Original Article

The Fetus Points to the Diagnosis of Rare Skeletal Dysplasia: Stuve–wiedemann Syndrome: Retrospective Case Series and Prenatal Review

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Abstract

Background: Stuve–Wiedemann syndrome (SWS) is a rare skeletal abnormality with extensive postnatal literature but limited prenatal studies. Our group had published a diagnostic algorithm to identify prenatal cases, yet, the challenge continues, especially when there is no family history of a similar condition. **Methods:** We retrospectively analyzed our experience of prenatal diagnosis of SWS over an 8-year period with ethical approval. Literature review of articles published until July 30, 2023 from PubMed, GeneReviews, and Genetics Home Reference using search parameters, "SWS," "prenatal," and "ultrasound" was conducted. **Results:** Three cases (diagnosed during the routine anomaly scan) were identified from our institutional review, and 11 cases from six studies from the literature review. Eight out of these 11 cases had a positive family history. SWS was recognized without positive family history in two patients from literature review and the three patients in the current study. The consistent findings that helped in reaching the suspicion were the typical pattern of long bone involvement (bowing of tibia > femora, relative sparing of the fibula and upper limb bones, normal scapulae, and clavicles), and the presence of camptodactyly. Despite the lack of sonographic evidence of narrow thorax, SWS is highly lethal, due to dysautonomic symptoms. **Conclusion:** In SWS, accurate ultrasound diagnosis is crucial to provide prognostic information as the lethality does not depend on pulmonary hypoplasia. Examination of the hands looking for camptodactyly is crucial in skeletal dysplasias to distinguish SWS from other bent bone osteochondrodysplasias, namely, campomelic and kyphomelic dysplasias. This prenatal distinction has important implications for prognosis.

Keywords: Prenatal, skeletal dysplasia, Stuve–Wiedemann syndrome, ultrasound

Introduction

Stuve–Wiedemann syndrome (SWS) is a rare skeletal abnormality and is characterized clinically by bowing and shortening of the lower limbs, contracture of elbows and knees, and talipes equinovarus.[1] Even though this disorder was described by two physicians in the year 1971,[2] its recognition as an unique entity, took several years to be achieved. Initially, the confusion arose due to overlapping features with another specific bowing syndrome, campomelic dysplasia (CMPD) which was later clarified. Spranger registered this condition in the classification of osteochondrodysplasias as a separate entity in 1992.[3] CMPD is caused by mutations in SOX9 mutations[4] that is transmitted in an autosomal dominant fashion, whereas SWS is secondary to leukemia inhibitory factor receptor (LIFR) mutations[5] and is transmitted in an autosomal recessive manner. The discovery of variants in both copies of LIFR in patients with SWS confirmed this pattern of inheritance.[5] Another challenge was posed when there was difficulty in its differentiation from Schwartz Jampelle syndrome Type 2. However, experts concluded that the two disorders fall under the same category owing to the similarities in the clinical and radiological aspects.[6] In the postnatal setting, the recognition of SWS is mainly due to the presence of

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associated features such as camptodactyly, respiratory distress/apneic spells, and hyperthermic episodes frequently associated with feeding/swallowing difficulties.[7] Other clinical findings are the mask-like face, pursed mouth, hypoplastic midface, congenital contractures, and muscular hypotonia.[7] SWS is unique as these individuals exhibit dysautonomic disturbances apart from the prominent bone involvement, thereby allowing its classification under both bent bone dysplasias and ciliary neurotrophic factor pathway-related disorders.[8] As these dysautonomic symptoms are difficult to be elucidated prenatally, there is a paucity of prenatal literature.[9-14] Our group has published the largest cohort of prenatally identified fetuses with SWS.[14]

In this article, we aim to report the prenatal diagnosis of SWS in fetuses from families with no known history, the helpful clues in a difficult prenatal setting, and to review the literature on SWS from a prenatal perspective.

