cm) and suffered from mandibular and dental deformities (Figure 4), as well as hearing loss. Her serum PTH level was 1214 pg/mL and she received a total daily dose of 2400 mg of sevelamer, 500 mg of oral calcium carbonate, and 0.75 µg/d of oral calcitriol.

DISCUSSION

Recent studies have detected new symptoms in patients with SS. These studies and their results are listed in the Table. Hearing loss is reported to exist in 60% of the patients with SS.¹⁹ In our study, 2 of the five patients suffered from hearing loss. Another study demonstrated psychiatric problems such as depression and anxiety disorder to coexist



Figure 3. Left, Mandibular and facial deformities. Right, Oral soft tissue swelling and dental abnormalities.



Figure 4. Left, Mandibular and facial deformities. Right, Oral soft tissue swelling and dental abnormalities.

Symptoms Reported to Coexist With Musculoskeletal Manifestations of Saglikler Syndrome

Study	Number of Patients	Symptom	Prevalence
Erkan et al ¹⁹	10	Hearing loss	60%
Ozenli et al ²⁰	13	Depression disorder	46%
Ozenli et al ²⁰	13	Anxiety disorder	23%

with other SS symptoms.²⁰ Our interviews with the patients revealed that one of them had the problem of depression.

It seems that the development of SS in ESRD patients is a hint to uncontrolled SHPT. Changes in patients' appearance and musculoskeletal function cannot be reversed even after kidney transplantation and this may affect their mental health and quality of life.²⁰ Therefore, more perseverance is needed in managing SHPT, especially in early stages, to prevent the development of such sequelae.

The cases introduced in this report may not all be typical of SS, but it should be noted that if the patients fully develop all SS criteria including short stature and facial deformities, the diagnosis of the syndrome will be of little benefit because few things can be done to improve the situation of the disease and almost none of the bone changes will regress. The diagnosis of the syndrome is of little benefit, because few things can be done to improve the situation of the disease and almost none of the bone changes will regress. The true value of diagnosing this syndrome is in its early stage, when changes are still mild. At this point, we would be able to cut the vicious cycle or slow down the progression of changes by modifying the factors causing SS including anemia, hypocalcemia, hyperphosphatemia, vitamin D deficiency, and SHPT.

Discovering genetic associations, and in particular, the 4 missense mutations on the *GNAS1* gene exons which are seen only in some of the SS patients, indicate that factors other than ESRD milieu play a role in the development of SS, too. Therefore, if we depend only on the full deformities of the syndrome for diagnosis, we will surely miss other cases of the disease with incomplete, but severely destructive pathology, and some patients will be deprived of essential therapeutic measures.

We suggest that all patients with young age and ESRD even without short stature and typical

