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Case Report

Developmental delay and autism with hypertrichosis cubiti: a clue to the diagnosis of Wiedemann-Steiner syndrome

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ABSTRACT

Wiedemann-Steiner syndrome (WSS) is a rare disorder with dysmorphic features, developmental delay, autism, and hypertrichosis. We report a case of a seven and half year-old female child born to a non-consanguineous couple with developmental delay, autism, behavioral abnormality and hypertrichosis cubiti diagnosed to have *KMT2A* gene associated WSS. It is important for the treating clinician to be aware of the characteristic signs and symptoms of the disorder and the necessity of genetic testing to be able to confirm the diagnosis and manage by multidisciplinary team in any child with developmental delay and autism.

Keywords: Wiedemann-Steiner syndrome, Autism, KMT2A, Hypertrichosis cubiti

INTRODUCTION

Wiedemann-Steiner syndrome (WSS) is a rare syndrome with specific dysmorphic features, developmental delay, intellectual disability and a wide variable clinical presentation.[1] It is important for the treating clinician to be aware of the characteristic signs and symptoms of the disorder in order to establish the exact diagnosis and provide multidisciplinary management.

CASE REPORT

We report a case of a seven and half year-old female child born by caesarean delivery to a non-consanguineous couple. Her antenatal and immediate perinatal periods were uneventful. Anthropometry at birth was corresponding to age and sex. She was exclusively breast fed for the first six months. During her infancy and toddler years she exhibited selective eating and difficult mealtime behaviours leading to suboptimal weight and height gain. Her gross motor and language milestones were delayed. Speech was unclear. At school she initially had difficulties with peer interaction, decreased sitting tolerance, poor response to name call and decreased eye contact. There was repetitive actions and bruxism. She would flap her hands when excited, would observe things closely and had tactile hyper-responsiveness. Her reading, writing and math skills were not grade appropriate. She was dependent for all her activities of daily living.

On examination she was found to have weight below the 3rd centile for her age and a height between 3rd and 10th centile. Dysmorphic features like a long broad forehead, flat depressed supraorbital ridges, and narrow palpebral fissure with ptosis, broad nasal bridge, smooth philtrum, thin upper lip, high arched palate and square shaped chin were present. Chest was flat. Neck and spine were normal. Extremities were thin. An excessive growth of villus type hair was present on the extensor part of the lower arm and upper forearm around the elbow joint bilaterally (Figure 1a and b). There was pilonidal sinus in the sacral region. Tips of fingers were square shaped (Figure 1c), 4th and 5th toes were proximally and anteriorly with mild deviation of 2nd and 3rd toe (Figure 1d).

During the session the child was cooperative, responded well to name call, had good eye contact and attention. She

could communicate in simple sentences through she was lacking in speech clarity occasionally. She could not jump high or hop on one foot and had a weak pencil grip. Tone and reflexes were normal.

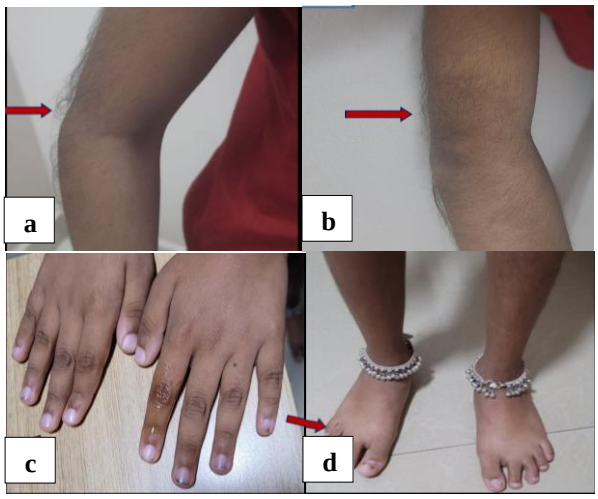

Figure 1: (a and b) Hypertrichosis cubiti; (c) square shaped tips of fingers; (d) proximally and anteriorly placed 4th and 5th toe with mild deviation of 2nd and 3rd toe in both foot.

