Introduction

Woodhouse-Sakati syndrome (WSS) (OMIM242108) is an autosomal recessive inheritance pattern. Ectodermal system findings, such as alopecia and changes in facial skin, endocrinological problems including hypogonadism, hypothryroidism, diabetes mellitus (DM), and decreased levels of insulin-like growth factor I (IGF-I), neurological disorders such as hearing loss and progressive extrapyramidal involvement, and non-specific T wave changes at electrocardiography can all be detected. Alopecia and loss of hearing are generally present before puberty. Puberty is delayed in all cases, and primary amenorrhea is typically present in girls, while delayed development of secondary sexual characteristics is seen on physical examination in both genders. Hypothyroidism and diabetes mellitus may be added to the manifestation after puberty, and neurological disorders in later decades.

The nature of hypogonadism in WSS is often difficult to characterize since both hypogonadotropic and hypogonadotrophic hypogonadism (hh) occur. However, hypogonadotropic hypogonadism (hh) is generally determined in girls, while male patients have moderate testosterone depression and inappropriately low gonadotropins, compatible with hh. The role of the pituitary gland in the etiopathogenesis of hypogonadism is unclear, since some WSS patients present with hh, while normal levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) may be determined in others.

C247T mutations were reported to be responsible for WSS in 2008. This gene was subsequently renamed DCAF17. Recent research has shown that the DCAF17 gene is involved in gonad development and functions in both sexes.

In our case, whole exome sequencing (WES) analysis revealed a novel homozygous variant c.1091+1G>A in the DCAF17 gene in a patient presenting with primary amenorrhea and with hh-type hypogonadism. This case is discussed together with a review of previously reported cases and of the characteristics of WSS.

Case Report

A 16-year-old girl presented with absence of breast development and amenorrhea. Third-degree consanguinity was present between the parents. The patient had six sibers and was the youngest member of the family. Delayed menstruation or secondary sexual characteristics were not present in other family members. On physical examination, the weight was 95 kg (±38 SDG), the height 165 cm (±14 SDG) and arterial blood pressure 100/70 mm Hg. Breast and pubic development were both Tanner stage 1, and no aillary hair development was observed. No significant developmental finding was present.

Comparative blood-scientific and biochemical parameters were normal at time of diagnosis. Thyroid function tests revealed TSH: 11 μU/ml (0.33-4.4 μU/ml), T4: 1.37 ng/dl (0.8-1.6 ng/dl), anti-TPO < 1 µU/ml (<6.5 U/ml), anti-TG antibody < 6 U/ml (<4.1 U/ml). Other biochemical results were serum FSH: 7.4 µIU/ml (1.8-11.2), LH: 19.4 µIU/ml (2.9), estrogen 2-10 pg/ml (10-100), cortisol: 14 µg/dl (13.4-26.5 µg/dl), and adrenocorticotropic hormone: 22.4 µg/ml (0-46). Supraocular ultrasoundography (USG) showed that the uterus was 25x10x7 mm in size, and that the ovaries could not be visualized. The patient was started on low-dose sex steroid replacement (10 capsules estradiol and 15 capsules medroxyprogestin). At the follow-up, the estradiol dose was increased to one tablet.

After the birth, a brain MRI was performed and abnormal brain structures were detected. The physical examination at the first visit, two years after the initial examination. A long, triangular facial appearance was also observed. Thyroid function were euthyroid with L-thyroxine therapy, with IGF-I: 118 ng/ml (<2 SDG). Fasting blood sugar was 82 mg/dl and HbA1c: 5.4%. Serum lipid levels were normal, and hearing test was also normal. Motor and cognitive developments were appropriate for age, but she is currently experiencing learning disabilities. In terms of hair, her verbal score was 46, performance score 42, and total intelligence score was 51, suggestive of borderline intellectual disability. Under sex steroid replacement, the pubertal stage was Tanner stage 4. Supraocular USG revealed a uterus size of 51x13 mm, endometrial thickness of 4.7 mm, right ovary size of 12.5x7x14 mm, and left ovary size of 16.2x15x15 mm, and four anechoic follicular cysts were reported in both ovaries.

Genetic testing: The patient’s karyotype was 46XX. WES was used to identify the underlying genetic etiology of hypogonadism. Molecular study revealed a novel homozygous splice-site variant NM_020503.3:c.1091+1G>A in intron 10 of the DCAF17 gene. The consanguineous parents were sequenced, and both were heterozygous for the same mutation. A novel homozygous splice-site variant NM_020503.3:c.1091+1G>A in intron 10 of the DCAF17 gene was identified in our patient (Figure 1).