Materials and Methods

Retrospective institutional review

A retrospective review of our ultrasound database over a period of 8 years (September 2014 to December 2022) was conducted in a leading tertiary hospital, the United Arab Emirates to identify prenatally diagnosed fetuses with SWS. Patients were included if the diagnosis of SWS was stated/suspected based on ultrasound findings and/or confirmation of the mutation by prenatal invasive procedures. This study was conducted in accordance with the Declaration of Helsinki and was approved by our institutional research committee (IRB number is MCME.CR.242.MAIR.2021). The patient informed consent was waived by the IRB.

Literature review

Our literature review included publications until July 30, 2023 that report an ultrasound finding (s) in a prenatally diagnosed case and publications that report a prenatal ultrasound finding (s) in a postnatally diagnosed case but excluded publications that report postnatal phenotype without explicitly stating whether the ultrasound findings were detected prenatally. Primary literature was searched using PubMed and Online Mendelian Inheritance in Man in addition to other resources such as GeneReviews and Genetics Home Reference. Search parameters included the name of the condition, SWS, "prenatal," and "ultrasound."

Results

Over the period of 8 years, we identified three prenatal cases of SWS from our retrospective institutional review. These patients presented for their routine antenatal care and were diagnosed during the routine 18–22 weeks anomaly scan. The total number of deliveries over the study period in our institute was 18,642. Hence, the prevalence of SWS at birth in the nonselected population was 1.7/10,000 births.

The salient features of the cases, obtained from the present study and the literature review, are shown in Table 1.

The literature review showed the reports of about 11 prenatal cases from 6 studies. It is worth to mention that 6 of the 11 previously reported cases were from our group[14] [Report No. 5, Table 1].

The median gestational age (±standard deviation) at the initial ultrasound examination was 21.7 (±5.2) weeks at which time the skeletal abnormality was recognized.

The manifestation of autosomal recessive conditions occurs typically by skipping generations, with the affected usually are children of unaffected carriers.[15] Further, the work of Dagoneau *et al*. has shown that the presence of an identical frameshift insertion (653_654insT) in families from the United Arab Emirates, suggesting a founder effect in that region.[5] Hence, a family history was considered positive if any member of the extended family was diagnosed with a similar condition as per the patient's information.

Among the 11 prenatally identified cases, 8 of them had a positive family history [Table 1].

Recurrent disease was identified with the fetuses showing similar manifestations as the siblings. One patient where there was no positive history was incorrectly identified as CMPD and SWS was diagnosed postnatally [Report No. 4, Table 1]. The remaining two patients from our previous series were strongly suspected as SWS without any positive family and were confirmed postnatally. In the current study involving three patients, SWS was recognized without positive family history in all of them [Report No. 7, Table 1].

Prenatal skeletal findings

The main prenatal ultrasound findings that were described in the earlier cases as short, bowed femur/long bones. A pattern of skeletal involvement was recognized in our previous series and the article by Catavorell *et al*.[13] [Report No. 6, Table 1] and continued to be observed in the fetuses from the current study. Micromelia was observed with the shortening of all the long bones. But, the extent of bowing was different. Lower limb bones, tibia more than femora were significantly bowed with relative sparing of fibula and upper limb bones [Figures 1 and 2]. Other bones such as scapulae and clavicles were normal, and the fetuses exhibited normal thoracic dimensions where it was reported.

Additional findings

The main associated features were the development of intrauterine growth restriction (IUGR) in the third trimester, the presence of camptodactyly (fixed flexion of all fingers in both hands except the index fingers and/or the little fingers, which extend freely and appear to frequently point at something) [Figures 3-5] (11 out of 14 fetuses, 78.5%) and talipes. Third-trimester oligohydramnios was present in 4 out of 12 reported cases (33%).