Her Vineland social maturity scale (VSMS) score was 51 which indicated a moderate deficit in socio-adaptive skills. Her IQ assessed by the Binet Kamat test of intelligence (BKT) was 58 which indicated a mild intellectual disability. Based on her Indian scale for assessment of autism (ISAA) score, which was 57, she was found to be on the autism spectrum. Her receptive and expressive language were delayed with a tested age of 3.9 years. An occupational therapy evaluation revealed sensory issues and delay in attaining activities of daily living (ADL's). Complete blood picture, serum calcium, phosphorous, electrolytes, liver and renal functions, CPK, and thyroid profile were normal. Magnetic resonance imaging (MRI) brain, 2 D ECHO, and ultrasound abdomen did not show any abnormalities. Chromosomal microarray of the child was normal. Whole exome sequencing revealed a pathogenic heterozygous variant c.3241C>T (p.Arg1081Ter) in exon 4 of the *KMT2A* gene associated with Wiedemann Steiner Syndrome. She had been recommended behaviour, speech, occupational and remedial education therapies following which she started showing improvements in all domains.

DISCUSSION

WSS (#605130) is a rare autosomal dominant disorder with a prevalence of less than 1 in a million. It was first described by Wiedmann in 1989 in a Caucasian boy.[1,2] The molecular basis of the syndrome was identified in 2012.[1,2]

Clinical diagnosis of WSS is challenging due to phenotypic heterogeneity. Though a standardised clinical criterion for the diagnosis of WSS is lacking, some of the suggestive features include developmental delay, intellectual disability, and characteristic facial features like thick eyebrows vertically narrow and down slanted palpebral fissures, widely spaced eyes, long eyelashes, wide nasal bridge, broad nasal tip, thin vermilion of the upper lip. The facial features become more pronounced with age. Hypertrichosis is one of the feature of this syndrome specifically hypertrichosis cubiti ("hairy elbows"), seen in around 60% of the cases of WSS. It is a very distinctive feature of this syndrome with vellum like hair around the elbow along with hypertrichosis of other body parts.[3] Phenotypic features like short stature and hypertrichosis overlaps with Cornelia de Lange syndrome, Coffin-Siris syndrome and Kabuki syndrome. Hypertrichosis cubiti has variable penetrance, expressivity and has also been reported in Weill–Marchesani syndrome and floating harbour syndrome.[4] Other features in WSS include feeding difficulties, failure to thrive, epilepsy, ophthalmologic, dental abnormalities, and visceral anomalies including vertebral anomalies, and immune dysfunction.[2]

Behavioural concerns and autism are present in one fifth of the cases. In WSS the social phenotype is characterized by some autistic features along with high social motivation and prosocial tendencies. Features like sleep difficulties and difficult mealtime behaviours are common.[5,6]

Heterozygous loss-of-function variants in *KMT2A* are associated with WSS. Though pathogenic variants reported till now are distributed in the entire gene many of them are clustered in exon 27. The *KMT2A* gene encodes H3K4 methyltransferase enzyme that is essential for chromatin remodelling and plays an important role in the embryonic development, haematopoiesis, and neural development.[7,8]

Since the signs and symptoms of the disorder overlap with other rare disorders. It is important that genetic testing should be considered as part of management to establish an exact diagnosis in any child with developmental delay and autism. The establishment of the syndromic diagnosis for autism would help in providing a more multidisciplinary approach to the child's care and help in surveillance of the child at a high risk of developing certain health related issues at a later stage.

In our case in addition to assessment of development and behaviour, monitoring for growth parameters, nutritional status, infections, dental and ophthalmology evaluation is recommended. Recombinant human growth hormone is an option to improve growth in these cases.[9]

CONCLUSION

WSS is a rare genetic disorder which presents with autism and remains under-diagnosed. There is phenotypic overlap with other chromatinopathies. Hypertrichosis cubiti is a clue to the diagnosis of this syndrome. The establishment

of the syndromic diagnosis for autism would help in providing appropriate multidisciplinary management.

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