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Stüve-Wiedemann Syndrome: A Very Rare Case in Qatar

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Abstract

Background: Stüve-Wiedemann syndrome (STWS) is an extremely uncommon disorder, which results in bent-bone dysplasia and dysfunction of the autonomic nervous system that controls involuntary processes, such as body temperature and breathing. In infants, this can result in respiratory distress, feeding and swallowing problems, and hyperthermic episodes. While STWS usually leads to infant mortality, some STWS patients might survive into early adulthood. The condition is caused by a mutation in the leukemia inhibitory factor receptor (LIFR) gene, which is inherited in an autosomal-recessive pattern. In this paper, we present a very rare case of STWS in Qatar.

Case description: The case was a female baby with the features of STWS. The parents were known carriers of this syndrome with a history of a previous child with the same condition. The baby was the product of a consanguineous marriage. After delivery, the diagnosis of STWS was confirmed by clinical features and genetic testing. Consultation with the related subspecialties was requested for the management of the case.

Conclusion: STWS is a rare disorder accompanied by bent-bone dysplasia and autonomic dysfunction that is generally caused by the autosomal recessive inheritance of a mutated LIFR gene. The symptoms of STWS are the result of a lack of LIFR signaling. There is currently no treatment available for STWS, but the symptoms are managed accordingly.

Highlights:

What is current knowledge?

The Stüve-Wiedemann syndrome (STWS) is a rare disorder characterized with bent-bone dysplasia and dysfunction of the autonomic nervous system.

What is new here?

Here we presented a case of female baby with STWS diagnosed according the clinical features (congenital anomalies in the form of bilateral club foot, bowing of both lower limbs, and middle finger deformity in the left hand) and history of genetic testing of family. The case was born by normal vaginal delivery and after birth she was managed appropriately with respiratory support, antibiotics and discharged with nasogastric tube.

Introduction

Stüve-Wiedemann syndrome (STWS) is a rare autosomal recessive disorder with a global prevalence of less than 1 in 1,000,000 people. It is characterized by symptoms of dysautonomia, bowing of the long bones with rarefaction and cortical thickening, blurred margins of the metaphyses, camptodactyly, osteopenia, contracture of fingers, and limited mobility of joints (1).

Most patients suffering from STWS do not survive beyond the first few months of life due to respiratory distress, difficulties with feeding and swallowing, or hyperthermic episodes (2). If the patient survives, with age, bowing of the long bones progresses with tubulation of diaphyses, rarefaction, and spontaneous fractures (3). Moreover, temperature instability remains, and other signs of dysautonomia persist, such as a smooth tongue, absent corneal and patellar reflexes, and reduced pain sensation. Furthermore, physical growth and motor development are delayed, but intelligence is normal (4).

In some cases, it is possible to predict STWS before birth via ultrasound as prenatal symptoms can sometimes be seen in the late second or third trimester including oligohydramnios, intrauterine growth restriction, camptodactyly, bowing of the lower bones, and micromelia (1).

An autosomal recessive inherited mutation in the leukemia inhibitory factor receptor (LIFR) gene may result in the development of STWS. The mutations have been either missense or nonsense, with the majority being nonsense within the exons encoding the extracellular domain. Fourteen distinct null mutations were observed in 19 families, most of which resulted in premature stop codons that altered the mRNA stability, resulting in an absence of the LIFR protein and impairment of the LIFR signaling pathway (5).

The first STWS case was recognized in 1971. Stüve and Wiedemann described 2 sisters and a male cousin who had been affected by the mentioned manifestations. All of them developed respiratory distress and died in the neonatal period (6). In this paper, we present a rare case of STWS with various manifestations.

Case presentation

Our case was a 40-week-old female baby, delivered to a 28-year-old Qatari mother at the Women's Wellness and Research Center (WWRC), Hamad Medical Corporation (HMC), Qatar. The mother was gravida 5 para 4, with previous vaginal deliveries and no history of medical problems. The parents were known carriers of this syndrome with a history of a previous child with the same condition.

The baby was the product of a consanguineous marriage. The previous child needed respiratory support in the form of continuous positive airway pressure for 1 month and then he improved. He was 6 years old and still alive. He went to school and had multiple surgeries. The mother was following in the feto-maternal unit. Scans were performed at gestation weeks 23 and 37, which revealed a female baby with short-long bones and femur bowing. The prenatal genetic testing (amniocentesis) confirmed the diagnosis of STWS with a mutated *LIFR* gene. A multidisciplinary meeting was arranged between the parents, the obstetrician, the neonatologist, and the geneticist to determine the management plan.

At the time of delivery, a female baby was born vigorously by normal vaginal delivery. No active resuscitation was required. The Apgar's score was 9 in 1 minute and 10 in 5 minutes. The birth weight was 2.5 kg. There were apparent congenital anomalies in the form of bilateral club foot, bowing of both lower limbs, and middle finger deformity in the left hand.

She needed a nasal continuous positive airway pressure for 12 days, then weaned to a nasal cannula for 7 days, and later to room air. Next, the feeding started and was tolerated well and gradually increased to full feeds by the 5th day using a nasogastric tube.

She had 2 spikes of fever up to 38 ºC; therefore, a sepsis screen was sent and she received second-line antibiotics for 48 hours. The antibiotic therapy was stopped as soon as receiving a negative sepsis screen.