Genetic workup (prenatal)

In our patients, the information regarding the carrier status was not available at the time of the first prenatal encounter in the mid-trimester of the pregnancy at which time the fetal

Table 1: Salient features of Stuve–Wiedemann syndrome from prenatally identified cases from the literature (report numbers 1–6) and the additional cases (report number 7)

Report number	Report	Family history	Antenatal diagnosis of SWS	Gestational age initial exam (weeks)	Antenatal skeletal findings	Fetal movement	Additional features	Amniotic fluid volume
1	Hunziker *et al*. (1989)[9]	Positive	Yes	17	Short mild bowing femur	Reduced	Camptodactyly	Normal
2	Philippe *et al*. (1993)[10]	Positive	Yes	22	Bowing femur, tibia bell-shaped thorax	-	Camptodactyly	Polyhydramnios
3	Sigaudy *et al*. (1998)[11]	Positive	Yes	28	Dwarfism and bent legs	Reduced	-	-
4	Rugolo *et al*. (2007)[12]	Negative	No (suspected as CMPD)	22	Short, bowed, hyperechogenic lower limb bones	Diagn. At birth	Camptodactyly talipes	Oligohydramnios
5	Begam *et al*. (2011)[14] Case 1	Positive	Yes	18+5	Micromelia, bowing of long bones in the lower limb (tibia more than femora), Relative sparing of fibula and upper limb bones	Normal	Tetralogy of Fallot	Normal
	Case 2	Positive	Yes	25	Micromelia, bowing of long bones in the lower limb (tibia more than femora), Relative sparing of fibula and upper limb bones	Normal	Talipes	Normal
	Case 3	Positive	Yes	25	Micromelia, bowing of long bones in the lower limb (tibia more than femora), relative sparing of fibula, and upper limb bones	Normal	Camptodactyly talipes	Normal
	Case 4	Negative	Yes	18	Micromelia, bowing of long bones in the lower limb (tibia more than femora), relative sparing of fibula, and upper limb bones	Normal	Camptodactyly	Oligohydramnios
	Case 5	Negative	Yes	24	Micromelia, bowing of long bones in the lower limb (tibia more than femora), relative sparing of fibula, and upper limb bones	Normal	Camptodactyly	Oligohydramnios
	Case 6	Positive	Yes	20	Micromelia, bowing of long bones in the lower limb (tibia more than femora), relative sparing of fibula, and upper limb bones	Reduced	Camptodactyly	Oligohydramnios
6	Catavorell A *et al*. (2013)[13]	Positive	Yes	23	Anterior bowing and shortening of the lower limbs, mainly femur and tibia	-	Camptodactyly talipes	-
7	Additional cases - Case 1	Negative	Yes	21	Micromelia, bowing of long bones in the lower limb (tibia more than femora), relative sparing of fibula, and upper limb bones	Normal	Camptodactyly talipes, flat facial profile	Normal
	Case 2	Negative	Yes	19	Micromelia, bowing of long bones in the lower limb (tibia more than femora), relative sparing of fibula, and upper limb bones	Normal	Camptodactyly talipes	Normal
	Case 3	Negative	Yes	22	Micromelia, bowing of long bones in the lower limb (tibia more than femora), relative sparing of fibula, and upper limb bones	Normal	Camptodactyly talipes	Normal

SWS: Stuve-Wiedemann syndrome, CMPD: Campomelic dysplasia

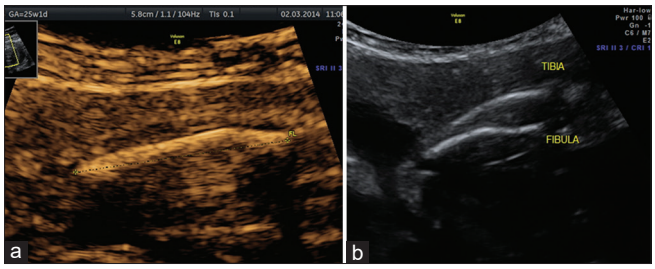

Figure 1: Ultrasound images of the lower limb bones, femur (a) and tibia, and fibula (b) in a fetus with Stuve–Wiedemann syndrome

