Wiedemann-Steiner syndrome: A case report

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Wiedemann-Steiner syndrome (WDSTS, OMIM #605130) is an exceptionally rare autosomal dominant syndrome with a prevalence of <1 in 1 000 000. Considerable phenotypical variation exists, with clinical characteristics encompassing dysmorphic facial and skeletal features, growth deficiency, developmental delay, hypertrichosis cubiti and various dental features. We present a 7-year-old female with premature exfoliation of primary teeth and premature eruption of permanent teeth.

1 | INTRODUCTION

Wiedemann-Steiner syndrome (WDSTS, OMIM #605130) is an exceptionally rare autosomal dominant syndrome with considerable phenotypical variation. Clinical features include dysmorphic facial and skeletal features, growth deficiency, developmental delay, hypertrichosis cubiti and various dental features. We present a 7-year-old female with premature exfoliation of primary teeth and premature eruption of permanent teeth.

2 | CASE REPORT

The patient is the oldest of three siblings. Her younger brother and sister do not have WDSTS. She was born at term following an uneventful pregnancy at a birth weight of 3.32 kg (25th centile). Feeding difficulties were experienced from birth requiring a tongue tie release. An assessment by a clinical geneticist aged 5 years, 10 months old, showed several distinctive facial features including telecanthus, flared medial eyebrows, long and narrow palpebral fissures, a long philtrum, and high arched palate. The rarity of WDSTS presents a challenge in describing the complete phenotypic spectrum.

WDSTS was initially reported by Wiedemann in 1989 and is classified as a chromatin remodeling defect. Genetically, whole exome sequencing in 2012 identified the etiology as heterogeneous de novo mutations in the KMT2A (lysine methyltransferase) gene. KMT2A encodes a histone methyltransferase, an enzyme important in the regulation of chromatin-mediated transcription.

Failure to thrive presents a nonspecific, but prominent feature in WDSTS patients. Early neuropsychiatric indications comprise difficulties sleeping, aggressive behavior, hyperactivity, autistic-like qualities, and a broad range of intellectual disability and developmental delay. Facial dysmorphic features generally become more noticeable with age and comprise down-slanting palpebral fissures, telecanthus, strabismus, synophrys, long eyelashes, wide nasal bridge, thin upper lip, long philtrum, and high arched palate. This case outlines a seven-year-old girl, with a confirmed diagnosis of WDSTS, who presented with a history of the exfoliation of all primary teeth between 24 and 36 months and commencement of the eruption of permanent dentition aged four.
osteotomies of the proximal femora. Ophthalmological input was arranged for intermittent exotropia and a right convergent squint which self-corrected. She had global developmental delay and her parents expressed concerns of autistic spectrum features such as resistance to changes in routine, educational difficulties, and sensory issues including textures. Subsequent testing for the Cornelia de Lange syndrome panel of genes revealed a heterozygous pathogenic variant c.3082A>T, p.(Lys1028Ter) in the KMT2A gene, confirming the diagnosis of WDSTS.

At age 6 years and 9 months, an orthodontic assessment was carried out. This revealed that all her primary teeth had erupted by eight months and that most of the primary teeth had exfoliated between the ages of 24-36 months. Her oral hygiene was fair, and no caries were present. The enamel appeared normal. The teeth present were:

- 6E4321/1234E6
- 654321/1234E6

An orthopantomogram (OPG) was taken (Figure 2). This showed that all the permanent teeth were developing including all four third permanent molars. The clinical examination showed a mild Class III incisor relationship (edge to edge)
and buccal displacement of both the erupting maxillary permanent canines with mild crowding (Figure 3). The palate was normal.

**TABLE 1** Dental abnormalities in WDSTS.5,6,9,10

| Dental Abnormality                          |
|---------------------------------------------|
| Premature eruption of dentition             |
| Premature exfoliation of primary dentition  |
| Hypodontia                                  |
| Dental spacing                              |
| Malocclusion                                |
| Cleft palate                                |
| Retrognathia                                |
| Supernumerary teeth                         |
| High arched palate                          |
| Glossoptosis                                |

**DISCUSSION**

WDSTS is a very rare autosomal dominant disorder with relatively few cases described in the literature. Considerable phenotypical variation has been described, which may increase as additional patients are diagnosed. Multiple anomaly syndromes such as Kabuki, Rubenstein Taybi, Pierpont, and Cornelia De Lange overlap phenotypically with WDSTS creating a diagnostic challenge. Etiologically, a substantial number of these genetic syndromes involve pathogenic variants in genes encoding histone modification and chromatin remodeling.3

