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Woodhouse-Sakati Syndrome with Unique Unreported Previous Findings

Amer O AlAli[1*], Mohammed A Soeid[1], Ahmed E Shamakhi[2], Mosa Hakami[2], Mohammed Q Masmali[2], Omar E Masmali[2], Amro Alomar[2], Mohammed A fagehi[2], Mohammad A Razzaque[2], Badi Alenazi[3], Shemah M hakami[4], and Nasir Al-Jurayyan[5]

[1]Pediatric Endocrine Consultant, King fahad central hospital, Jazan, Saudi Arabia
[2]Pediatric Consultant, King fahad central hospital, Jazan, Saudi Arabia
[3]Endocrine Assistant Consultant, Alyamamah Hospital, Riyadh, Saudi Arabia
[4]Nurse, alsafa primary health care, jazan Saudi Arabia
[5]Proffesor of pediateric endocrine, King Saud Uneveristy Hopsital, Riadh, Saudi Arabia

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***Corresponding author:** Amer O AlAli

Abstract **Case Report**

We present here at 16 years old a Saudi girl with alopecia which noted since birth and delayed puberty and short stature, dyslipidemia, diabetes and hypothyroidism. Family history was positive for similar complaints. Genetic study shows a mutation at DCAF17 which is known a common founder mutation confirming diagnosis of Woodhouse-Sakati Syndrome. This patient has many unreported findings of hepatic hemangioma, with Hepatomegaly, high indirect bilirubin, high uric acid, focal segmental Glomerulonephritis and low growth hormone level. Presentation of this syndrome may overlap with other important differential diagnosis like autoimmune polyendocrine syndrome, Alopecia-progressive neurological defect (ANE syndrome), and Turner and Mitochondrial disease. In such presentation, the presence of dysmorphic features and low intelligence quotient (IQ) scores, should alert the physician to look for WSS as a possible diagnosis.

Keywords: Woodhouse-Sakati Syndrome, Hypogonadism, Alopecia, hepatic hemangioma, Hepatomegaly, focal segmental Glomerlunephritis and Extrapyramidal Syndrome.

INTRODUCTION

Woodhouse-Sakati syndrome (WSS) is a rare, multisystem genetic condition with autosomal recessive inheritance. First described in 1983 in Saudi Girl Dr. Sakkati and DR. Woodhouse. It may present with various nonspecific presentations like: alopecia (first symptom), Hypothyroidism, Hypogonadism, Diabetes, Dyslipidemia, but short stature with low growth hormone level, is not a known part of this syndrome [1].

Extrapyramidal neurologic manifestation with cognitive impairment, magnetic resonance imaging (MRI) abnormalities like:

Small pituitary gland, iron deposition in the globus pallidus, leukoencephalopathy, and basal ganglia calcification [2-4].

Other common findings includes: sensorineural hearing loss, premature aging, electrocardiography (ECG) changes, distinctive facial features (e.g., elongated triangular face, prominent ears, and prominent nasal root). This syndrome is caused by homozygous or compound heterozygous mutations in the DCAF17 gene that encodes a nuclear protein with a poorly understood function. The pathogenic mechanism underlying WSS is not known, but hypothetically, the syndrome may result from defective ribosome biogenesis or other nuclear dysfunction affecting cell cycle regulation or cellular aging [5-7].

CASE PRESENTATION

A 16 years old, female, who had alopecia totalis since birth, presented with delayed puberty and primary amenorrhea.

She had chronic and frequent joint pain, and learning disability, but no history of polyuria or polydipsia. Family history was positive for similar complaints in 3 other sibling but both parents are healthy.

- Examination
- short girl (Ht = 139 cm, < 3 SD), (BMI= 24.4), High BP, dysmorphic features include:

- Alopecia totalis, Triangular face, Flat occipit, High forehead with long face, Frontal bossing, Hypotolerism ,Short sparse eyebrow
- Wide space between 1st, 2nd toes.
- Dystrophic Yellow, thick big toe, pincer nail.
- Eye : compound myopic astigmatism but , no keratoconus
- Tanner stage 1.
- Scoliosis.
- No goiter
- No acanthosis nigrican
- Cardiac examination and ECG was normal
- Chest and abdomen exam was normal.
- CNS examination was normal with no dysarthria, or dystonia or abnormal movement
- Low I. Q of 70 and intellectual disability.
- hearing is intact with normal audiogram

Investigation

Test	Result (normal range)	Comments	Action
FSH	27 (0.3 to 10.0 mIU/mL)	High	Ovarin failure, causing osteopenia Estrogen started initally then OCT.
LH	43 (5 to 25 IU/L)	High	
estrogen	16 , (30 to 400 pg/mL)	Low	
Vitamin D25	8 (20- 40 ng/mL)	Vitamin D deficiency, started on cholecalciferol	
PTH , Ca ,Po4	Normal		
Dexa scan	severe osteopenia		
US pelvis	Small uterus ovary		
GH stimulation test	4 ng/ml (Above 10)	Low	GH defeiciency started on GH with minimal response
IGF1	66 (154-485 ng/ml)	Low	