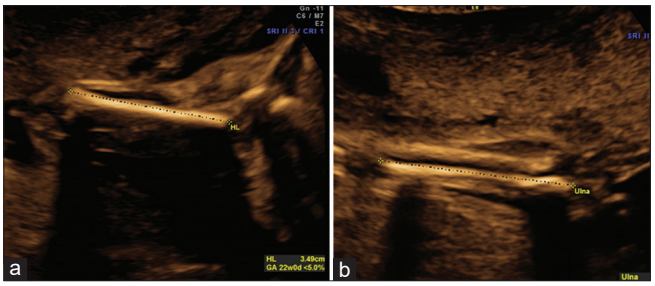

Figure 2: Ultrasound images of the upper limb bones, humerus (a) and ulna, and radius (b) in a fetus with Stuve–Wiedemann syndrome

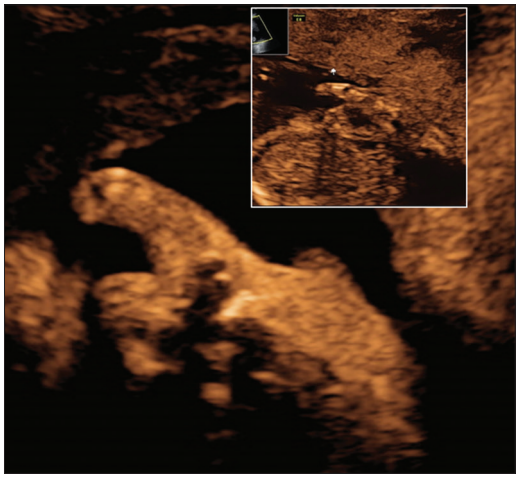

Figure 3: Ultrasound images showing camptodactyly (fixed pointing of index finger) in two fetuses with Stuve–Wiedemann syndrome

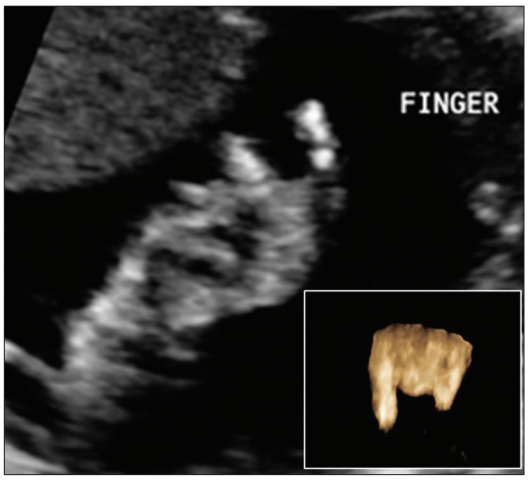

Figure 4: Ultrasound images (two-dimensional and three-dimensional) showing camptodactyly (fixed pointing of index and little fingers) in a fetus with Stuve–Wiedemann syndrome

skeletal dysplasia was recognized as there was no affected family member.

In our cases, the affected index fetus was a proband, who brought us the concern of the genetic disorder, SWS in the family, and facilitated further genetic studies.

Molecular diagnostic testing by amniocentesis for LIFR mutations was offered and was positive in one patient. The other two patients declined and opted for postnatal testing. They had prenatal presumptive diagnosis and were confirmed after delivery.

Genetic workup (postnatal)

For all the patients, the genetic testing for LIFR mutations was performed as "trio" confirming the affected case and the carrier status of the parents. Extended carrier screening was offered to the family members after the mutation confirmation in the proband. Some of them were found to be carriers for the same mutation in the family. The detailed pedigree analysis of one family obtained in the postnatal setting is described [Figure 6].

Discussion

In this study, we have described the review of SWS from the prenatal literature which is further highlighted by the addition of new cases identified from our institutional review.

