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CASE REPORT

Denys-Drash syndrome in Saudi Arabia

Ahmed AbuAlreesh[1]*, Zuhair Rahbeeni[2], Rayah Asiri[3]

ABSTRACT

Background: Denys-Drash syndrome (DDS) is a very rare genetic disease. Wilms' tumor, genital abnormalities, and congenital glomerulopathy are the main features of DDS which resulted from a heterozygous mutation in the *WT1* gene.

Case Presentation: First case of DDS has been diagnosed in Saudi Arabia in 4-months newborn who admitted to Nephrology Department with ambiguous bilateral undescended testis and nephropathy. On admission, he had normal vital signs except high blood pressure. His kidney function tests showed abnormal kidney function. Ultrasonography and magnetic resonance imaging (MRI) were done to figure out his nephropathy and undescended testis, respectively. Both abdominal ultrasonography and kidney histopathology confirmed diffuse mesangial sclerosis. The MRI graph located the un-identical ectopic testis. The autosomal dominant inherited pathogenic missense mutation in exon 9 of *WT1* gene [c.1181G>A; (p.Arg394GLu)] was confirmed by DNA direct sequencing analysis. At his 4th year of age, his nephropathy developed to end stage renal disease.

Conclusion: DDS should be considered in newborn baby with nephrotic syndrome and ambiguous gonads. DNA direct sequencing analysis for *WT1* gene is very helpful for confirmation of DDS.

Keywords: Denys-Drash syndrome (DDS), *WT1* gene, Wilm's tumor, nephropathy, diffuse mesangial sclerosis (DMS), undescended testis.

Introduction

Denys-Drash syndrome (DDS) is a very rare genetic disease. Nearly, 150 cases reported over the world. Wilms' tumor, genital abnormalities, and congenital glomerulopathy are the main features of DDS (1). The most common cause of DDS is a heterozygous mutation in the *WT1* gene (Wilms tumor suppressor gene) on chromosome 11p13. *WT1* contains a zinc-finger transcription factor that plays a crucial role in the development of both kidney and genitalia (2). This mutation usually occurs in the zinc-finger DNA binding region in exon 8 or 9 (3–5).

At the first few months after delivery, the patient suffers from nephrotic syndrome associated with diffuse mesangial sclerosis (DMS) which developed to end stage kidney disease during the upcoming years (1).

This patient came to the hospital with identical symptoms of DDS. Therefore, this case was reported for educational purpose because this is the first typical case o f DDS diagnosed in Saudi Arabia.

Case Presentation

Four-month-old newborn was referred to King Faisal Specialists Hospital and Research Center (KFSH) for nephrology consultation because the patient had bilateral undescended testis, epistaxis, and nephropathy.

He was a full-term baby born via cesarean section at 40 weeks of gestation, with a 4,150 g birth weight. He was admitted to the neonate intensive care unit in one of the local hospital for 1 week because of unspecified thrombocytopenia where he received platelets and discharged. At 1 month of age, the patient starts to have shortness of breath and bilateral epistaxis with decrease activity and decrease feeding. The patient received diuretics and his parents sought medical advice; therefore, he was referred to KFSH for further investigation.

He is the second child of a 26-year-old healthy housewife and 30-year-old healthy military father. Parents were first degree cousins and have another alive and healthy child. They have no history of neonatal deaths, metabolic disease, or acidosis.

At the time of admission, His blood pressure was 130/80 mmHg which is above the 95th percentile. The patient

Correspondence to: Ahmed Abualreesh
*Clinical Pharmacy Department, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia.
Email: ahmedaboalreesh1989@gmail.com
Full list of author information is available at the end of the article.
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was having generalized edema involving the whole lower limb with puffiness of the face and periorbital edema also the scrotum was swollen bilaterally, and no ascites was appreciated upon the examination. The pediatric early warning system score was 3; two points for the irritable behavior and one point for his pale cardiovascular feature (6). The stretched penile length was 1.5 cm (<10th percentile) with penoscrotal hypospadias, bifid scrotum, and nonpalpable gonads. He was afebrile (36.5 C) with heart rate 135 beats/minute and respiratory rate 44 breaths/minutes. His oxygen saturation was normal (98%). His weight was 7.36 kg which is in the 64th percentile and his length 62.5 cm which is in the 24th percentile. Chest examination showed equal air entry bilaterally with no added sound. Cardiovascular examination showed S1 and S2 with no murmur and no added sounds. His abdomen was soft and lax.

