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CASE REPORT

One in Three: Congenital Bent Bone Disease and Intermittent Hyperthermia in Three Siblings with Stuve-Wiedemann Syndrome

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واحدة في ثلاثة : أمراض انحناء العظام الخلقية وحرارة مفرطة متقطّعة في ثلاثة أشقاء مع متلازمة ستوف–ويدمان

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الملخص: متلازمة ستوف–ويدمانّ اضطراب نادر يتميّز بإنحناء خلقي للعظام الطويلة، تقفعات المفاصل، ضيق في التنفس منذ الولادة، صعوبات في المص و البلع، اضطراب عصبي ذاتي يكون على شكل حمى مفرطة عرضيّة، وعادة موت مبكّر. ثلاثة اشقاء ولدوا من زواج اقارب و ظهرت عليهم سمات سريريّة مماثلة على مدى 16 عاما. تم تشخيص المتلازمة لدى العائلة عند ولادة اخر طفلة في بداية 2012. كان جميع الأطفال في البداية يعانون منذ الولادة من حمى مفرطة ونقص التوتر العام. كشف الفحص السريري لجميع الرضع عن انعطاف الإصبع المستديم، صغر الفك، انحناء العظام الطويلة مع كراديس واسعة، ونقص التوتر. فقط كان الطفل الثاني متضررا من التوتر العضلي من خلال رسم كهرباء العضل. الحمى المفرطة سمة غير عادية في هذه المتلازمه ويمكن ان تساعد على التعرف المبكر لهذه المتلازمة بحيث يمكن تجنب عمل فحوصات موسعة ومفصلة. هذه المتلازمة نتيجة طفرة في جين مستقبلات العامل المثبط لسرطان الدم.

مفتاح الكلمات: متلازمة ستوف–ويدمان؛ متلازمة شوارتز جامبل؛ التوتر العضلي؛ حمى؛ تقرير حاله؛ عمان.

ABSTRACT: Stuve-Wiedemann syndrome (STWS) is a rare disorder characterised by congenital bowing of the long bones, contractures of the joints, neonatal onset of respiratory distress, sucking and swallowing difficulties, dysautonomia presenting as episodic hyperthermia, and usually an early death. Three siblings from a consanguineous marriage presented with similar clinical features over 16 years. STWS was established with their last child at the beginning of 2012. All the children exhibited the onset of STWS in the neonatal period with fever and generalised hypotonia. Examinations of all the infants revealed camptodactyly, micrognathia, bent long bones with wide metaphyses, and hypotonia. Only the second affected child had myotonia, demonstrated by electromyography. Unusual pyrexia as a presenting feature in this syndrome needs early recognition so that extensive and elaborate investigations can be avoided. The disorder is usually caused by a mutation in the leukaemia inhibitory factor receptor gene.

Keywords: Stuve-Weidemann syndrome; Schwartz-Jampel syndrome; Myotonia; Pyrexia; Case report; Oman.

Stuve-Weidemann syndrome (STWS) [MIM #601599], also known as neonatal Schwartz-Jampel syndrome type 2 (SJS-2), is a severe neuromuscular disorder of prenatal onset characterised by congenital joint contractures, distinctive campomelic metaphyseal skeletal dysplasia, respiratory and feeding difficulties, dysautonomia with a tendency towards hyperthermia, and frequent death in infancy.[1] The condition is classified as a genetic skeletal disorder in the congenital bent bone dysplasia group, as the bowing of the long bones in these disorders is a major manifestation. Infants with STWS usually present with joint stiffness, and difficulty in feeding or opening their eyes. These infants are usually affected with mask-like facies, hypotonia, bowing of the long bones (particularly the tibia and the femur), camptodactyly, and autonomic disturbances. Hypotonia is a common presentation in childhood, and STWS should be considered in the differential diagnosis.[2]

We report three Omani siblings born with STWS to consanguineous parents, having neonatal hypotonia as the presenting feature, with intermittent pyrexia, mild incurvature and shortening of their long bones, and myotonia in one case. The constellation of these signs, family history, and radiographic features pointed to the

