

Genetic counseling in a case of congenital hemivertebrae

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Abstract A case of in utero spondylothoracic dysostoses is diagnosed during a routine third trimester ultrasound scan in a low-risk patient. Ultrasound showed spine deformation, hemivertebrae and crab-like ribs. The newborn had no other associated anomalies except inguinal hernia, and karyotype was normal. Bidimensional and 3-4D ultrasound imaging as well as radiograph of the fetus and photos of the newborn are presented and discussed. Sporadic cases are difficult to diagnose and classify, as they are probably due to genetic heterogeneity. Sporadic cases of hemivertebrae are rare and not always lethal. Fetal ultrasound scan findings can help predict prognosis, enabling the parents' informed decision making.

Keywords Pregnancy · Dysostoses · Prenatal diagnosis · Musculoskeletal abnormalities · Spine · Ultrasound

Introduction

Vertebral segmentation anomalies are found in more than 50 congenital syndromes whose classification has often been confusing in literature [1–3]. Hemivertebra is not usually an isolated finding but part of a dysostosis syndrome

and considered to be a lethal anomaly in up to 50% of the cases [4]. Spondylothoracic dysostosis (STD), spondylocostal dysostosis (SCD) and Jarcho–Levin syndrome (JLS) are considered to be different entities with different inheritance and survival patterns, although they may overlap [2, 5, 6]. However, lethality due to vertebral segmentation anomalies is probably overestimated as some patients choose to terminate pregnancy upon prenatal diagnosis, where legally available.

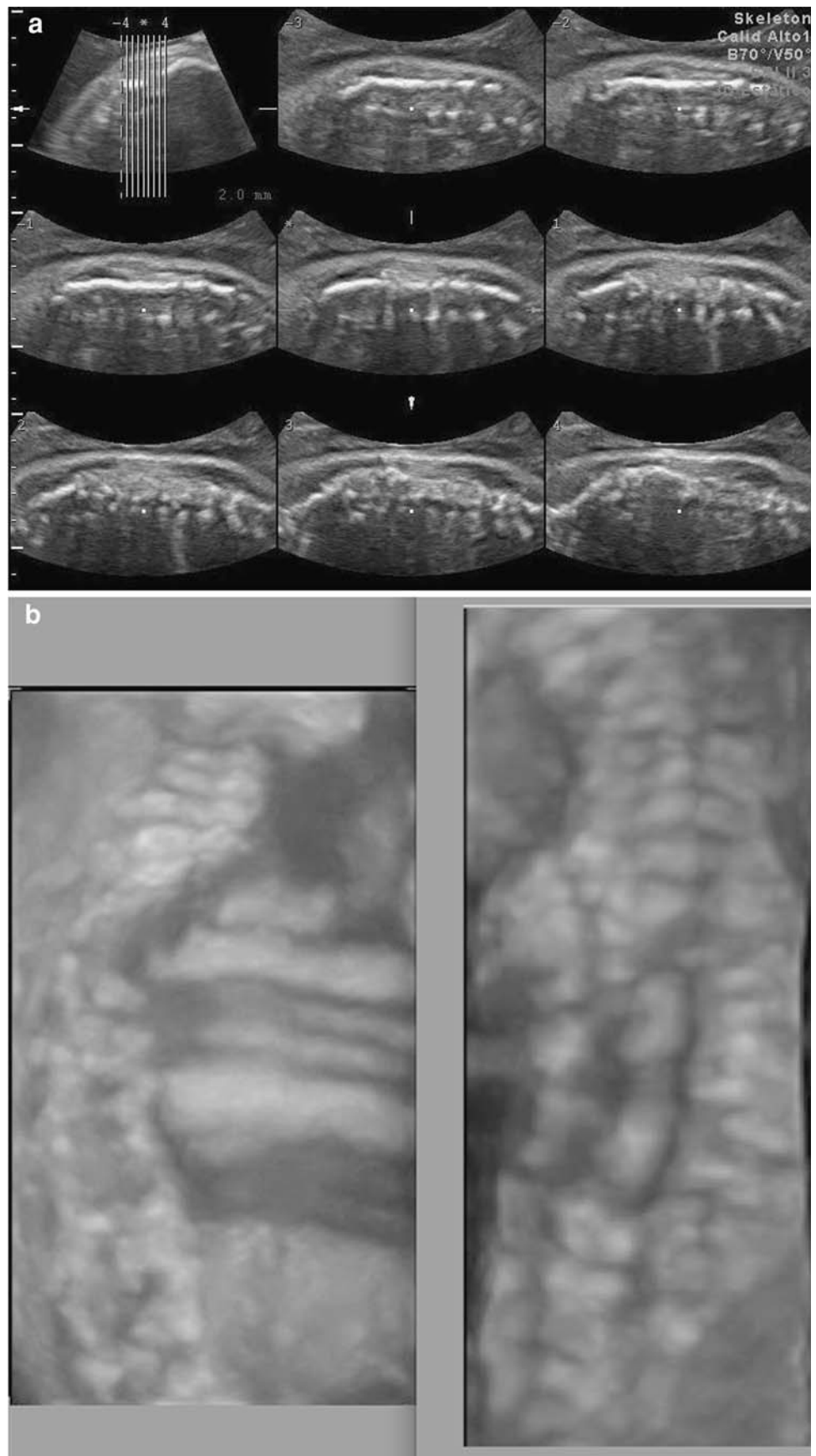
Associated anomalies are most commonly observed in lethal cases. Sporadic cases of vertebral segmentation defects are difficult to classify as to etiology, genetic versus nongenetic origin, and probably represent a heterogeneous group, where even diabetic embryopathy has been involved [7]. Only recently has the inheritance pattern of SCD been partially elucidated [3, 5]. The form of autosomal recessive SCD that maps to chromosome 19q13 is caused by mutation in *DLL3*, a somitogenesis gene. Both the *DLL3* and *MESP2* genes are important components of the Notch signaling pathway, which has multiple roles in development and disease [5]. A third Notch pathway gene, *LFNG*, has also been related to the autosomal recessive form of SCD. These were the first mutations in a human delta homolog, thus highlighting the critical role of the Notch signaling pathway and its components in patterning the mammalian axial skeleton. Another form is caused by mutations in the *MESP2* gene. However, in a family segregating autosomal recessive SCD, Iughetti et al. could find no evidence of linkage to 19q, indicating genetic heterogeneity in this disorder [8].

