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Stüve-Wiedemann syndrome with a novel mutation in a Saudi infant

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ABSTRACT

A full-term male infant born from consanguineous Saudi parents, with one other live child, is suspected to have skeletal dysplasia on a fetal anomaly scan. Clinical findings at birth included short stature, bowed long bone affecting the lower limbs more than the upper limbs, severe joint contractures with restricted movement, failure to thrive, hypertonia, and camptodactyly of the index fingers. During infancy, the baby is noted to have sucking and swallowing difficulties necessitated nasogastric tube feeding, and recurrent respiratory distress episodes with frequent admissions due to respiratory failure required intensive care admission and mechanical ventilation. The skeletal survey demonstrated dysplasia of long bones and spine. To investigate a suspect genetic syndrome, a whole-exome sequencing test was performed, which identified a novel homozygous mutation in the *LIFR* gene.

1. Introduction

Stüve-Wiedemann syndrome (SWS) is a rare autosomal recessive congenital bone dysplasia caused by a pathogenic variant in the leukemia inhibitory factor receptor (LIFR) gene on chromosome 5p13.1 [1]. SWS was first described by Stüve and Wiedemann in 1971 in two sisters with congenital bowing of the leg bones, respiratory distress, and camptodactyly; they eventually died within a few days of birth. The syndrome is characterized by intrauterine growth restriction, bowing of the long bones, hypertelorism, mandibular hypoplasia, camptodactyly, respiratory distress, and myotonia with a masked face [1,2]. In this study, we report the case of a full-term infant born to consanguineous Saudi parents who presented at birth with phenotypic features and radiological findings suggestive of SWS. In addition, the infant presented with skeletal dysplasia characterized by short stature, bowed long bones affecting the lower limbs more than the upper limbs, severe joint contractures with restricted movement, failure to thrive, hypertonia, swallowing difficulties, and respiratory distress, which often required frequent admissions to the intensive care unit (ICU) and prolonged mechanical ventilation. Genetic testing also confirmed the same diagnosis for the infant's elder sister.

2. Case presentation

A male infant weighing 2.98 kg was delivered by emergency cesarean section due to bradycardia fetal distress at 40 + 5 weeks gestation. The infant was born to consanguineous Saudi parents (second cousins); the mother is a 28-year-old G2P1+0 with gestational diabetes and a positive Group B streptococcus screen. However, the mother is on diet and received appropriate treatment for the infection. Furthermore, the infant had a 5-year-old sibling with undiagnosed skeletal dysplasia. Fetal anomaly scan showed bilateral bowing of the femur, tibia, and fibula, rocker-bottom feet, and mandible receding.

After delivery, infant crying was noted, vital signs were stable, and Apgar scores at 1 and 5 minutes were 7 and 8, respectively. The infant presented with dysmorphic features, abnormal head trait,

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micrognathia, retrognathia, short arms, genu varum, and an abnormally curved index suggestive of camptodactyly (Fig. 1). Furthermore, a pansystolic murmur was heard over the left lower sternal border.

The infant was born in fair condition until 5 minutes of age and later developed grunting and retractions with fluctuating SpO2 between 70 and 85. He was then shifted to neonatal ICU (NICU) due to respiratory distress and required nasal continuous positive airway pressure. Chest X-ray showed ground-glass opacity in the upper zone of the left lung with bilateral peribronchial cuffing.

At NICU, the infant developed bilateral pneumothorax and hyperpyrexia, which were managed appropriately. He was placed on mechanical ventilation. A nasogastric tube was inserted as he was unable to tolerate oral feeding. The neurological examination indicated that the baby was active and could move all his limbs; however, hypertonic limbs with fisting and rhizomelia were noted.

Over his course, the baby developed recurrent episodes of upper respiratory tract infections and respiratory distress and remained intolerable to oral feeding of expressed breast milk/regular formula except through the nasogastric tube.

During the admission, the infant underwent other extensive investigations, including bronchoscopy, which revealed laryngomalacia, and brain magnetic resonance imaging, cranial ultrasound, and eye examination, which were reportedly normal. In addition, an echocardiogram revealed a 2-mm anterior muscular ventricular septal defect and mild-to-moderate tricuspid regurgitation.

A skeletal survey showed bilateral symmetric bowing of the femur and tibia, associated with marked diaphyseal cortical thickening, and similar changes were identified bilaterally on the humerus, radius, and ulna (Fig. 2). A normal spine with no thoracic cage deformity was noted. Skull X-ray demonstrated micrognathia, with no evidence of other skull changes. X-ray of the feet and hands showed normal appearance of the short bones, except for bilateral flexion of the thumb. Furthermore, serial spine X-rays showed mild spinal asymmetry at the mid-thoracic and thoracolumbar regions with convexity towards the right and the left, respectively.