In-hospital investigations revealed that his urinary protein was 1.33 g/l while his serum creatinine level was 223 μmol/l and the BUN was 8.6 mg/dl. The glomerular filtration rate was 8.12 ml/min/1.73m^2. His liver function tests were within the normal limits, blood glucose was 9.1 mmol/l, his WBC was 17.5 * 10^3/ml while his RBCs was 3.2 * 10^6/ml, Hgb level was 8.3 g/dl, platelet level was 428 * 10^3/ml.

Abdominal ultrasound showed bilateral nephromegaly, mild dilatation of both kidneys, and small amount of ascites and the picture was going with nephrotic syndrome.

After 1 month, another abdominal ultrasonography was done to make comparison with the previous ultrasonography. The latter one revealed that the moderate diffuse increased bilateral renal parenchymal echogenicity with reduced corticomedullary differentiation. No hydronephrosis was detected.

The histopathological examination of a biopsy from the left kidney showed that there is advanced renal sclerosis with moderate arteriosclerosis. The differential diagnosis is between congenital nephrotic syndrome of Finnish type or DMS. However, with the clinical presentation of hypertension and rapid progression to renal failure, DMS was more likely.

Standard ultrasonography of the scrotum and bilateral inguinal regions exam was done to evaluate the undescended testis. No testes were visualized within the inguinal regions or scrotum, whether they were very atrophied or not descended from the abdomen. Therefore, magnetic resonance imaging abdomen and pelvis without contrast was done. Ectopic high position right testicle was noted in the pelvis adjacent to the lateral right psoas muscle, measuring around 1.2 × 1 cm. On the other hand, the left testicle was in the left lower pelvis, adjacent to the left external iliac vessels, measuring around 1 × 0.5 cm.

DNA direct sequencing analysis of exon 9 has been done for nephrotic syndrome evaluation. This test revealed that the patient has a heterozygous missense mutation in WT1 gene. This mutation is a pathogenic mutation which resulted from Guanine transitioning to Adenine in the nucleotide position 1181 in codon 394 resulted in replacement of the arginine amino acid into glutamine [c.1181G>A (p.Arg394GLu)]. This autosomal dominant inherited pathogenic mutation leads to nephrotic syndrome. Due to his nephrotic syndrome, bilateral nephrectomy was done.

The result of DNA direct sequencing analysis, in addition to the previous findings, confirmed that the patient has DDS.

Discussion

WT1 gene is a protein producing gene. It includes a zinc-finger transcription factor which provides instructions for making crucial kidney and gonads proteins (7). *WT1* gene produces four different messenger RNAs through 10 exons within this gene. Exon 9 has crucial role in inclusion and exclusion of three amino acids, lysine, threonine, and serine (KTS). Inclusion of the KTS amino acids produces the KTS-positive isoform while KTS-negative isoform produced when these amino acids excluded. The normal function of WT1 gene depends on the precise ratio between KTS-positive and KTS-negative isoforms. Mutation in the exon 9 resulted in the replacement of amino acids and loss of this biological ratio (8–12).

"The WT1 protein mediates the mesenchymal-epithelial transition and differentiation during morphogenesis of the kidney and gonad by repressing genes that encode cell proliferation factors and by activating genes that encode markers of epithelial cell differentiation" (12). DDS resulted from point mutation in *WT1* gene which leads to the malformation of the kidney and gonads. Alteration in the KTS-positive and KTS-negative isoforms ratio from 2:1 to 1:2 results in Frasier syndrome. Wilms tumor, aniridia, genitourinary malformations, and mental retardation syndrome resulted from the complete deletion of the band 11p13 (8–12).

This mutation is an autosomal dominant inherited pathogenic mutation; therefore, parent's genetic examination was not done but they were counseled by the genetic counselors that provided genetic counseling about primary prevention of this genetic disease through intensive family education and preventive reproductive options.