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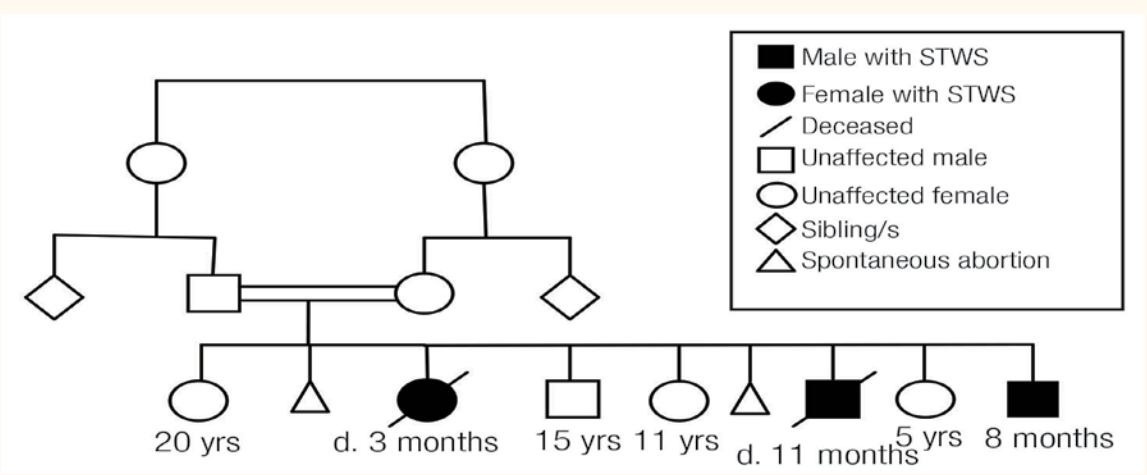

Figure 1: The family tree showing affected siblings and consanguineous parents.

diagnosis of STWS, especially when associated with myotonia as this is an uncommon presentation during childhood. Pyrexia as a presenting feature due to autonomic instability and should not always be considered as a sign of infection. Although the condition is rare worldwide, it is relatively common in the Middle East.[3]

Case One

The couple's third child, a female, was first seen 16 years ago at Sultan Qaboos University Hospital (SQUH), Oman. She was referred at 26 days of age with poor feeding, hypotonia, severe failure to thrive, intermittent fever, and recurrent infections. On examination, she had micrognathia, low-set ears, narrow and short palpebral fissures, long eyelashes, and short curved limbs. She was hypotonic with flexion deformities of both the upper and lower limbs. The basic blood work-up was normal including a septic work-up and a serum creatine kinase (S-CK) test. The nerve conduction study (NCS) and electromyography (EMG) were both normal. No definitive diagnosis was made and the child died at 3 months of age from a respiratory infection.

Case Two

The second affected infant was the couple's seventh child. He was referred to SQUH at the age of 4 months with poor feeding habits and failure to thrive. He was born full-term after a vacuum extraction for shoulder dystocia. His Apgar scores were 6 and 8 at 1 and 5 minutes, respectively. He had a history of abnormal movements (shaking of the lower limbs) noted transiently in the first week of life, and presented with recurrent episodes of a high-grade fever. On examination, he was microcephalic and emaciated, with hypotonia, bilateral elbow contractures and facial myotonia presenting with blepharospasms and pursing of the lips on stimulation. In addition, he was micrognathic and dysmorphic, with long eyelashes, low-set ears, an inverted V-shaped mouth, and *pectus carinatum*. A baseline blood work-up, septic work-up, and S-CK were normal, as was the NCS. An EMG showed myotonia at rest and at action with no denervation pattern. In view of the infant's clinical features and the EMG findings, a diagnosis of SJS-2 was made. The child died at 11 months of age.