The literature describes several oral and dental anomalies in patients with WDSTS (Table 1), with premature eruption of primary and permanent teeth being commonly cited.5,6,9,10

**TABLE 2** Commonly cited systemic disorders associated with premature eruption of secondary teeth and premature exfoliation of primary teeth, presented from the most to the least common11-21

| Diagnosis                                      | Classification               | Common Clinical Features                                                   |
|-----------------------------------------------|------------------------------|----------------------------------------------------------------------------|
| Premature exfoliation of primary teeth        |                              |                                                                            |
| Rare disorders                                |                              |                                                                            |
| Acute Lymphoblastic Leukemia                  | Hematological Malignancy     | Gingival Hemorrhage and Hyperplasia, Petechiae, Periodontal Disease, Lymphadenopathy |
| Prevalence: 11.0/100 000                        |                              |                                                                            |
| Acute Myeloid Leukemia                        |                              |                                                                            |
| Prevalence: 10.0/100 000                       |                              |                                                                            |
| Ehlers-Danlos Syndrome                        | Connective Tissue Disorder   | Periodontal Disease, Fragile Skin, Bruising of Skin, Muscle Fatigue and Pain, Loose Joints. |
| Prevalence: 5.0/100 000                        |                              |                                                                            |
| Acatalasia                                    | Metabolic Disorder           | Oral Ulceration, Gangrene                                                 |
| Prevalence: 3.2/100 000                       |                              |                                                                            |
| Ultra-Rare Disorders                          |                              |                                                                            |
| Coffin-Lowry Syndrome                         | Genetic Multisystem Disorder | Cardiac Abnormalities, Kyphoscoliosis, Short Stature, Cognitive Difficulties |
| Prevalence: 1.5/100 000                        |                              |                                                                            |
| Langerhans Cell Histiocytosis                 | Hematological Disorder /     | Single / Multiple Lytic Bone Lesions, Gingival Inflammation, Drifting of Teeth, Ulceration, Bone Destruction |
| Prevalence: 1.5/100 000                       | Malignancy                   |                                                                            |
| Erythromelalgia                               | Neurovascular Disorder       | Erythema / Swelling of Soft Tissue, Burning Sensation of Extremities        |
| Prevalence: 1.0/100 000                        |                              |                                                                            |
| Papillon-Lefèvre Syndrome                     | Dermatological Disorder      | Hyperkeratosis of Palms and Soles of Feet, Early Onset Periodontal Disease |
| Prevalence: 0.25/100 000                       |                              |                                                                            |
| Hypophosphatasia                              | Metabolic Bone Disease       | Taurodontism, Hypoplastic or Absent Cementum, Skeletal Deformities, Widened Fontanelles. |
| Birth Prevalence: 0.21/100 000                 |                              |                                                                            |
| Chediak Higashi Syndrome                      | Genetic Immunological Disorder | Recurrent and Persistent Infections, Albinism, Strabismus, Nystagmus, Periodontal Destruction |
| Documented Cases: 500                         |                              |                                                                            |
| Leukocyte Adhesion Deficiency                 | Immunological Disorder       | Recurrent Bacterial Infections, Gingival Inflammation and Alveolar Bone Loss. |
| Documented Cases: 350                         |                              |                                                                            |
| Hajdu-Cheney Syndrome (Acroosteolysis)        | Connective Tissue Disorder   | Osteoporosis, Short Stature, Skull and Facial Abnormalities.               |
| Documented Cases: 100                         |                              |                                                                            |
| Singleton Merten Syndrome                     | Genetic Multisystem Disorder | Calcification of Aortic Arch, Glaucoma, Photosensitivity                   |
| Documented Cases: 22                          |                              |                                                                            |

(Continues)
The premature exfoliation of primary dentition and/or the premature eruption of permanent dentition can be attributed to local, environmental, or systemic factors or be considered as a mild nonpathological variation from normal. While it is very unlikely that a patient with WDSTS would see a pediatric dentist without a confirmed diagnosis, it is important to be aware of this and other medical conditions which affect the usual dates for tooth eruption and exfoliation, for both primary and secondary dentition. The conditions listed in Table 2 are known to present with the premature exfoliation of the primary teeth and/or premature eruption of the permanent dentition.