SS bone deformities be evaluated against SS considering the five factors of anemia, hypocalcemia, hyperphosphatemia, vitamin D deficiency, and PTH levels. Appropriate treatment should be initiated for them to prevent their deterioration into irreversible syndrome.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Aghighi M, Mahdavi-Mazdeh M, Zamyadi M, Heidary Rouchi A, Rajolani H, Nourozi S. Changing epidemiology of end-stage renal disease in last 10 years in Iran. *Iran J Kidney Dis.* 2009;3:192-6.
2. Kestenbaum B, Belzeroff V. Mineral metabolism disturbances in patients with chronic kidney disease. *Eur J Clin Invest.* 2007;37:607-22.
3. Mahdavi-Mazdeh M, Zamyadi M, Norouzi S, Heidary Rouchi A. Management of calcium and phosphorus metabolism in hemodialysis patients in Tehran Province, Iran. *Iran J Kidney Dis.* 2007;1:25-8.
4. Johansen KL, Chertow GM. Chronic kidney disease mineral bone disorder and health-related quality of life among incident end-stage renal-disease patients. *J Ren Nutr.* 2007;17:305-13.
5. Nikodimopoulou M, Liakos S. Secondary hyperparathyroidism and target organs in chronic kidney disease. *Hippokratia.* 2011;15:33-8.
6. Pavlovic D, Brzac HT. Prevention and treatment of secondary hyperparathyroidism: still a challenge for the nephrologist? *Nephrol Dial Transplant.* 2003;18:v45-6.
7. Reichel H. Current treatment options in secondary renal hyperparathyroidism. *Nephrol Dial Transplant.* 2006;21:23-8.
8. Kovesdy CP, Kalantar-Zadeh K. Diuretics and secondary hyperparathyroidism in chronic kidney disease. *Nephrol Dial Transplant.* 2011;26:1122-5.
9. Moe SM, Drueke T, Lameire N, Eknoyan G. Chronic kidney disease-mineral-bone disorder: a new paradigm. *Adv Chronic Kidney Dis.* 2007;14:3-12.
10. Noordzij M, Boeschoten EW, Bos WJ, et al. Disturbed mineral metabolism is associated with muscle and skin complaints in a prospective cohort of dialysis patients. *Nephrol Dial Transplant.* 2007;22:2944-9.
11. Saglikler Y, Balal M, Saglikler Ozkaynak P, et al. Saglikler syndrome: uglifying human face appearance in late and severe secondary hyperparathyroidism in chronic renal failure. *Semin Nephrol.* 2004;24:449-55.
12. Saglikler Y, Acharya V, Ling Z, et al. International study on Saglikler syndrome and uglifying human face appearance in severe and late secondary hyperparathyroidism in chronic kidney disease patients. *J Ren Nutr.* 2008;18:114-7.
13. Yildiz I, Saglikler Y, Demirhan O, et al. International evaluation of unrecognizably uglifying human faces in late and severe secondary hyperparathyroidism in chronic

- kidney disease. saglikler syndrome. a unique catastrophic entity, cytogenetic studies for chromosomal abnormalities, calcium-sensing receptor gene and GNAS1 mutations. Striking and promising missense mutations on the GNAS1 gene exons 1, 4, 10, 4. *J Ren Nutr.* 2012;22:157-61.
14. Stubbs JR, Wetmore JB. Does it matter how parathyroid hormone levels are suppressed in secondary hyperparathyroidism? *Semin Dial.* 2011;24:298-306.
 15. Kakuta T, Tanaka R, Kanai G, et al. Relationship between the weight of parathyroid glands and their secretion of parathyroid hormone in hemodialysis patients with secondary hyperparathyroidism. *Ther Apher Dial.* 2008;12:385-90.
 16. Saliba W, El-Haddad B. Secondary hyperparathyroidism: pathophysiology and treatment. *J Am Board Fam Med.* 2009;22:574-81.
 17. Tomasello S. Secondary hyperparathyroidism and chronic kidney disease. *Diabetes Spectrum.* 2008;21:19-25.
 18. Saglikler Y, Acharya V, Golea O, et al. Is survival enough for quality of life in Saglikler Syndrome-uglifying human face appearances in chronic kidney disease? *J Nephrol.* 2008;21:S134-8.
 19. Erkan AN, Saglikler Y, Yildiz I, Ozluoglu L. Audiological findings in chronic kidney disease patients with Saglikler syndrome. *J Ren Nutr.* 2010;20:S56-8.
 20. Ozenli Y, Giray S, Saglikler Y, Adam SM. A controlled study of psychiatric manifestations and electroencephalography findings in chronic kidney disease patients with Saglikler syndrome. *J Ren Nutr.* 2010;20:S51-5.

Correspondence to:

Seyed Mansour Gatmiri, MD
Nephrology Research Center, Dialysis Ward, Imam Khomeini Hospital, Keshavarz Blvd, Tehran, Iran
Tel: +98 21 6119 2679
Fax: +98 21 6658 1568
E-mail: gatmiri@tums.ac.ir

Received April 2012

Revised May 2013

Accepted May 2013

Archive of SID