Based on these features, whole exome sequencing (WES) was performed to investigate the suspected genetic syndrome, The test detected a previously unreported pathogenic variant in the LIFR gene (OMIM: 601559) c.1387_1390del p.(Asn463Phefs*24). It created a shift in the reading frame starting at codon 463. The new reading frame ended in stop codon 23 positions downstream, causing autosomal recessive SWS, also known as neonatal

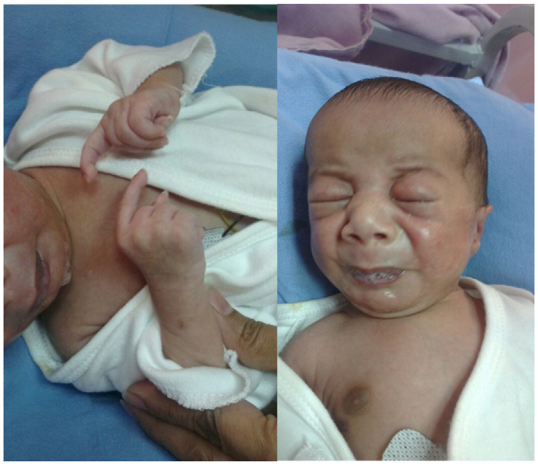

Fig. 1. Clinical findings show dysmorphic features, abnormal head trait, micrognathia, retrognathia, and abnormally curved index suggestive of camptodactyly.

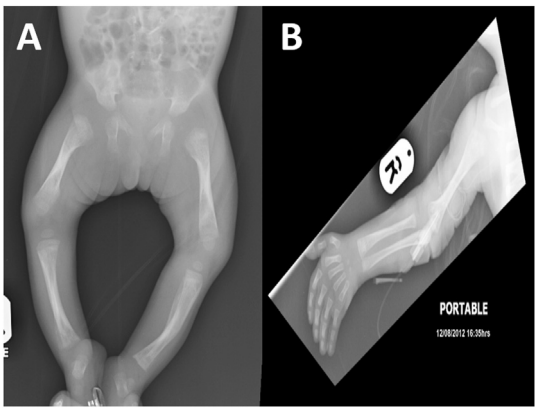

Fig. 2. Radiological findings show bilateral symmetric bowing of the femur and tibia, associated with marked diaphyseal cortical thickening. Similar findings are seen bilaterally on the humerus, radius, and ulna.

Schwartz-Jampel syndrome type 2. Parents were counseled regarding the disease, such as poor long-term outcomes associated with the syndrome, and recommended genetic testing for their elder child as well, which confirmed a similar diagnosis as our patient. In addition, they were recommended prenatal counseling for future pregnancies.

Management is symptomatic, such as prevention of lung aspirations primarily. Due to recurrent episodes of aspiration and chest infection and the presence of significant gastroesophageal reflux shown by milk scan, our patient was referred to pediatric surgery. He then underwent uncomplicated gastrostomy tube insertion, open Nissen fundoplication procedure, and pyloromyotomy. The infant was subsequently discharged home in a stable condition. Progressive skeletal abnormalities post-discharge from the pediatric ICU (PICU) were managed by physiotherapy and rehabilitation services. The infant was seen regularly by a clinical nutritionist for dietary management.

Within the course of the follow-up, recurrent episodes of chest infection and respiratory distress were reported, of which some were managed without admission. However, at around 31 months of age, the infant was brought to the emergency department appearing toxic, with documented fever, decreased activity, and poor feeding. He was intubated and shifted to PICU and placed on high frequency ventilation, inotropic support, and antibiotics. The infant died at the age of 31 months with multi-organ failure due to septic shock secondary to severe bronchopneumonia and acute respiratory distress syndrome.

3. Discussion

According to Dagoneau et al., cases of SWS have been identified to have pathogenic variants in the LIFR gene [3]. Normally, the LIFR activates the JAK/STAT3 signaling pathway, which plays an important role in gene transcription activation. In patients with SWS, the signaling pathway is impaired and therefore the JAK/STAT3 signaling pathway activation, which is important in fetal and neonatal bone resorption and neuronal development [1]. Other than the characteristics mentioned previously, SWS should be suspected if a patient also presents with camptodactyly, contracture of fingers, and symptoms of dysautonomia [1]. In our case, the clinical presentation immediately after birth suggested Crisponi syndrome (cold-induced sweating syndrome) as our differential diagnosis; the syndrome is characterized by dysmorphic facial features, camptodactyly, difficulty with sucking and swallowing, and hyperthermia. Other skeletal dysplasias, such as campomelic

dysplasia, and Larsen syndrome were excluded by molecular genetic testing.

