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A wiedemann-steiner syndrome patient characterized by amenorrhoea, hypertrichosis, short stature, intellectual disability

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Abstract

Wiedemann-Steiner syndrome (WSS) is a rare genetic disease characterized by intellectual disability, hypertrichosis, short stature, and abnormal facial features. Its genetic cause is mutation in KMT2A. In this study, we present a female Chinese patient with amenorrhoea, hypertrichosis, short stature, intellectual disability, comparing it with data in previous studies. In addition to reporting a novel KMT2A variant, this case highlights the manifestations of amenorrhoea, pituitary microadenoma and adrenal adenoma, expanding the clinical phenotype associated with KMT2A mutations.

Keywords

Wiedemann-Steiner syndrome; Intellectual disability; Amenorrhoea; Pituitary microadenoma.

Abbreviations

WSS: Wiedemann-Steiner syndrome; MRI: Magnetic resonance imaging; BMI: Body Mass Index; LH: Luteinizing hormone; FSH: follicle-stimulating hormone; DHEA: Dehydroepiandrosterone; IGF-1: Insulin-like growth factor 1; ACTH: adrenocorticotrophin; CT: Computed tomography; PCOS: Polycystic ovary syndrome; NCCAH: Congenital adrenal hyperplasia.

Introduction

Wiedemann-Steiner syndrome (WSS), originally described by Wiedemann in 1989 [1], and Steiner in 2000 [2], is a congenital malformation syndrome characterized by intellectual disability, hypertrichosis, short stature, abnormal facial features including long eyelashes, thick or arching eyebrows, broad nasal bridge, blepharoptosis, and narrow palpebral fissures [3]. In 2012, Jones first reported the causative gene

responsible for WSS, KMT2A. Also known as MLL-1, the gene encodes a protein involved in the methylation of lysine 4 of histone H3 and is associated with gene activation [4]. The mechanism behind KMT2A and WSS is yet to be fully described. KMT2A mutation is reportedly related to the dysregulation of endothelial (e) NOS/cGMP pathway and BMP pathway, which leads to increased vascular circulation toward hair follicle, and eventually hypertrichosis [5]. Here we present a case of amenorrhoea with hypertrichosis, short stature, and intellectual disability, which was diagnosed as WSS with genetic testing.

Case Report

A 23-year-old Chinese woman presented with menopause beginning from March 2017. In December 2017, the morning blood cortisol was found to be as high as 41.94 μg/dl at a local hospital; enhanced MRI of the pituitary suggested slight bulging accompanied with heterogeneous signal intensity, and pituitary microadenoma was suspected. Afterwards the patient was referred and admitted to our ward of endocrinology for further evaluation of Cushing's syndrome in January 2018. Bodyweight was stable across the year before admission. Her parents were not consanguineous. She was born at full term by normal delivery, but with ptosis and exotropia of the right eye. At the age of 2, mental retardation was noticed, and medical examination revealed encephalodysplasia, but did not receive further investigation or therapy. At the age of 13, the patient had menarche with a period of 3-5 days and a cycle of 28 days. Her family denied history of pituitary diseases or mental retardation symptoms.

On admission, physical examination indicated a height of 150 cm and a weight of 60 kg (BMI: 26.7 kg/m^2), blood pressure 117/70 mmHg, ptosis of the right eye, overall hypertrichosis. No purple striae, hyperpigmentation, edema of lower limbs was noticed. Eyesight, muscular tension, and tendon reflex were normal. Intelligence Quality score was unavailable due to the patient's refusal of examinations.

Routine test of blood and urine showed normal results. Thyroid function test result and aldosterone/renin ratio were normal. She had a LH level of 4.77 IU/L, FSH 4.06 IU/L, estrogen 253.4 pmol/L, progesterone 0.9 nmol/L, testosterone 2.3 nmol/L, prolactin 26.47 ng/mL, DHEA 14.69 μmol/L(high), IGF-1 280 ug/L (reference range 115-358 ug/L). MRI showed basilar invagination (Figure 1A) and a small low-enhanced lesion in the pituitary indicating microadenoma (Figure 1B,1C). Contrast enhanced CT of the adrenal gland showed small nodular masses in the left junction of adrenal gland sizing 8.5 X 8.4 mm (Figure 2). No abnormality was found with ultrasound scan result of the thyroid, heart, liver, spleen, kidneys, or uterus. No sign of polycystic ovaries was found. 24 h urine free cortisol was normal. The overnight low-dose dexamethasone suppression test yielded a morning blood cortisol of 0.78 μg/dl (less than 1.8 ug/dl) excluding the diagnosis of Cushing Syndrome. 17α – OH progesterone rose from a baseline of 0.7 ng/ml to a peak of 3.91 ng/ml (<10 ng/ml) in the ACTH stimulating test, excluding diagnosis of non-classical Congenital adrenal hyperplasia (NCCAH). The gonadorelin test showed that LH was well stimulated and increased from 8 IU/L to 63.7 IU/L, excluding amenorrhea resulting from pituitary hypofunction.

