HDR SYNDROME: A CASE REPORT OF HYPOPARATHYROIDISM, HEARING LOSS AND RENAL AGENESIS

M. Dimitrova-Mladenova[1], Z.Todorova[1], E. Stefanova[1], A. Kostova[2], D. Yordanova[1], P. Miteva[3], D. Rusinov[3]

1. University Children’s Hospital, Sofia, Bulgaria, Endocrinology Department, Medical University of Sofia, Bulgaria.
2. Medical Center "Children's Health", Sofia, Bulgaria,
3. University Children’s Hospital, Sofia, Bulgaria, Nephrology Department, Medical University of Sofia, Bulgaria.

Disclosure: The authors declare no conflict of interest.

Background: Hypoparathyroidism, sensorineural deafness, and renal disease (HDR syndrome, Barakat syndrome) is a genetic disorder, which was first described in 1977, in two siblings with hypocalcemia and proteinuria. The disease is very rare and there is equal prevalence across ethnic groups and genders. The syndrome is caused by a mutation on chromosome 10p, usually a deletion, which affects the *GATA3* gene. Inheritance is autosomal dominant. In some cases, the genetic cause is unknown. *GATA3* encodes a transcription factor, which is important for the embryonic development of the parathyroid gland, the auditory stem and the kidneys. Its expression has also been found in the thymus and the central nervous system. *GATA3* mutations have not been reported in association with isolated hypoparathyroidism.

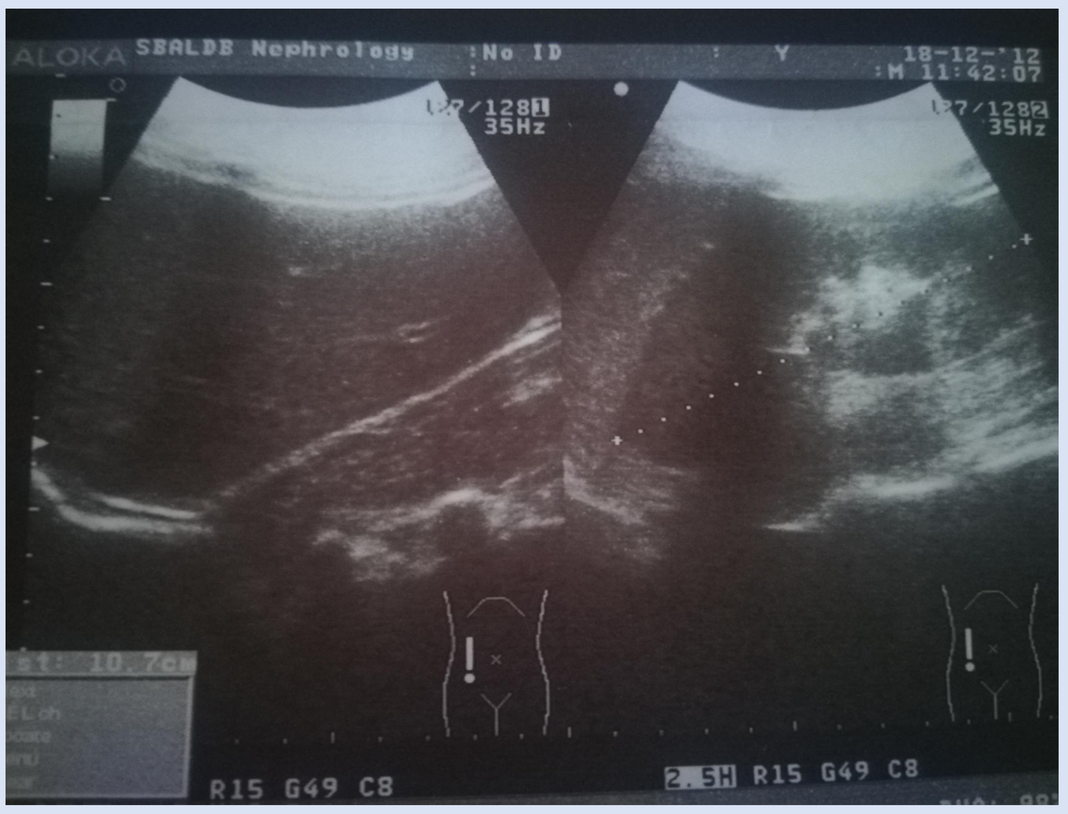
Specific symptoms and their severity can vary. About 65% of people with HDR syndrome have all three of these features. Hypoparathyroidism is reported in 93% of the patients. It causes low levels of blood calcium (hypocalcemia), which leads to muscle pain, muscle spasms, seizures, and cardiomyopathy. Hearing loss is found in 96 % of the cases. It is usually bilateral and can range from moderate to profound. A wide range of renal involvement has been reported in the literature - agenesis, hypoplasia, cystic kidneys, vesicoureteral reflux, nephritic syndrome, hematuria, chronic kidney disease and renal failure. With the routine prenatal ultrasound, congenital anomalies of the kidney and urinary tract may be the presenting finding. Various additional features have been described in some patients with Barakat syndrome such as distinctive facial features, growth failure, intellectual impairment, congenital heart disease, birth defects, retinitis pigmentosa, etc.