The postnatal diagnosis of SWS is enabled by the observation of dysautonomic symptoms, namely, respiratory distress/apneic spells and hyperthermic episodes frequently associated with feeding/swallowing difficulties in the setting of short and bowed long bones.[7] Obviously, these dysautonomic features cannot be ascertained by the prenatal scan. Hence, in sharp contrast to postnatal literature, it is a rarity to see prenatally published cases.[9-14]

A systematic analysis of the medical literature to identify all published clinical cases of SWS reporting antenatal and neonatal features using the online database PubMed, until May 31, 2021, has identified few antenatal features in a cohort of 69 SWS patients.[16] Similarly, in this current review, it is not surprising that the majority (8 out of 11) of the prenatally diagnosed cases occurred mainly in patients with a positive family history [Table 1]. When a skeletal dysplasia is recognized by a sonologist, it is relatively easier to associate this with the known familial condition, resulting in straightforward identification of recurrent disease. However, as many as 90% of dysplasias occur in the absence of any known parental risk factors.[17] Therefore, it is important to be aware of this rare condition when physicians are faced with this type of skeletal disorder *de novo*.

Furthermore, the diagnosable characteristics of this syndrome such as short bowed long bones, IUGR, and talipes occur in a

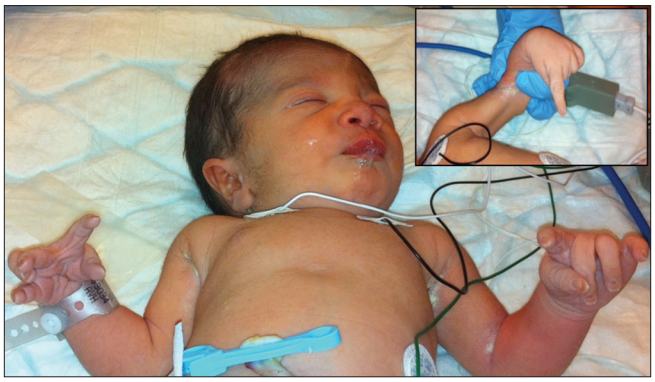

Figure 5: Postnatal images showing pursing of lips and camptodactyly (fixed pointing of index fingers) in a baby with Stuve–Wiedemann syndrome

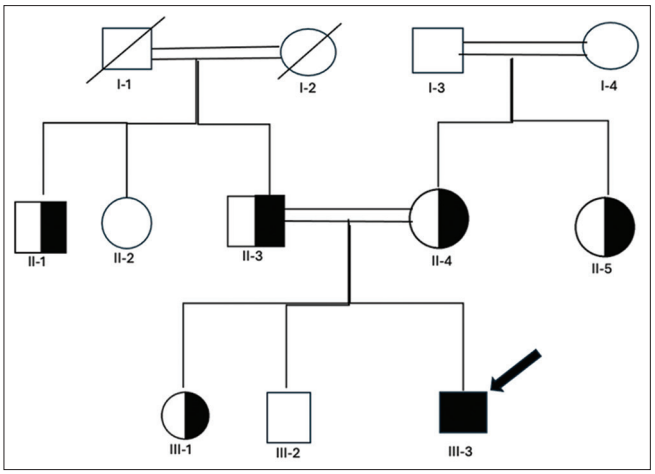

Figure 6: Pedigree chart obtained postnatally in one family after the mutation confirmation in the proband (arrow). Extended carrier screening shows several closely related members as carriers

multitude of skeletal dysplasias compounding the difficulties in diagnosis.[18] SWS is often confused with other bent bone dysplasias such as CMPD[12] and kyphomelic dysplasia (KD).[18] The prenatal distinction between these different osteochondrodysplasias has important implications for prognosis: KD has a good prognosis with regression of skeletal abnormalities and further normal development,[19] whereas SWS and CMPD have a poor prognosis with high lethality rate and major disabilities in survivors.[20] Involvement of scapulae is typical of CMPD;[21] hence, it is worth attempting to look for scapular dimensions in fetuses presenting with bent-bone dysplasias, and 3-dimensional ultrasound further aids in the diagnosis.