The skeletal survey revealed bowing and shortening of the long bones of both lower limbs with normal bone density (Figure 1). The ultrasound of the skull and abdomen was normal.

The laboratory investigations were unremarkable. We did not repeat the genetic testing. The baby was discharged with the nasogastric tube and was followed by a team at home and by the related subspecialties.

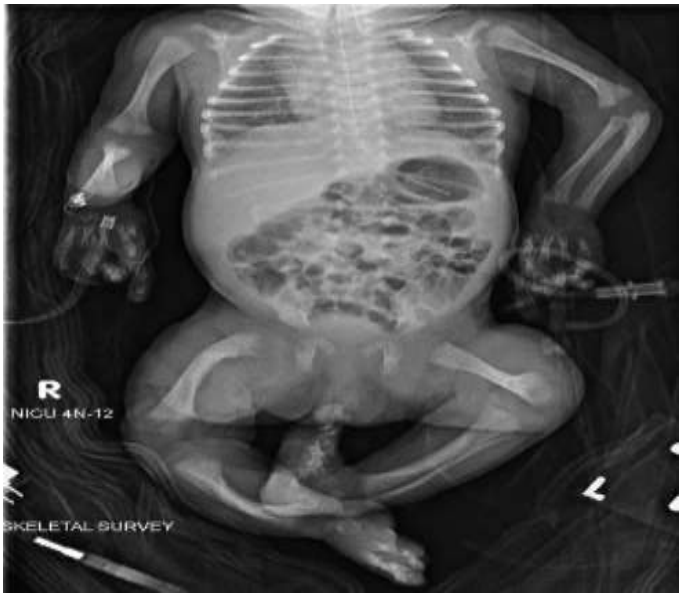

Figure 1. The skeletal survey of the case revealed bowed long bones, short, long bones, internal cortical thickening, and wide metaphysis

Discussion

As mentioned earlier, STWS is an autosomal recessive disorder that is mainly caused by mutations in the LIFR gene (5p13.1). The LIFR protein acts as a receptor for a ligand known as leukemia inhibitory factor that can control several cellular processes, including proliferation, differentiation, and survival. It also appears to play an important role in the normal development and functioning of the autonomic nervous system. Some patients diagnosed with STWS lack the LIFR mutations, suggesting that other genes may also be involved in the development of STWS (2). Similar conditions include Schwartz-Jampel Syndrome type 2 (SIS2), Neonatal Schwartz-Jampel Syndrome, and Stuve-Wiedemann/Schwartz-Jampel type 2 Syndrome (7).

The clinical manifestations of STWS include facial dysmorphisms, pursed mouth, mask-like face, hypoplastic midface, smooth tongue, corneal opacities, corneal ulceration, reduced corneal reflex, decreased sensation of the eye, alacrima, reduced blinking, and recurrent keratitis. Muscular and skeletal findings in the form of bowing of extremities, short stature, camptodactyly, joint restriction, foot malposition, severe spinal deformities, osteoporosis, spontaneous fractures, luxation of the patellae, and impaired growth. The delayed motor development is late (8). Dysautonomia, sweating anomalies, temperature dysregulation, paradoxical sweating, bouts of hyperthermia (with increased risk for malignant hyperthermia), and respiratory distress/apneic spells, which is the main cause of death. No intellectual deficit has been reported in patients with STWS. Swallowing disorders are probably related to pharyngoesophageal dyskinesia (9).

The antenatal diagnosis by ultrasound examination may predict the presence of STWS before birth, especially during the 3rd trimester. It usually reveals oligohydramnios, and intrauterine growth restriction despite normal Doppler, micromelia, camptodactyly, and bowing of the lower bones (10).

There is currently no treatment available for STWS. However, aminoglycosides are capable of inducing the read-through of premature stop codons that are present in many LIFR mutations associated with STWS. (11). Currently, STWS is managed symptomatically, with prevention of lung aspirations being a top priority. Since STWS patients are unable to maintain a respiratory rhythm or swallow during the first year of life, intubation, nasogastric tube feeding, and/or gastrostomy are essential (9). Although swallowing abilities generally improve over time, the presence of caretakers is important while the patient is eating for at least the first 5 years of life as aspiration and choking can still occur later in childhood (3).

Osteopenia or osteoporosis in STWS may be treated using bisphosphonates with calcium, 1,25 OH vitamin D, and/or human growth hormone. Surgery is often necessary to improve other bone malformations (12), and physical therapy may be beneficial (9). It is also important to protect the eyes from damage, including sunlight, to prevent visual loss. For hypolacrimation, the frequent use of artificial tear drops and ointment at night is recommended (13). During the neonatal period, STWS was is initially described as a fatal disorder; however, more patients are surviving into adolescents and adulthood (14).

Conclusion

Although STWS is a rare condition, the prognosis remains poor and there are many unanswered questions regarding its pathology. Therefore, further research is needed to provide a better understanding of the underlying mechanisms and proper management of the condition.

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Ethical statement

Written informed consent was obtained from the parents of the patient. All clinical investigations were conducted according to the principles of the declaration of Helsinki.

Conflict of interest

The authors declare that they have no competing interests.

Author contributions

Both authors were shared in manuscript design, content, data acquisition, manuscript preparation, manuscript editing and manuscript review.

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