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Sagliker Syndrome – A Case Report

Saglikerov sindrom – prikaz slučaja

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Abstract. ***Aim:*** To present a case of Sagliker syndrome (SS), a rare syndrome caused by long-term heavy tertiary hyperparathyroidism (HPT) in end-stage renal disease (ESRD). ***Case report:*** In the year 2000, the 38-year-old man was diagnosed with ESRD. He is currently of low height, paraplegic, pigeon and barrel chested, with elongated upper extremities, deformed fingers, mandibular and maxillary asymmetric deformities with teeth malformations. Due to extremely high serum parathormone (PTH), resistant to pharmacological treatment, subtotal parathyroidectomy (PTx) was performed in 2007. However, he underwent parathyroid resurgery in 2010 for persistently high PTH of more than 2500 pg/mL (upper normal limit 69). In 2012, imaging found two suspected parathyroid glands and one of them was surgically removed. Postoperatively, the expected decrease in calcium and PTH serum concentrations did not occur. Ten years after the diagnosis of ESRD, the patient began to notice more pronounced skeletal deformities (upper, lower jaw, extremities, deformities of fingers, kyphoscoliosis) along with depressive disorder. Laboratory findings still show extremely high PTH (1994 pg/mL), low calcium, 1.89 mmol/L (normal range 2.14–2.53), and high alkaline phosphatase, 837 U/L (normal range 60–120), despite continuous pharmacological treatment. ***Conclusion:*** SS was firstly recognized by Yahya Sagliker in 2004 and it has not been described in Croatia to date. Pervasiveness and knowledge of the syndrome is still poor. The most efficient way of treating/preventing SS is early total PTx in severe secondary HPT related to ESRD. However, it can only stop progress of the disease, but cannot return skeletal deformities.

Keywords: facial asymmetry; hyperparathyroidism; kidney failure, chronic

Sažetak. ***Cilj:*** Prikazati slučaj Saglikerovog sindroma (SS), rijetkog sindroma uzrokovanog teškim oblikom tercijarnog hiperparatireoidizma (HPT) u završnom stupnju kronične bubrežne bolesti (ZSKBB). ***Prikaz slučaja:*** 2000. godine 38-godišnjaku je dijagnosticiran ZSKBB. Trenutačno je niskog rasta, paraplegičan, deformiranih prsa "poput goluba", izduženih gornjih udova, deformiranih prstiju, asimetričnih deformacija gornje i donje čeljusti i zuba. Zbog izrazito visokog parathormona (PTH) u serumu, rezistentnog na farmakološko liječenje, pacijentu je 2007. godine napravljena suptotalna paratireoidektomija (PTx). Zbog trajno visokog PTH, većeg od 2500 pg/ml (normalno < 69) reoperiran je 2010. godine. 2012. su detektirane dvije sumnjive paratireoidne žlijezde te je jedna od njih uklonjena, no očekivano smanjenje koncentracije kalcija i PTH u serumu nije uslijedilo. Deset godina nakon dijagnoze ZSKBB-a bolesnik primjećuje progresiju deformiteta kostiju (gornje i donje čeljusti, udova i prstiju, kifoskoliozu) te pojavu depresije. Trenutačne laboratorijske vrijednosti i dalje pokazuju izrazito visoku razinu PTH (1994 pg/ml), nizak kalcij – 1,89 mmol/l (normalan raspon 2,14 – 2,53) i visoku koncentraciju alkalne fosfataze – 837 U/l (normalan raspon 60 – 120) unatoč dugotrajnom i kontinuiranom liječenju. ***Zaključak:*** SS je prvotno dijagnosticirao Yahya Sagliker 2004. godine te do danas nije bio opisan u Hrvatskoj. Poznavanje ovog sindroma još je oskudno. Najučinkovitiji način liječenja SS-a je rani totalni PTx u bolesnika s teškim oblikom tercijarnog HPT-a povezanog sa ZSKBB-om. Ipak, učinkovito liječenje može jedino zaustaviti napredak bolesti, ali ne i izliječiti nastale deformitete.