Conclusion

To conclude, DDS is a very rare disease, and this is the first diagnosed case in Saudi Arabia. DDS should be considered in a new born baby with nephrotic syndrome and ambiguous gonads. DNA direct sequencing analysis for WT1 gene is very helpful for confirmation of DDS.

Declaration of conflicting interests
The authors of this report have no affiliations with or involvement in any organization or entity with any financial

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Consent of publication
Parent's consent form was taken, but, unfortunately, they refused to publish the photos of their baby's symptoms.

Ethical Approval
Ethical approval is not required at our institution to publish an anonymous case report.

Author details
Ahmed AbuAlreesh[1], Zuhair Rahbeeni[2], Rayah Asiri[3]
1. Clinical Pharmacy Department, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia
2. Department of Medical Genetics, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia
3. College of Pharmacy, King Khalid University, Abha, Saudi Arabia

References

1. Hakan N, Aydin M, Erdogan O, Cavusoglu YH, Aycan Z, Ozaltin F, et al. A novel WT1 gene mutation in a newborn infant diagnosed with Denys-Drash syndrome. Genet Couns 2012; 23(2):255–61.
2. Pritchard-Jones K, Fleming S, Davidson D, Bickmore W, Porteous D, Gosden C, et al. The candidate Wilms' tumour gene is involved in genitourinary development. Nature 1990; 346(6280):194–7; https://doi.org/10.1038/346194a0
3. Little M, Holmes G, Bickmore W, van Heyningen V, Hastie N, Wainwright B. DNA binding capacity of the WT1 protein is abolished by Denys-Drash syndrome WT1 point mutations. Hum Mol Genet 1995; 4(3):351–8; https://doi.org/10.1093/hmg/4.3.351
4. Mueller RF. The Denys-Drash syndrome. J Med Genet 1994; 31(6):471–7; https://doi.org/10.1136/jmg.31.6.471
5. Pelletier J, Bruening W, Kashtan CE, Mauer SM, Manivel JC, Striegel JE, et al. Germline mutations in the Wilms' tumor suppressor gene are associated with abnormal urogenital development in Denys-Drash syndrome. Cell 1991; 67(2):437–47; https://doi.org/10.1016/0092-8674(91)90194-4
6. Duncan H, Hutchison J, Parshuram CS. The pediatric early warning system score: a severity of illness score to predict urgent medical need in hospitalized children. J Crit Care 2006; 21(3):271–8; https://doi.org/10.1016/j.jcrc.2006.06.007
7. Al-Hussain T, Ali A, Akhtar M. Wilms tumor: an update. Adv Anat Pathol 2014; 21(3):16673; https://doi.org/10.1097/PAP.0000000000000017
8. Andrade JGR de, Guaragna MS, Soardi FC, Guerra-Júnior G, Mello MP de, Maciel-Guerra AT. Clinical and genetic findings of five patients with WT1-related disorders. Arq Bras Endocrinol Metabol 2008; 52(8):1236–43; https://doi.org/10.1590/S0004-27302008000800006
9. Furtado L V, Pysher T, Opitz J, Lamb R, Comstock J, Batish S, et al. Denys-Drash syndrome with neonatal renal failure in monozygotic twins due to C. 1097G> A mutation in the WT1 gene. Fetal Pediatr Pathol 2011; 30(4):266–72; https://doi.org/10.3109/15513815.2011.555814
10. Guaragna MS, Soardi FC, Assumpção JG, Zambaldi L de JG, Cardinalli IA, Yunes JA, et al. The novel WT1 gene mutation p. H377N associated to Denys-Drash syndrome. J Pediatr Hematol Oncol 2010; 32(6):486–8; https://doi.org/10.1097/MPH.0b013e3181e5e20d
11. Da Silva TE, Nishi MY, Costa EMF, Martin RM, Carvalho FM, Mendonca BB, et al. A novel WT1 heterozygous nonsense mutation (p. K248X) causing a mild and slightly progressive nephropathy in a 46, XY patient with Denys–Drash syndrome. Pediatr Nephrol 2011; 26(8):1311–5; https://doi.org/10.1007/s00467-011-1847-4
12. Kučinskas L, Rudaitis Š, Pundzienė B, Just W. Denys-Drash syndrome. Medicina (B Aires) 2005; 41(2):132–4.