Case Three

The third affected child was the couple's ninth child. The mother had had two spontaneous mid-trimester abortions before this baby's birth, but her four other offspring were healthy [Figure 1]. Antenatally, she had had oligohydramnios late in the pregnancy and reported normal fetal movements. This child was first seen at 14 days of age with hypotonia, a weak cry, and poor sucking. He was born post-term at 41 weeks' gestation by an emergency lower segment Caesarean section due to non-progress of the labour. The infant's Apgar scores were 8 and 9 at 1 and 5 minutes, respectively. His birth parameters were appropriate for gestation. He developed respiratory distress and

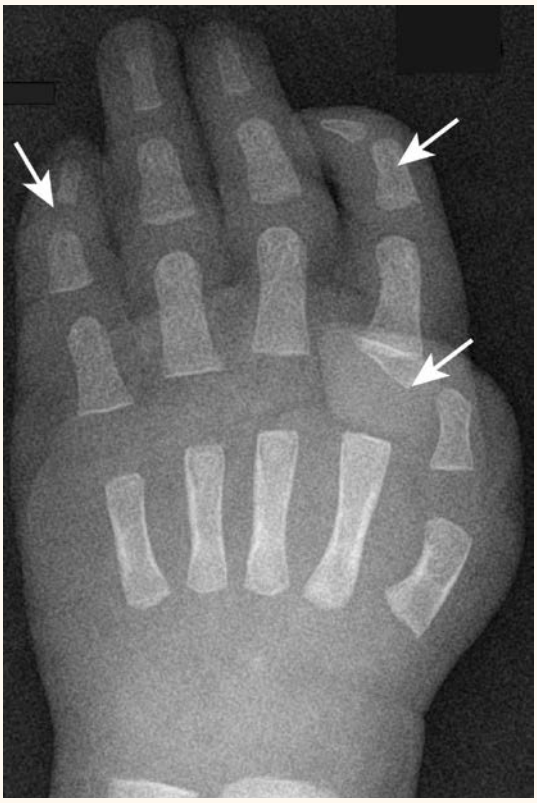

Figure 2: X-ray of the left hand showing camptodactyly (bent fingers and thumb).

desaturation one hour after birth and required facial oxygen. Clinically, he had a poor sucking reflex, a weak cry, hypotonia, and generalised weakness of grade 4/5 with normal reflexes. He also had recurrent episodes of pyrexia with a normal septic work-up. He was still tube-fed at 8 months of age and exhibited a failure to thrive, with his weight well below the 3rd centile, a head circumference on the 3rd centile, and length on the 50th centile. He was noted to have dysmorphic features including a narrow and short palpebral fissure, a broad nasal bridge, a short nose with a wide base, low-set ears, and micrognathia. He had limited extension of the elbow and knees and camptodactyly [Figure 2]. He had fixed contracture of the right thumb and single palmar creases. His lower extremities were short and mildly curved with bilateral prominent heels. He had no myotonia clinically or on EMG. The blood tests at SQUH, including complete blood count, liver function, electrolytes, blood gases, lactate, and ammonia, were all normal. Tandem mass spectrometry and S-CK levels were also normal.

A complete skeletal survey revealed bent long bones and an increase in cortical thickness of the tibia bone at the point of angulation (dysplastic femora epiphysis) [Figures 3–5]. There was a widening of the metaphyses with trabeculation [Figure 3]. Echocardiography showed a small atrial septal defect. An ultrasound and computed tomography (CT) scan of the head and an ophthalmology examination were normal. The parents refused molecular studies despite detailed genetic counselling. At the time of writing this child was still alive.

Discussion

All three siblings had similar clinical features with a neonatal onset of hypotonia, feeding difficulties, and hyperthermia. Clinically, they all exhibited short, bowed long bones and camptodactyly. Only Case Two had clinical and EMG evidence of myotonia. The classical facies of STWS with blepharospasm and pursing of the lips were also noted in this case. The clinical and radiological features of these 3 cases were characteristic of STWS. Although this is a rare condition affecting all ethnic groups, it is over-represented in Middle Eastern populations due to the high coefficient of inbreeding. It should be