Routine ultrasound scan can miss hemivertebrae as an isolated finding unless careful sagittal and transversal views of the spine are focused. Careful search for other malformations is mandatory as prognosis depends upon them. We describe a case without previous family history where

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Fig. 1 **a** Multiplanar ultrasound reconstruction of the fetal spine (32 weeks gestational age).
b Three-dimensional ultrasound rendering of the fetal spine: frontal view on the right side (32 weeks)



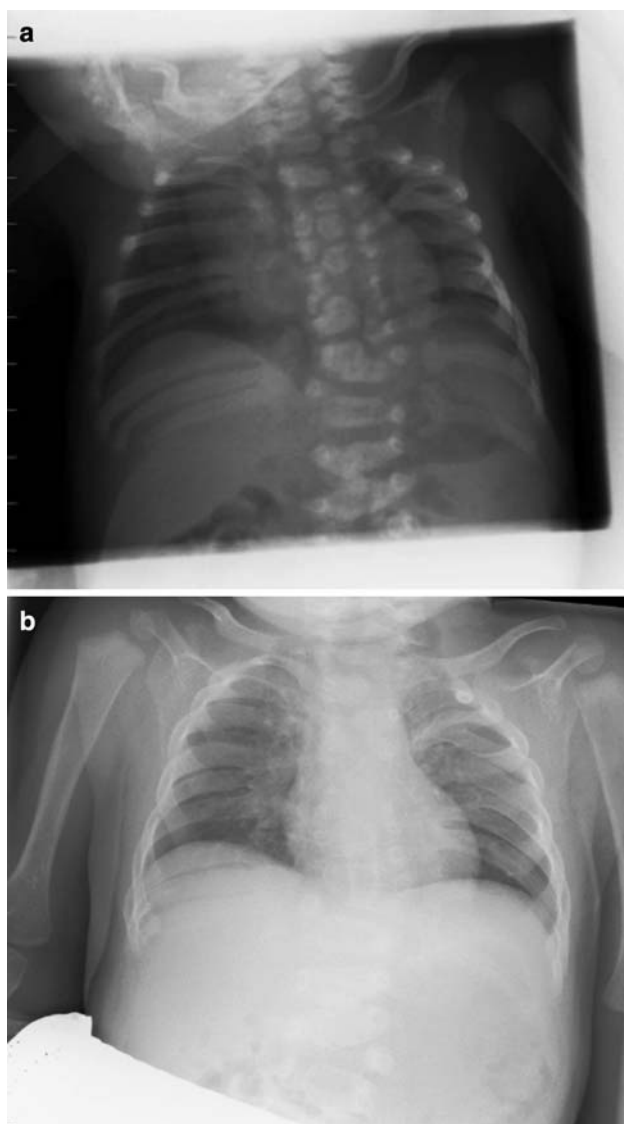


Fig. 2 **a** Thoracic X-ray in the newborn. **b** Thoracic X-ray at 12 months of age