Ključne riječi: asimetrija lica; hiperparatireoidizam**;** kronično zatajenje bubrega

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INTRODUCTION

Yahya Sagliker was the first to describe unique patients with uglifying human face appearance and associated that phenomenon with tertiary hyperparathyroidism due to chronic kidney disease (CKD)[1].

The diagnosis of the syndrome is established clinically, based on the most common SS signs: maxillary and mandibular disfiguring bone changes (usually progressing throughout the years), pigeon chest, teeth abnormalities, deformed fingertips, short stature, hearing loss and psychiatric disorders, along with the long-term and severe tertiary hyperparathyroidism. The aim of our case report is to present a patient with clinical features of the stated syndrome and to warn about the severe consequences of the alleged metabolic disorder.

Even though several researches have mentioned the mutations of GNAS and GNAS-AS1 genes on the 20th chromosome as a potential cause of Sagliker syndrome, the exact cause of the syndrome has still not been confirmed.

CASE REPORT

We present a case of a 38-year-old man. He is of low height, short stature, paraplegic, pigeon and barrel chested, with elongated upper extremities and deformed fingers, having mandibular and maxillary asymmetric deformities, with teeth malformations and depression (Figure 1). His paraplegia came as a consequence of congenital lumbosacral meningomyelocele and the related surgery performed at the age of 3 months. In 2000 he presented with painful cramps. By that time his obstructive uropathy resulted in end-stage renal disease (ESRD) and he was treated with chronic hemodialysis three times a week thereafter. In 2007, due to extremely high parathormone (PTH), resistant to pharmacological treatment, subtotal parathyroidectomy (PTx) was performed. The principle of surgical treatment of tertiary hyperparathyroidism includes leaving a part of glandular tissue (partial PTx) in place, or autotransplanting the part ectopically, in order to produce some PTH needed for its physiological function. However, he underwent parathyroid re-operation in 2010 for persistently high PTH of more than 2500 pg/mL (upper normal limit 69 pg/mL). In 2012 neck ultrasound showed two suspected parathyroid glands and in the same year one of the two was surgically removed. Postoperatively, the expected decrease in calcium and PTH serum concentrations did not occur, again. It was ten years after the diagnosis of ESRD when the patient began to notice more pronounced skeletal deformities (upper and lower jaw, extremities with deformities of fingers and kyphoscoliosis). Additionally, in 2018 transversal spontaneous fracture of the proximal diaphysis of the right femur was radiologically confirmed as a consequence of demineralization of the skeleton, with complete absence of radiologic presentation of both sciatic bones and ankylosis of the right hip joint. His current laboratory findings still show extremely high PTH – 1994 pg/mL, low calcium, 1.89 mmol/L (normal range 2.14 – 2.53 mmol/L) and high alkaline phosphatase (ALP), 837 U/L (normal range 60-120 U/L). Pharmacological treatment of the patient included phosphate binders, calcitriol and cinacalcet throughout the disease course, in combinations depending on the serum calcium, phosphate and PTH dynamics

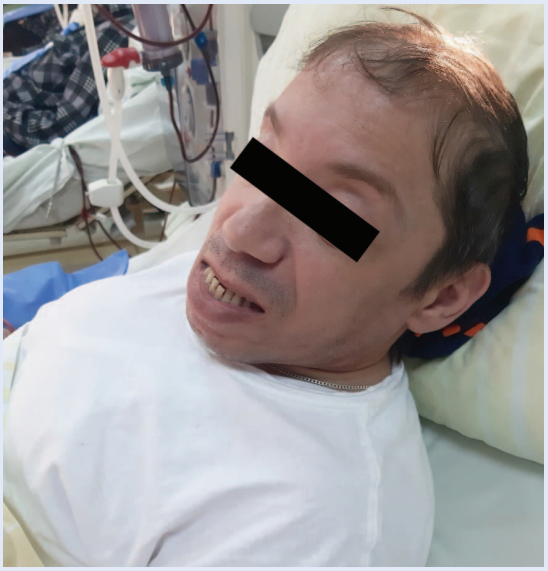

Figure 1. Mandible and maxillary asymmetric deformities with teeth malformations and pigeon chest.

along with the drugs availability at the time. The results of the patient's genetic testing did not show any changes on GNAS and GNAS-AS1 genes. The patient gave informed consent for his data and photo to be published.