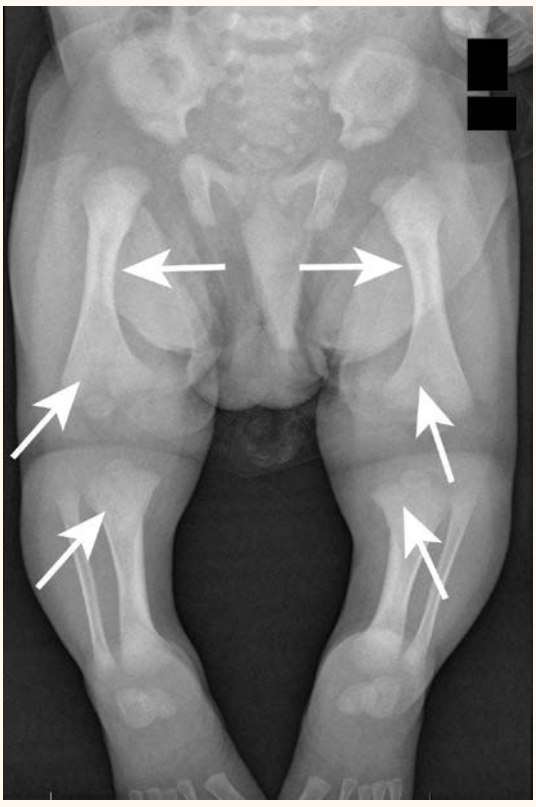

Figure 3: X-ray of lower limbs showing the thickened cortex and bent long bones with enlarged diaphysis.

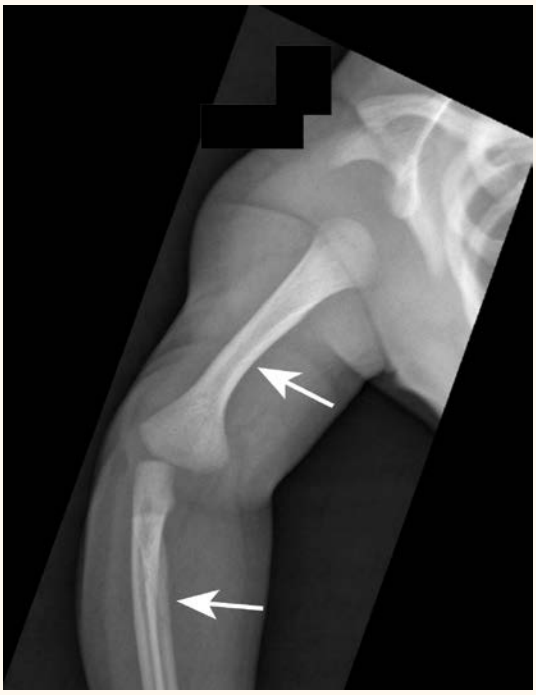

Figure 4: X-ray of right upper limb showing the thick and bent long bones.

considered in the differential diagnosis of a neonate presenting with recurrent fevers, hypotonia, and respiratory and feeding difficulties who is not responding to broad-spectrum antibiotics and who presents with a normal metabolic work-up. These infants usually have bent long bones and camptodactyly with evidence of facial myotonia on clinical examination.[1]

The condition was first described by Stuve and Wiedemann in 1971 in a patient with bowing of the long bones, camptodactyly, respiratory distress, hyperthermic episodes, and death in the first year of life.[2] Long term survival has rarely been reported.[1] This syndrome has features similar to SJS-2, which was once described as a separate entity but is now regarded as STWS.[3–5] There have been a number of reports from the Arabian Gulf in genaral, and Oman in particular, of children with SJS-2.[3,6] STWS should be suspected in the prenatal period when encountering ultrasonographic findings of oligohydramnios; sometimes in cases of intrauterine growth restriction; in cases of mild to moderate shortening and bowing of the long bones; when noting reduced fetal movements, or in a family with a previous history of a similarly affected child. Abnormal skeletal features can be recognised on examination, and a skeletal survey can confirm the campomelic dysplasia affecting the tibia more than the femur, with internal cortical thickening of the medial part of the long bones, relative sparing of fibula and upper limb involvement, and normal thoracic dimensions. Enlarged metaphyses with an abnormal trabecular pattern are invariably present. STWS is one of the differential diagnoses of campomelic dysplasia. The myotonia, if present, can be clinically recognised by pursed lips and blepharospasms. Recurrent respiratory infections and hyperthermia are typical features in the first year of life usually resulting in early death. Other typical features, apart from the bowing and shortening of the lower limbs which can be recognised *in utero*, are the enlarged joints and contractures at the elbows, knees, and fingers. Differential diagnoses include other congenital bent long bone dysplasias such as campomelic dysplasia [MIM #11429]. This is an autosomal dominant condition that usually presents with sex reversal and severe respiratory distress due to severe tracheobronchial and pulmonary hypoplasia, and distinctive skeletal radiographic abnormalities. Another differential diagnosis is kyphomelic dyslasia [MIM #211350], a probable