Table 1: Description of the principal symptoms described by patients and causative mutations in all WSS cases.

CONCLUSION

An adolescent girl who presented with absence of secondary sexual characteristics due to primary gonadal insufficiency and received the diagnosis of WSS after identification of a novel mutation in DCAF17 by a whole-exome sequencing analysis, was reported here. Whole-exome sequencing provided an important benefit for this patient in terms of receiving the definitive diagnosis before the onset of other systemic findings of the syndrome. Since various manifestations of WSS, such as alopecia, endocrine and neurological disorders do not emerge until late in life, it is difficult to make diagnosis in pediatric cases. Alopecia can initially be mild and may become more remarkable by age. Similarly, diabetes and extrapyramidal findings usually emerge after adolescence or in early adulthood.

The responsible gene for WSS, DCAF17, was discovered in 2008, and many cases have since been reported in the literature. To the best of our knowledge, 42 cases of WSS were identified prior to 2008 but could not be subjected to genetic analysis. After that, 64 cases from 26 families underwent genetic analysis. Including our case, hypogonadism was present in 61/65 cases (93.84%) (Table 1). When female patients are classified according to hypogonadism, hh was reported in 19 out of 35 cases, normogonadotropic hypogonadism (hh) in seven, and hh in one. Hypogonadism was uncommon in a further 12 cases. Among male patients, one case was hh, four cases were Nh, 11 cases were hh, and six were unknown. The majority of female cases (46.7%) had hypogonadism in the form of hh. In contrast, hypogonadism in the form of hh has been detected in the majority of male cases (88.18%). In addition, while the tests may be normal or subnormal, ovarian tissue in some of them could not be visualized at USG or magnetic resonance imaging. The nature of hypogonadism is not only peripheral, but also has a central and peripheral etiology, suggesting that DCAF17 play a role in the development of the pituitary gland and/or hypothalamus as well. Although iron deposition in the central nervous system (CNS) and extrapituitary involvement have been reported, the role of DCAF17 in the CNS is still unknown.

The height of our patient was normal range despite regular short stature. Short stature is not an expected finding in this syndrome. IGF-1 levels were reported in 28/65 cases. IGF-1 was normal in three of these and low in 25. The low IGF-1 levels may reflect the low sex steroids resulting from hypogonadism. However, we detected a low IGF-1 level in our case following sex steroid replacement, suggesting that this derived from liver function in the DCAF17 gene, because this gene has previously been shown to be overexpressed in the liver.

Thyroid function tests were reported in 29/65 cases, and hypothyroidism was detected in 11 (37.3%) of these. As in the present case, subclinical or marked hypothyroidism may be observed. However, autonomic levels in these cases are negative. This suggests a possible role in thyroid gland development similar to that in gonadal development. Although this patient and previous cases had hypothyroidism, suggesting that DCAF17 has an effect on thyroid gland development, further studies are needed to conclude this. Despite the hypothyroidism-hypogonadism-adelipoid axis in some cases, no central hypothyroidism was observed.

Extrapituitary findings such as dystonia, chorea, dystarhria, and dysphagia that commence focally and convert to the generalized form are seen in the advanced stages. In contrast, pyramidal and cerebral effects are not expected. Varying levels of extrapituitary disorder may be determined in cases. Mental capacity was also limited in our case, although no additional pathological finding developed at other neurological system examinations at follow-up. Severe gait disorder, scoliosis, and wheelchair confinement have been reported as a result of progressive impairment in the extrapituitary system. Changes in periocular white matter and iron accumulation in the globus pallidus may also be observed at MRI.

Seven missense/nonse and four splice-site variants, five small deletions, one small insertion, and one gross deletion have been defined to date (Figure 1). All loss-of-function mutations have been associated with WSS, but two missense variants (p.Y186H and p.C507R) have been linked to thyroid dysmorphogenesis. The most common c.436EC mutation has been proved to constitute the founder mutation for the Arab population. Our scan of the literature revealed no evidence of any correlation between different DCAF17 mutations and phenotype. Even subjects with the same Saudi Arabian founder DCAF17 pathogenic variant (c.436E<del>) exhibit pronounced phenotypic variability.

In conclusion, previous studies revealed no obvious genetic-phenotype correlation in patients having DCAF17 mutations. WSS may be defined as a progressive neuroendocrinological disorder accompanied by alopecia. Particular attention should be paid to these additional findings, which may lead to early diagnosis and may reduce genetic evaluation costs in patients with hypogonadism.