The eruption of the permanent teeth in advance of the expected time means that orthodontic treatment can commence earlier than usual. For this patient, the plan is to use, in the first instance, a fixed palatal arch to maintain the leeway space and then once both maxillary second premolars (UR5, UL5) have erupted, fixed appliances to align the teeth and correct the incisor relationship. What is not known at this stage is the extent and direction of future facial growth which could affect the outcome.

For patients with WDSTS, an early referral to an orthodontist is recommended to compliment the pediatric dental care.

**ACKNOWLEDGEMENTS**
Informed verbal and written consent was obtained from all parents / legal guardians of all cases. The purpose of the case series was explained to all participants including what information would be published. All participants were advised that declining consent would not impact their clinical care and that they have the right to withdraw their consent at any point prior to publication.

**CONFLICT OF INTEREST**
None declared.

### Table 2

| Diagnosis                        | Classification                          | Common clinical features                                                                 |
|----------------------------------|----------------------------------------|------------------------------------------------------------------------------------------|
| Premature Eruption of Permanent Dentition |                                        |                                                                                           |
| **Commoner Diseases**            |                                        |                                                                                           |
| Hyperthyroidism                  | Endocrinological Disorder              | Heat Intolerance, Weight Loss, Hand Tremor, Irritability, Sleeplessness, Tachycardia       |
| Prevalence: 81.0/100 000          |                                        |                                                                                           |
| Type 1 Diabetes Mellitus         | Endocrinological Disorder              | Polyuria, Polydipsia, Polyphagia                                                         |
| Prevalence: 59.0/100 000          |                                        |                                                                                           |
| **Rare Diseases**                |                                        |                                                                                           |
| Soto Syndrome                    | Congenital, Genetic Overgrowth Disorder| Overgrowth, Facial Deformities, Advanced Bone Age, Developmental Issues, Cardiovascular, Ophthalmological and Urogenital Manifestations |
| Birth Prevalence: 7.1/100 000     |                                        |                                                                                           |
| Congenital Adrenal Hyperplasia   | Congenital Endocrinological Disorder    | Premature Adrenarche, Advanced Bone Age, Accelerated Growth, Pubertal Disturbances        |
| Prevalence: 7.0/100 000          |                                        |                                                                                           |
| Turner Syndrome                  | Genetic Endocrinological Disorder      | Short Stature, Gonadal Dysgenesis, Lymphoedema, Micrognathia                             |
| Birth Prevalence: 5.5/100 000     |                                        |                                                                                           |
| Sturge-Weber Syndrome            | Congenital Neurocutaneous Syndrome     | Cutaneous Vascular Malformations; Unilateral and Facial                                   |
| (Encephalotrigeminal Angiomatosis)|                                        |                                                                                           |
| Birth Prevalence: 3.5/100 000     |                                        |                                                                                           |
| **Ultra-Rare Diseases**          |                                        |                                                                                           |
| Chondroectodermal Dysplasia       | Genetic Skeletal Dysplasia              | Ectodermal Dysplasia, Cardiac Defects, Disproportionate Dwarfism                          |
| (Ellis-Van Creveld Syndrome)      | Birth Prevalence: 1.1/100 000           |                                                                                           |
| Klippel–Trénaunay Syndrome        | Congenital Vascular Disorder           | Unilateral Soft Tissue and Bony Hypertrophy, Hemifacial Hypertrophy, Hemangiomas, Varicosities |
| Prevalence: 0.007/100 000         |                                        |                                                                                           |
| Pachyonychia Congenita           | Genetic Dermatological Disorder        | Hyperkeratosis of Palms and Soles, Paronychial Infections, Corneal Dyskeratosis, Alopecia, Hyperhidrosis. |
| Documented Cases: 1000            |                                        |                                                                                           |
| Hemihyperplasia-multiple Lipomatosis Syndrome | Genetic Overgrowth Syndrome | Craniofacial Deformities, Ipsilateral MacroGLOSSIA, MacrosOMIA |
| Documented Cases: 10              |                                        |                                                                                           |

*European Data.*
AUTHOR CONTRIBUTION
LH: wrote the first draft of the manuscript and revised subsequent drafts. RE: selected the case and reviewed, edited, and provided guidance for subsequent drafts of the manuscript.

ETHICAL APPROVAL
Informed written consent was obtained from the parents in this case report prior to submission regarding the publication of images and data.

DATA AVAILABILITY STATEMENT
Data sharing was not applicable to this article as no datasets were generated or analyzed in the production of the manuscript.

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