After ruling out Cushing Syndrome, NCCAH, thyroid disease, hyperprolactinemia, and hypopituitarism, polycystic ovary syndrome (PCOS) was considered due to the patient's hypertrichosis and amenorrohea. However, as the patient was intellectually underdeveloped and had basilar invagination, congenital

single-gene disorder was suspected. Genetic testing revealed that the patient was heterozygous for a pathogenic de novo mutation in the KMT2A gene (c.568delC, p.L190sfs*10), supporting the diagnosis of WSS. No mutation of CYP21A2 for congenital adrenal hyperplasia (CAH) was found. In summary, the patient was diagnosed with WSS, companied with non-functioning adenoma of the left adrenal gland, clinical non-functioning microadenoma of the pituitary, secondary amenorrohea. Medical suggestion including weight control with diet and exercise, combined oral contraceptives for regulating menstruation in short-term, and follow up on the condition of the pituitary and the adrenal glands were given.

Discussion

The number of WSS cases reported worldwide has grown significantly in recent years, offering a clearer understanding of the clinical features of WSS. WSS was originally referred to as "hairy elbows" syndrome, and hypertrichosis cubiti was thought to be one of its chief manifestations [6]. However, in a 2018 French study of 33 cases and a 104-patient cohort international study led by Sheppard, the largest WSS cohort to date, hypertrichosis cubiti accounted for 61% and 57% of the reported cases, respectively[7, 8]. Other common clinical manifestations include developmental delay or intellectual disability, constipation, failure to thrive, feeding difficulties, short stature, and vertebral anomalies. It's worth Sheppard's study included only 23 adults, which might explain the lack of data on menstrual abnormalities. Among the cohort, more than half (57.8%) had short stature, but only one-fifth (18.8%) of the 6 patients tested had GH deficiency [7]. In our case, the patient had overall hypertrichosis and short stature (150 cm). IGF-1 level was normal and there was no evidence for GH deficiency, suggesting other genetic causes for short stature in WSS.

In addition, our case showed microadenoma in pituitary MRI, which was consistent with Sheppard's study. Among the 11 reported patients, 7 had abnormal pituitary MRI results [7], indicating possible correlation between pituitary abnormality and the occurrence of WSS.

Importantly, previous case studies have not reported amenorrhoea [4,8,9] or suggested correlation between KMT2A mutation and menstrual abnormalities [7], while our case is characterized by amenorrhoea. As the main causes for amenorrhoea, such as PCOS, Cushing syndrome, NCCAH, have been excluded for our patient, WSS is likely to be playing a role. Since most cases of WSS are diagnosed during childhood, data on female adult patients is scarce. More data on endocrine phenotype of WSS patients are needed to determine the relationship between amenorrhoea and WSS, a common condition and a rare disease. KMT2A is an 87-kb gene located at chromosome q23.3 containing 36 exons. It encodes lysine methyltransferase 2A, which consists of 3972 amino acids, and domains including three DNA-binding AT-hooks at the N terminus, a cysteine-rich CXXC domain, a plant homeodomain finger motif, a bromodomain, a transactivation (TAD) domain, a FYRN domain, a WDR5 interaction (Win) motif, and a C-terminal SET domain. The KMT2A protein induces methylation of lysine through its conservative C-terminal SET domain, mediating the epigenetic activation of transcription [10] and playing a crucial role in the gene expression of early development and hematopoietic function. KMT2A is expressed extensively, especially in the heart, the lung, the brain, T cells and B cells. Aside from WSS, mutations in KMT2A may also lead to lymphoblastic leuke-

mia [11] or primary mediastinal large B-cell lymphoma [12]. However, there is no report of cases of more than one condition. In our case, the patient had normal blood test results and no evidence of lymphoma. We identified a de novo KM2TA variant (c.568delC, p.L190sfs*10), an unreported mutation that may lead to premature termination of peptide synthesis. According to the guidelines of ACMG (American College of Medical Genetics and Genomics), this mutation can be classified as "likely pathogenic" [13]. The pathological mechanism behind the variation remains to be discovered.

To this date there is no cure for WSS. Patients who meet medical indications can be supplemented with growth hormone to improve their short statures. In our case, the patient was sexually developed and had epiphyseal closure, so growth hormone therapy was not given. Clinicians, gynaecologists and general practitioners should be especially suspicious of WSS when treating amenorrhoea, short stature and hypotrichosis, because early diagnosis and treatment will bring better clinical outcome. Genome sequencing provides an effective way to diagnose rare diseases as well as genetic counseling, which is crucial for the offspring of patients, since WSS is an autosomal dominant monogenic disorder. As advocated by Rehm days ahead of this year's Rare Disease Day (February 28), "global data sharing is needed to further advance our knowledge of all causes of rare disease" [14]. The research Wiedemann-Steiner syndrome is one such disease that would benefit greatly from evidence and data sharing. We hope that one day WSS can be diagnosed and treated readily through global effort.

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