Case Report

Iran J Pediatr
Mar 2010; Vol 20 (No 1), Pp:123-126

HDR Syndrome (Hypoparathyroidism, Sensorineural Deafness and Renal Disease) Accompanied by Hirschsprung Disease

Mohsen Akhavan Sepahi*[1], MD; Behrouz Baraty[2], MD and Fatemeh Khalifeh Shooshtary[2], MD

1. Clinical research Development Center, Qom University of Medical Sciences, Qom, IR Iran
2. Isfahan University of Medical Sciences, Isfahan, IR Iran

Received: *Sep 25, 2008*; Final Revision: *Jan 23, 2009*; Accepted: *Jul 08, 2009*

Abstract

Background: HDR syndrome (hypoparathyroidism, sensorineural deafness and renal disease) is an autosomal dominant condition, defined by the triad hypoparathyroidism, renal dysplasia and hearing loss. Hirschsprung (HSCR) disease is a variable congenital absence of ganglion cells of the enteric nervous system resulting in degrees of functional bowel obstruction. Rarer chromosomal anomalies are reported in combination with Hirschsprung disease like DiGeorge syndrome, mosaic trisomy 8, XXY chromosomal constitution, partial duplication of chromosome 2q, tetrasomy 9p, and 20p deletion.

Case Presentation: Here, we describe an 8 year-old girl with HDR syndrome accompanied by Hirschsprung disease. Although the association of Hirschsprung disease with chromosomal anomalies has been reported, according to our knowledge, this is the first report of associated HSCR with HDR syndrome.

Conclusion: The association of HSCR with HDR syndrome has not been reported in previous studies. This association should be evaluated genetically to assess chromosomal relationships.

Iranian Journal of Pediatrics, Volume 20 (Number 1), March 2010, Pages: 123-126

Key Words: Hirschsprung Disease; Deafness; Sensorineural Hearing Loss; Hypoparathyroidism; HDR Syndrome

Introduction

Hypoparathyroidism, sensorineural deafness and renal disease, also known as HDR syndrome, was first described by Barakat et al. in 1977. It is a genetic developmental disorder with clinical diversity[1]. Patients usually present with hypocalcaemia, tetany, or afebrile convulsions at any age[2,3,4]. Hearing loss is usually bilateral and may range from mild to profound impairment. Renal disease includes nephrotic syndrome, cystic kidney, renal dysplasia, hypoplasia or aplasia, pelvicocalyceal deformity, vesicoureteral reflux, chronic renal failure, hematuria,

*** Corresponding Author;**
Address: Clinical Research Development Center, Fatemi pediatric Hospital, Shahid Lavasani St, Qom, IR Iran
E-mail: akhavansepahim@yahoo.com

proteinuria and renal scarring. Inheritance mode is probably autosomal dominant[5,6,7]. The frequency is unknown, but it is considered to be very rare[8].

This syndrome is primarily caused by haplo-insufficiency of the dual zinc finger transcription factor, GATA3 (glutamyl amidotransferase subunit A), or mutations in the GATA3 gene, which is contained on the short arm of chromosome 10[9,10].

A thorough diagnosis should be performed on every affected individual, and siblings should be studied for deafness, parathyroid and renal disease. The prognosis depends on the severity of the kidney disease[7].

Hirschsprung disease (HSCR, aganglionic megacolon) represents the main genetic cause of functional intestinal obstruction[11]. The absence of intramural ganglion cells of the myenteric (Auerbach) and submucosal (Meissner) plexuses downstream of the dilated part of the colon was recognized as the cause of the disease in 1940. This allowed a simple and reliable diagnostic confirmation from rectal suction biopsies using histochemical staining for acetylcholine-esterase. Coding sequence mutations are identified in about 50% of familial and 15% of sporadic HSCR cases[12,13].

We report a case of HDR syndrome accompanied with Hirschsprung disease in an 8 year-old girl. According to our knowledge, this is the first report of such concordance.

Case Presentation

The patient was an 8 year-old girl referred to our hospital due to recurrent seizures and decreased level of consciousness. She was the family's second child born at term by caesarean section (repeat section) with birth weight of 3500gr. She had blue eyes, normal skin and hair pigmentation as well as normal phenotypic features. She had passed meconium not spontaneously but after anal stimulation. When she was 1 month old, she underwent colostomy and at the age of 18 months, a pull-through operation with closure of colostomy was performed. A 10×1.5 cm portion of small intestine with serosa and mesentry which contained many lymph nodes and a 10×3 cm portion of colon, inside-out with rough and congested mucosa and abnormal folds was sent for histopathological study.