DISCUSSION

Even though there is no exact diagnostic criteria for SS, different studies reported physical diagnostic criteria based on clinical presentation including maxillary, mandibular and dental deformities, skeletal changes like short stature, knee and scapula deformities, benign epithelial hyperplasia, fingertip changes, neurological and psychiatric disorders[2]. In 2019 Muhammad Ajmal Panezai et al. reported a case about a 31-year-old African American man in the USA with ESRD on hemodialysis with severe secondary hyperparathyroidism. He noticed swelling of his gums, facial bones, and cheeks that began to increase in size over several years, which was the same case as in our patient[3]. Other symptoms that occured in our patient which are also characteristics of SS are deformed fingers, pigeon and barrel chest, hearing loss and depression. Etiology of the syndrome is tertiary hyperparathyroidism of the chronic kidney disease. However, literature does not provide a clear etiopathological pathway for such bone deforming changes so authors try to hypothesize it. Cholakova et al. explains that commensurate increased serum alkaline phosphatase is responsible for this type of skeletal changes[4]. Yu Yu et al. hypothesized that intramembranous ossification is hyperactivated in this syndrome, which then leads to thickening of the maxilla, anterior mandible and skull[5]. Moreover, in the international research of Yahya Sagliker et al. they concluded that the GNAS1 gene missense mutations, which are possibly activated during the hemodialysis, might be responsible for genesis of SS[6].

Laboratory values that are dominant in this syndrome are high serum PTH and ALP. High PTH (2815.07 pg/mL) and ALP (2350 U/L) with lower range of calcium (2.31 mmol/L) were presented for the patient in the case report done by Yu Yu et al. in China[5]. Moreover, similar laboratory results were given in the research done by A. M. Pineda et al[7]. In the both researches total PTx was performed which resulted in rapid decrease in PTH level. After more than four months, postoperative values of PTH were 131.01 pg/mL in one patient and 15.8 pg/mL in the other[5, 7]. On the other hand, due to unchanging high level of PTH, our patient underwent PTx in 2007. Expected decrease in PTH eventually did not occur, thus parathyroid reoperation was performed in 2010 and again in 2012. After that, the level of PTH was still high. According to the stated results, the most efficient way of treating/preventing SS would be total PTx. We consider it to be a better choice than subtotal PTx, which was also confirmed by the study published by Schneider et al. that reported rates of 4.1 % of persistent renal HPT in patients that underwent subtotal PTx compared to 0 % of persistent renal HPT after total PTx without autotransplatation[8]. Furthermore, recombinant PTH (teriparatide) availability could help with deciding for total PTx in the case of SS in the future. Teriparatide is currently one of the growing solutions in treating osteoporosis. In the research of N. Ayati et al. it was reported how the mutations on the GNAS1 gene were some of the main causes of SS[2]. Moreover, in the study of Azin Mohebi-Nejad et al, it was mentioned how genetic researches have detected 4 missense mutations on the GNAS1 gene among 40 % of patients with SS[9, 10]. However, the results of our patient's genetic testing did not show any changes on GNAS and GNAS-AS1 genes. Even though some other researchers have also mentioned this gene on the 20th chromosome as a potential cause, the exact cause of the syndrome has still not been confirmed.

> The most efficient way of treating/preventing Sagliker syndrome is early total parathyroidectomy in those with severe secondary or tertiary hyperparathyroidism due to ESRD.

CONCLUSION

After the syndrome was described for the first time in 2004, only few cases have been described in the world so far and it has not been described in Croatia to date. Pervasiveness and knowledge

of the syndrome is extremely low, thus there is a possibility of unrecognized patients with the alleged signs. The most efficient way of treating/preventing SS is early total PTx in those with severe secondary or tertiary HPT due to ESRD. However, it can only stop disease progression but cannot return skeletal deformities.

Conflicts of interest: Authors declare no conflicts of interest.

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