The diagnosis of Barakat syndrome is based on the clinical findings of hypoparathyroidism, sensorineural deafness, and renal disease The “HDR” triad was found in around 65% of reported cases. The diagnosis is confirmed in patients who have two of the findings and a positive family history. For those, who have only deafness or renal disease, genetic testing for mutations in *GATA3* gene is needed.

Treatment depends on the symptoms and their severity in each patient. Hypocalcemia is treated with calcium and calcitriol, or parathyroid hormone injection. Hearing amplification and/or cochlear implantation may be needed for hearing loss. Treatment of kidney disease depends on the abnormality and can vary from none to kidney transplantation. Prognosis usually depends on the severity of kidney disease.

Clinical Case: A 14-year old boy was admitted to Endocrinology department with a history of a bilateral sensorineural hearing loss, which was diagnosed at the age of 7 years and tic disorder at the age of 11 years. He had been experiencing 2 episodes of generalized seizure earlier that month, for which he was hospitalized at Neurology department. Cranial CT was performed, showing calcification in the basal ganglia. The boy’s father had hearing loss, but there was no history of kidney disease or hypoparathyroidism. The patient’s vital signs were within the normal range. Neurological examination showed positive Chovestek's sign. Initial biochemical tests revealed hypocalcemia: total Ca 5.01 mg/dl (8.6 -10.2), ionized Ca 2.60 mg/dl (4.8 – 5.5) and hyperphosphatemia: 10.04 mg/dl (2.7 - 4.5). Serum level of parathyroid hormone was not consistent with the hypocalcemia: 20 pg/ml (15-65). Levels of ACTH, cortisol rhythm, TSH and fT4 were also measured and they were in the reference range. There was no impairment of liver and renal functions. Urinalysis did not show proteinuria and hematuria. Urine volume in 24 hours was 1500 mL with normal urine calcium, phosphorus, and creatinine levels. Ultrasound of the kidneys revealed absence of the right kidney with a compensatory hypertrophy of the left one (picture 1). Renal agenesis was subsequently diagnosed by DMSA scintigraphy. Audiometry showed bilateral moderate hearing loss. Echocardiogram revealed normal heart function. No chromosomal abnormalities were detected on standard G-banding analysis.

Initial treatment of the patient included parenteral calcium gluconate infusion, followed by peroral calcitriol and calcium supplementation. The patient was on treatment with valproic acid for symptomatic epilepsy. He was discharged with peroral dihydrotachysterol and a high-calcium, low-phosphorous diet. The patient was followed up in our department. Microalbuminuria was detected at the age of 16 years and a small dose of ACE inhibitor was included to the therapy. The boy was subsequently followed up by endocrinologist and nephrologist.



Picture 1. Ultrasound of the liver and the left kidney. The right kidney is absent, and the left one has compensatory hypertrophy.

Conclusion: HDR syndrome is a genetic disorder with phenotypic variability. Diagnosis is based on the clinical finding. In conclusion, we recommend that, a patient presenting with seizures, associated with deafness, should undergo determination of serum calcium, phosphate and parathyroid hormone, as well as renal imaging.

References:

1. Barakat AJ, Raygada M, Rennert OM. Barakat syndrome revisited. Send to Am J Med Genet A. June, 2018; 176(6):1341-1348.
2. Muroya K, et al. GATA3 abnormalities and the phenotypic spectrum of HDR syndrome. J Med Genet 2001; 38: 374-80.
3. van Esch H, P. Groenen P, Nesbit M.A. et al., GATA3 haplo-insufficiency causes human HDR syndrome, Nature, vol. 406, no. 6794, pp. 419–422, 2000.
4. Taslipinar A., Kebapcilar L., Kutlu M. et al., HDR syndrome (hypoparathyroidism, sensorineural deafness and renal disease) accompanied by renal tubular acidosis and endocrine abnormalities, Internal Medicine, vol. 47, no. 11, pp. 1003–1007, 2008.
5. Ranjbar-Omrani G., Zamiri N., Sabayan B., Mohammadzadeh, A. Concomitant hypoparathyroidism, sensorineural deafness, and renal agenesis: a case of Barakat syndrome, Archives of Iranian Medicine, vol. 11, no. 3, pp. 337–340, 2008.
6. Maleki N., Bashardoust B., Alamdari, MI, Tavosi Z., Seizure, Deafness, and Renal Failure: A Case of Barakat Syndrome, Case Reports in Nephrology, Vol. 2013, ID 261907, 2013.
7. J van Looij M., Meijers-Heijboer H., Beetz R. et al., Characteristics of hearing loss in HDR (hypoparathyroidism, sensorineural deafness, renal dysplasia) syndrome, Audiology and Neurology, vol. 11, no. 6, pp. 373–379, 2006.