TSH	15 mIU/L. (0.5 – 5)	High	primary hypothryodism thyroxine started
T4	4 µg/dL (5.0 to 12.0µg/dL)	Low,	
Thyroid antibody	Negative	Non autoimmune primary hypothrodism	
HBA1C	11.5 (4 - 5.6)	High, indicating DM	Started on Metformine and lantus and HBA1c drop to 7 after 3 months
Random Blood glucose	23.9 mmol (3.8 -7.7)		
Fasting glucose	14.5 mmol (6.1)		
IA2 antibody	Positive	Possible autoimmune type of diabetes	Request other Antibody (1)
Other antibody *1	negative	Against autoimmune disorder	
urea	12 (1.8 to 7.1 mmol urea per liter)	High	Started on ACE inhibitor, hydrochlorothiazide and renal function normalised after 3 months
Creatinine	4.2 (0.6 to 1.1 mg/dL)	High , indicating renal failure	
Urine examination	Glucosurea = +3 RBS +3	- protinurea +3 No ketone	
renal biopsy	Interstitial fibrosis and tubular atrophy with primary non autoimmune moderate Focal segmental Glomerulonephritis		
Uric acid	18 mg/dL (2.7-7.3 mg/dL)	High	Allopurinol started
Chromosomal analysis	46 xx		Normal female
Cholesterol	280mg/dL (less than 200 mg/dL)	High	dyslipidemia Lipitor started
TG	210 (Less than 150 mg/d)	High	
Liver enzyme	Normal		
Indirect bilirubin	2,4 (0.2-0.8 mg/dL)	High , indicating possible obstruction biliary tract	US abdomen
US abdomen	Intrahepatic hemangioma and hepatomegaly		
skin biopsy	reduced number of eccrine gland		congenital hypotrichosis
Lactic acid	Normal		

1*include: anti endomyseal, Anti 21 hydroxylase antibody, Anti. GAD, Anti Insulin Receptor ,Thyroid M AB, Thyroid peroxidase Ab, Anti Endomyseal Ab, Anti TTG Ab, ANA, Anti Ds DNA, Anti Ro Ab, Anti LA , C – ANCA, P-ANCA

Computed Tomography (CT)

CT show Basal ganglia calcification, Figure (1)

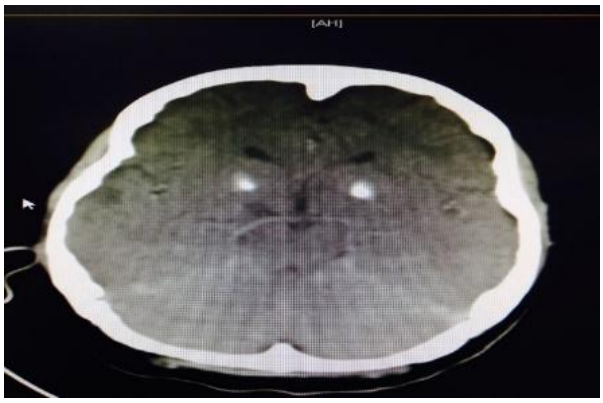

Fig-1

Genetic study
Gene: DCAF17 or C2 or f37
Mutation: NM- 025000: c.436delC: p. (Ala147Hisfs89)
Variant Alleles: 2
Final diagnosis
Woodhouse Sakati syndrome

DISCUSSION

Our patient was diagnosed as WSS based on the positive genetic result, DNA analysis showed a homozygous single nucleotide deletion (c. 436delC) in exon 4 of the DCAF17 gene**.**

This pathogenic variant results in protein truncation and was originally reported in a Saudi family by Alazami et al. [5].

To our knowledge this is the first case of WSS with the unique findings of: Short stature with low growth hormone, hepatic hemangioma, with hepatomegaly, high indirect bilirubin, focal segmental Glomerulonephritis, and high uric acid.

The main reason that we are reporting this case is to raise the attention toward the existence of WSS which can present in a similar picture like other polyglandular disease and a delay in diagnosis is expected because it is a rare disease.

In our patient the picture was so overlapping with a polyglandular disorder like APS, since both may present with Alopecia totalis (early in WSS but late in APS), Primary Ovarian failure, Hypothyroidism, Diabetes, Nail changes and Growth hormone deficiency.

So, because of those features the impression of the cause of this disorder was APS, since it is more common than WSS but screening for antibody was negative except for IA2 which might be due to insulin that was started prior to sampling. This negativity of all others antibody together with the dysmorphic features and mild intellectual disability, those make us think about the possibility of WSS, and hence we request the genetic study for WSS.

Not to forget that other important differential diagnosis that could present in a similar pictures of Polyglandular pictures (other than WSS, APS) include: A) Turner syndrome, which should be ruled out in any girl with delayed puberty, or unexplained short stature .Turner syndrome may explain most of the features the patient have (alopecia, ovarian failure, short stature, DM, hypothyroidism, mild learning difficulty), this is why Chromosomal analysis was done but it was negative.

B) Mitochondrial disease, that could present with a similar picture of WSS, both may have, alopecia, hypothyroidism, diabetes, deafness, ovarian failure fatigability, muscle weakness, intellectual disability [10] and other CNS manifestation like generalized hypotonia, ECG changes similar to WSS like T wave depression and like WSS both are AR inherited, but patient will with Mitochondrial disease will have high lactic acidosis but it will be normal in WSS [4-14].

C- ANE syndrome (alopecia, neurological defects, and Endocrinopathy) [15].

Conflict of Interest

All the authors have reported no conflict of interest.

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