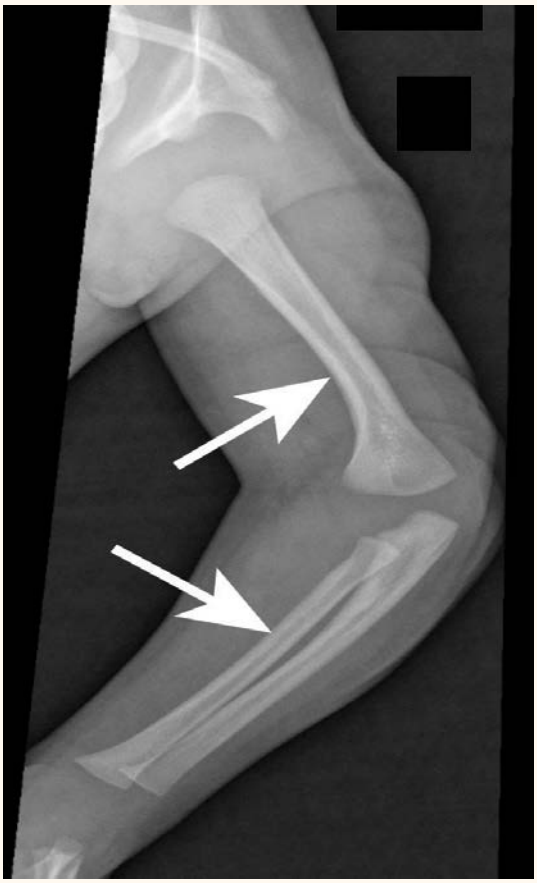

Figure 5: X-ray of left upper limb showing the thick and bent long bones.

X-linked, autosomal recessive disorder with major incurvature of the femur and short stature, sometimes associated with immunodeficiency.[7]

Management of STWS is symptomatic, requiring intensive care initially, including attention to feeding and nutrition, physiotherapy, and orthopedic intervention for the progressive skeletal abnormalities and osteopaenia in the few long term survivors.[8] The main cause of death in infancy is aspiration pneumonia due to defective swallowing, which improves with age in some patients. Management of the consequences of dysautonomia include protection of the tongue and eyes against repeated trauma because of the reduced pain sensation. Excessive sweating and intermittent hyperthermia should be managed by hydration and environmental modification without antipyretics. The microcephaly seen in our second and third cases could be a result of overall malnutrition. Microcephaly is not a feature of STWS and development is usually normal in these children.

The diagnosis of STWS can usually be confirmed molecularly by a finding of null mutations in the leukaemia inhibitory factor receptor (LIFR) gene which usually leads to the absence of LIFR protein. This is a transmembrane protein important in intracellular signalling of the Janus kinase-signal transducer and activator of transcription (JAK/STAT)-3 signalling pathway.[9] The JAK-STAT signalling pathway plays an important role in transmitting information from extracellular polypeptide signals to target gene promoters in the nucleus. JAK-STAT signalling regulates many cellular processes, including development, cell proliferation, differentiation, and apoptosis. However, the causative mutations in the LIFR gene are not found in some patients with STWS, suggesting genetic heterogeneity. Null mutations in the LIFR gene have also been found to cause both SJS-2 and STWS, leading to the conclusion that these disorders should be considered a single, homogeneous disease.[7]

Conclusion

Neonatal presentation of campomelic dysplasia with normal thoracic dimensions, unexplained fevers, and consanguinity in the Middle Eastern population should alert paediatricians to a differential diagnosis of STWS, a potentially lethal condition. Myotonia is a classic symptom of this condition. Molecular testing can not only confirm the clinical diagnosis but also provide reproductive choices for the family and their relatives. Extensive genetic counselling, coupled with carrier screening and premarital testing, should be undertaken as a preventative strategy in families with a history of this mutation.

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