SWS can be diagnosed prenatally via ultrasound, thus helping to detect birth defects as early as possible, and confirmed by molecular genetic testing. Similarly, Catavorello et al. reported a case of SWS that was detected prenatally by ultrasound and confirmed by prenatal genetic testing [2]. The affected female infant had respiratory distress, hyperthermia, and anterior bowing and shortening of the lower limbs [2]. Chen et al. reported another case of SWS [4]. The child was a 9-year-old who presented with characteristic features of the syndrome, in addition to the lack of patellar and corneal reflexes, gingival abscesses, mottled, poor dentition, blotchy pigmentation of the skin, smooth tongue with no fungiform papillae, infections, fractures, and scoliosis [4]. Another case of one of the longest survivors of SWS was reported by Dagoneau et al. of a 12-year-old girl, characterized by difficulty in swallowing and autonomic and skeletal symptoms [3].

The prevalence of SWS in the United Arab Emirates is approximately 0.5/10,000 births owing to the high prevalence of consanguineous marriages [6,7]. In Saudi Arabia, the prevalence of the syndrome is probably underestimated due to the difficulty in diagnosing it, considering the complex phenotype with typical neonatal and evolutive features.

Early diagnosis of patients suspected of this syndrome is important to monitor possible complications, counsel families regarding the heritability, and determine the overall prognosis [8]. Although patient survival is improved dramatically after the first year of life, the overall prognosis remains poor. Until 1996, SWS was considered fatal, with a high mortality rate and death occurring within the first year of life, and after which, cases of survival beyond infancy were reported by Kozlowski and Tenconi [9]. In our study, the infant survived the first year of life, suggesting that survival beyond the first year of life is possible. The high early infancy mortality rate associated with SWS was reported to be due to respiratory insufficiency and fatal hyperthermic episodes. Other risk factors for early fatality reported in the literature were severe pulmonary hypertension due to premature closure of ductus arteriosus and underlying cardiovascular abnormalities [10]. In addition, central adrenal insufficiency is another early fatality risk as the JAK/STAT3 signaling pathway is assumed to play a role in the control of the basal and stress-related adrenal steroidogenesis [11].

At present, SWS management primarily focuses on preventing aspiration pneumonia. Others include intubation, nasogastric tube feeding, or gastrostomy, as in our patient, because these patients experience difficulty in maintaining respiratory rhythm or swallowing [1]. Improving the patient's quality of life is crucial through multidisciplinary approaches such as physiotherapy, occupational therapy, and orthopedic procedures [12].

4. Conclusion

Our study indicates that a triad of facial dysmorphism, skeletal deformities, and myotonia is highly suggestive of SWS. Although the syndrome is usually diagnosed based on clinical and radiological findings after birth, it is confirmed by molecular genetic testing. The clinical course is complicated by respiratory insufficiency, feeding difficulties, and hyperthermic episodes. Early death is expected. Management is symptomatic, including care related to feeding difficulties, preventing aspirations, and physical therapy to address contractures and scoliosis. This study emphasized the need for close and multidisciplinary follow-up. Prenatal counseling and genetic testing should be offered for future pregnancies.

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Ethical statement

Drs Alallah, Alamoudi, Makki, AlHarbi and Shawli, confirmed that all procedures followed were in accordance with the ethical standards of the ethics committee (IRB approved the research, IRB with reference number: RJ19/001/J.

Informed consent was obtained from all individuals for whom identifying information is included in this article.

All Authors assure the following is fulfilled:

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3) The paper reflects the authors' own research and analysis in a truthful and complete manner.

4) The paper properly credits the meaningful contributions of co-authors and co-researchers.

5) The results are appropriately placed in the context of prior and existing research.

6) All sources used are properly disclosed (correct citation). Literally copying of text must be indicated as such by using quotation marks and giving proper reference.

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We the listed authors declare that this manuscript is original, has not been published before and is not currently being considered for publication elsewhere.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

We understand that the Corresponding Author, Jubara Alallah, is the sole contact for the Editorial process. She is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs.

Declaration of competing interest

Drs Alallah, Alamoudi, Makki, AlHarbi and Shawli, have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

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