The report indicated that ganglion cells were present below and also above the aganglionic segment (zonal colonic aganglionosis), although the distal ganglion cells were degenerated. Hirschsprung disease was documented histopathologically.

When 9 months old, she developed microscopic hematuria; bilateral renal stone was reported in ultrasound study. She experienced several hospitalizations due to recurrent urinary tract infections (UTI). Hypocitraturia and hyperuricosuria were identified as the main causes of stone formation. Routine audiological assessment showed bilateral sensorineural hearing loss. When 3 years old, total colectomy was carried out.

There was second degree consanguinity between her parents. Although they were without any congenital or developmental disorder, they carried a positive family history of bilateral sensorineural deafness in father's uncle. At the same time the patient's healthy sister showed no congenital or developmental disorder.

On primary clinical assessment, she was 100.0 cm in height and 17 kg in weight [failure to thrive; Gomez classification: grade II; moderate malnutrition, Welcome classification: undernutrition and Waterlow classification; percent weight for height (wasting): normal and percent height for age: severe stunting], pulse rate 80 beats/min, blood pressure 100/80 mmHg in recumbent position. Other physical examinations revealed no significant finding. Laboratory data are listed in table 1.

In kidney and urinary tract sonography, both kidneys were bigger than normal (right kidney: 86 mm and left kidney: 80 mm), with echogenic parenchyma, without hydronephrosis, stone or space occupying lesion. Acute parenchyma involvement was suggested. Voiding cystourethrogram (VCUG) showed Christmas tree pattern, offering neurogenic bladder, with no vesicoureteral reflux. Echocardiography had

Table 1: Laboratory data of our patient with HDR Syndrome

Test	Measured level	Normal values
Hemoglobin (gr/dl)	10.7	12-17
White blood cells (10^3/µl)	6.5	4-10
Polymorphs(%)	68	
Lymphocyte (%)	21	
Monocyte (%)	10	
Eosinophil (%)	1	
Platelet (10^3/µl)	182	150-450
Sedimentation Rate (mm [1hr])	20	
C-Reactive Protein	Positive (1+)	
Blood Urea Nitrogen (mg/dl)	38	5-22
Creatinine (mg/dl)	1.8	0.9-1.6
Serum Calcium (mg/dl)	7.5	8.1-10.4
Serum Phosphor (mg/dl)	3.5	3.5-5.5
Serum Sodium (mEq/l)	134	135-145
Serum Potassium (mEq/l)	3.1	3.5-5.5
Serum Cloride (mEq/l)	104	96-106
Serum Magnesium (mg/dl)	1.7	1.8-3.0
Uric Acid (mg/dl)	3.5	2.1-8.5
Total Protein (gr/dl)	7.08	6.5-8.2
Albumin (g/dl)	4.13	3.8-5.1
FBS (mg/dl)	75	70-110
Parathyroid hormone (PTH) (pg/ml)	3.5	9-52
Blood pH	7.2	7.35-7.45
Blood pCO2 (mmHg)	28.9	35-45
Blood pO2 (mmHg)	110.4	80-100
Blood HCO3 (mmol/l)	12	22-26

no evidence of cardiac involvement. Auditory brainstem responses were not observed at 80 dB in both ears. On dimercaptosuccinic acid (DMSA) scan minimally decrement in cortical function of the upper and lower pole of both kidneys were reported.

The present case was diagnosed as HDR syndrome in association with Hirschsprung disease based on the patient's clinical manifestations and laboratory evaluations; unfortunately it is analyzed without deletion-mapping studies and subsequent mutation analysis.

Discussion

This is a report on a case of HDR syndrome associated with Hirschsprung disease. Hirschsprung disease is the variable congenital absence of ganglion cells from the enteric nervous system resulting degrees of functional bowel obstruction.

HSCR occurs as an isolated trait in 70% of patients, in association with a chromosomal abnormality it exists in 12% of cases, and 18% of cases are associated with additional congenital anomalies[11,13]. Hearing loss in combination with hypoparathyroidism and renal dysplasia was first described in 1977 by Barakat et al[7]. Hasegawa et al termed this disease "HDR syndrome" and identified the responsible gene map on chromosome 10p[5,9].

A large number of chromosomal anomalies have been described in HSCR patients[13]. DiGeorge syndrome, mosaic trisomy 8, XXY chromosomal constitution, partial duplication of chromosome 2q, tetrasomy 9p, and 20p deletion, have been observed at least once with HSCR[13,14].

Santos et al reported association of Hirschsprung disease with polydactyly, unilateral renal agenesis, hypertelorism, and

congenital deafness in sibs (brother and sister) of consanguineous parents[6].