It is often emphasized that the sonologists who recognize the skeletal dysplasia should be able to determine the lethality.[22] Degree of femoral shortening, lung volumes, femur length to abdominal circumference ratio, and chest circumference to abdominal circumference ratio are the most tested tools for predicting lethality.[22] However, despite the lack of sonographic evidence of a narrow thorax,[14] SWS is lethal in the majority of the cases, mainly due to dysautonomic symptoms, such as respiratory distress/apneic spells and hyperthermic episodes.[7] Hence, the sonologist will be deceived if the prognosis of this condition will be ascertained mainly based on the standard criteria for testing lethality for skeletal dysplasias.

As the prognosis of a skeletal disorder is based on the prediction of lethality, it is believed that a specific prenatal diagnosis of skeletal dysplasia is important only to give guidance to the family with regard to genetic counseling, molecular testing, and reproductive options.[22] However, in SWS, accurate ultrasound diagnosis is crucial to provide future parents with prognostic information, especially if the question of termination of pregnancy (TOP) arises.

As SWS presents with a multitude of prenatal ultrasound signs, it has been proposed that testing for LIFR pathogenic variant should be included in prenatal genetic panels not only in case of micromelia or bowed long bones but also in case of other prenatal abnormalities: IUGR, oligohydramnios, or feet malposition, as these anomalies may be the only prenatal finding in some patients with SWS.[16] This approach is confusing and may not be cost-effective, especially in low-resource settings.

Our previously proposed algorithm aids to differentiate SWS from other similar bent bone dysplasias.[14] SWS is known to present with few associated anomalies.[9-14] The two consistent findings that we have noted across all the fetuses with SWS are the typical pattern of long-bone involvement [Figures 1 and 2] (bowing of long bones in the lower limb [tibia more than femora], relative sparing of fibula and upper limb bones), and the presence of camptodactyly (pointing finger) [Figures 3-5 and Table 1]. CMPD also shares the similar pattern of long-bone involvement.[20] However, camptodactyly stands out as the differentiating ultrasound feature seen only in SWS unlike the other bent bone dysplasias, namely, CMPD and kyphomelic dysplasia.[19,20] Using this approach, in the current study, we were able to diagnose three cases during the routine anomaly scan in families without positive history.

Indeed, we believe that camptodactyly is a tell-tale finding in SWS among the bent bone dysplasias, as though the fetus points itself to the diagnosis. We suggest that the sonologists should look for camptodactyly in all cases of bent bone dysplasias. However, this sign will be difficult to be identified if there is development of oligohydramnios which was the case in 33% of cases. Since oligohydramnios develops mainly in the third trimester, with advancing gestation in SWS, it is important to pick camptodactyly at the earliest possible recognition of the skeletal dysplasia.

Once the presumptive diagnosis is made, it is feasible to reach the definite molecular diagnosis by testing for the LIFR panel which will help in the prenatal counseling and guide the parents about decision-making. In our series, LIFR mutational testing was positive in one patient and the other two had postnatal confirmation. In general, the uptake of invasive prenatal genetic testing is low in our population as there is no option for legal TOP for this condition.

Further, identifying the proband will facilitate extended carrier analysis by deploying DNA-based genetic screening to identify the individuals within the family that are at increased risk.[23,24] This family-oriented approach is particularly beneficial for communities with consanguineous marriages and large families.[23,24]

Conclusion

As though the fetus points itself to the diagnosis, camptodactyly is a tell-tale finding that distinguishes SWS from other bent bone osteochondrodysplasias, such as CMPD and kyphomelic dysplasia with which it is often confused. This sign should be looked at in all the bent bone dysplasias as the prenatal distinction between these different conditions has important implications for prognosis. In SWS, accurate ultrasound diagnosis is crucial to provide future parents prognostic information as the lethality does not depend on sonographic evidence of pulmonary hypoplasia, i.e., narrow thorax. Ultimately, definite molecular diagnosis through LIFR panel testing will help in the prenatal counseling, guide the parents about decision-making, and extended family-oriented carrier screening.

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Conflicts of interest

There are no conflicts of interest.

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