Reish et al reported two half brothers (maternally related) with similar pattern of malformations including brain anomaly, retardation of mentality and growth, ectodermal dysplasia, skeletal deformities, Hirschsprung disease, ear deformity and deafness, eye anomalies, cleft palate/cryptor-chidism, and kidney dysplasia/hypoplasia and reflux. They named this condition BRESEK/BRESHECK syndrome[15].

Although the studies mentioned above report the association of HSCR with deafness and renal disease, none of them had hypoparathyroidism, so according to our knowledge, this is the first report of HSCR associated with HDR syndrome.

HSCR, resulting from the effects of at least 9 known susceptibility genes[12,14]; one of the chromosomal interstitial deletions reported in combination with HSCR is 10q11[13], on the other hand, mutations in the GATA3 gene, which is located on the short arm of chromosome 10, cause HDR syndrome[10]. Therefore gene that affects HDR syndrome may cause HSCR. This hypothesis should be evaluated by chromosomal studies.

Conclusion

The association of HSCR with HDR syndrome has not been reported in previous studies. This association should be evaluated genetically to assess chromosomal relationships.

References

1. Bilous RW, Murty G, Parkinson DB, et al. Autosomal dominant familial hypopara-thyroidism, sensorineural deafness, and renal dysplasia. New Eng J Med. 1992;327(15):1069-74.
2. Goodyer PR. Renal Dysplasia/ Hypoplasia. In: Avner E, Harmon W, Niaudet P. Pediatric Nephrology. Philadelphia, Lippincott Williams & Wilkins. 2004; Pp:83-92.
3. Marcdate KJ. Nephrology and urology. In: Kliegman RM, Marcdate KJ, Jenson HB, Behrman RE. Nelson Essentials of Pediatrics, 5th edition. Philadelphia, Elsevier Saunders, 2006; Pp:751-70.
4. Parks JS, Felner EI. Disorders of the hypothalamus and pituitary gland. In: Behrman RE, Kliegman RM, Jenson HB. Nelson Textbook of Pediatrics, 18th ed. Philadelphia, Elsevier Saunders, 2007; Pp: 2291-3.
5. Adachi M, Tachibana K, Asakura Y, et al. A novel mutation in the GATA3 gene in a family with HDR syndrome (Hypoparathyroidism, sensorineural deafness and renal anomaly syndrome). J Pediatr Endocrinol Metab. 2006; 19(1):87-92.
6. Santos H, Mateus J, Leal MJ. Hirschsprung disease associated with polydactyly, unilateral renal agenesis, hypertelorism, and congenital deafness: A new autosomal recessive syndrome. J Med Genet. 1988;25(3):204–5.
7. Barakat AJ. Hypoparathyroidism, sensorineural deafness, and renal disease. Orphanet Encyclopedia. March 2006.
8. Barakat AY, D'Albora JB, Martin MM, et al. Familial nephrosis, nerve deafness, and hypoparathyroidism. J Pediatr. 1977;91(1):61-4.
9. Hasegawa T, Hasegawa Y, Aso T, et al. HDR syndrome (hypopara-thyroidism, sensorineural deafness, renal dysplasia) associated with del (10)(p13). Am J Med Genet. 1997; 73(4): 416-8. Review.
10. van Esch H, Groenen P, Nesbit MA, et al. GATA3 haplo–Insufficiency causes human HDR syndrome. Nature. 2000;406(6794):419-22..
11. Karim S, Hession C, Marconi S, et al. The identification of ganglion cells in Hirschsprung disease by the immunohistochemical detection of ret oncoprotein. Am J Clin Pathol. 2008; 129(5):827.
12. Kim HJ, Kim AY, Lee CW, et al. Hirschsprung disease and hypoganglionosis in adults: radiologic findings and differentiation. Radiology. 2008;247(2):428-34.
13. Amiel J, Sproat-Emison E, Garcia-Barcelo M, et al, Hirschsprung disease, associated syndromes and genetics: a review. J Med Genet. 2008; 45(1):1-14.
14. Moore SW, Zaahl MG. A review of genetic mutation in familial Hirschsprung's disease in South Africa: towards genetic counseling. J Pediatr Surg. 2008;43(2):325-9.
15. Reish O, Gorlin RJ, Hordinsky M, et al. Brain anomalies, retardation of mentality and growth, ectodermal dysplasia, skeletal malformations, Hirschsprung disease, ear deformity and deafness, eye hypoplasia, cleft palate, cryptorchidism, and kidney dysplasia/ hypoplasia (BRESEK/BRESHECK): new X-linked syndrome? Am J Med Genet. 1997; 68(4): 386–90.