Fig. 3 Note the short neck and flat-base nose in the newborn



Fig. 4 Computer X-ray frontal view at 12 months of age

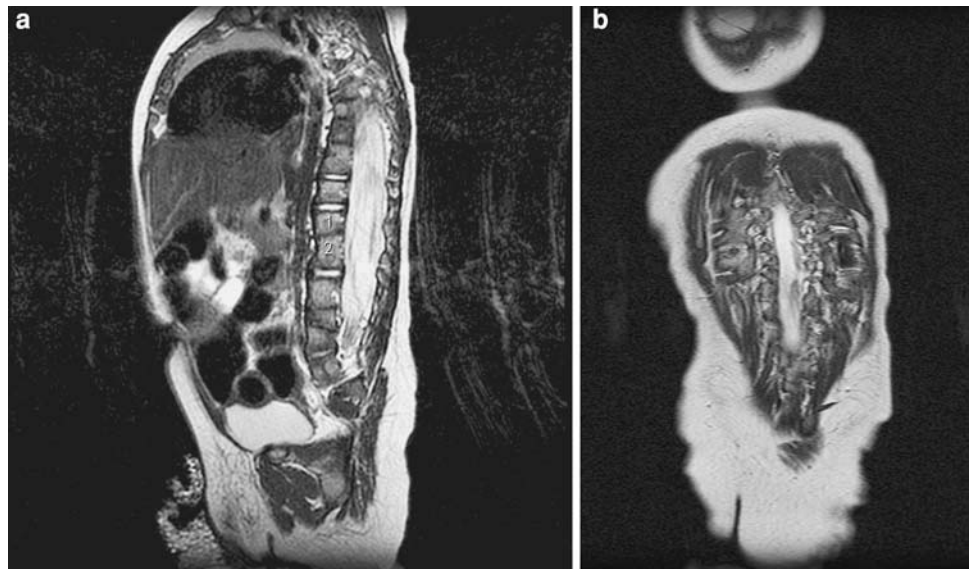
diagnosis was made in the third trimester as a sporadic non-lethal case of STD from a low-risk mother.

Case report

A 20-year-old patient presented at 32 weeks for a third trimester routine ultrasound scan. The patient is a Caucasian healthy woman. The pregnancy was uneventful with a low-risk first trimester Down screening test and normal O'Sullivan test. No consanguinity or significant previous family history was reported. Ultrasound scan (Voluson 730 Expert Pro, GE Medical Systems, Milwaukee, WI, USA and Toshiba Xario, Toshiba America Medical systems, Tustin, CA) showed spine deformation compatible with scoliosis, hemi-vertebrae, intact skin above spine deformation and anomalous disposition of ribs (Fig. 1a, b). The heart was not displaced, and there were no associated malformations.

Karyotype was performed on the newborn and turned out to be normal. The malformation ultrasound image did not change for the rest of the pregnancy. Fetal biometry corresponded to a small for gestational age male fetus and amniotic fluid volume was normal. Fetal movements as observed and reported by the mother were always normal.

Fig. 5 **a** Coronal T2-weighted MRI showing block vertebrae (numbered) at 7 months of age. **b** Coronal T2-weighted MRI showing fused ribs



An elective cesarean section was performed in week 38. The newborn weighed 2,410 g, measured 45 cm (small for gestational age), had an Apgar Test of 9/9 and showed normal rib number but severe disorganization of the ribs in a mild crab-like fashion: fourth to sixth right posterior rib shaft fused as well as sixth and seventh left posterior rib shaft fused. Other anomalies found in X-Ray and MRI included: cervical, dorsal and lumbar hemivertebrae (affectation is more severe in that order, with hypoplasia of sacral vertebrae), first and second as well as fifth and sixth lumbar vertebrae were block vertebrae (Figs. 2a, b, 3, 4, 5a, b). Then infant also showed left dorso-lumbar scoliosis, short neck and thorax, short nose, facial asymmetry and congenital right torticollis. There were no renal or cardiac defects and spinal cord had normal volume and shape. Due to evolutive changes in ossification, the extent of scoliosis and the final appearance of hemivertebrae are yet to be determined.

At 3 months of age the baby had bilateral inguinal hernia surgery. The infant is now 16 months old and under going physiotherapy treatment with an orthopedic brace. Timing of surgical treatment will depend on progression of the scoliosis. Neurologic and motor development are within normal range.

Discussion

Vertebral segmentation anomalies result in deformation of the spine such as scoliosis, due to development of only one side of the vertebral body. Since 1966 when Lavy et al. [9] observed four of seven offspring of a third-cousin marriage who had characteristic vertebral anomalies including hemivertebrae and block vertebrae accompanied by deformity of the ribs, there are less than 150 cases reported in the litera-

ture, most of them postnatally, until 1987 [10, 11]. The vast majority of so called JLS cases reported in literature come from consanguineous families [12] and the disorder is lethal [13]; some published cases could correspond to misclassified cases of SCD or STD [2]. Since 1978 various classifications have been published: on one hand, Solomon [14], who pointed out the prevalence of JLS in the Puerto Rican ethnicity, considered STD and SCD to be subtypes of JLS, on the other hand Mortier [6] studied 141 patients and concluded that SCD, STD and JLS are three different entities that may overlap, thus, the eponym JLS has been used as synonym to both or at least to the most severe lethal autosomal recessive form of STD. More recently, the Nosology group of the International Skeletal Dysplasia Society (2006) [15] grouped genetic skeletal disorders into 37 groups. Group 32 correspond to *dysostosis with predominant vertebral and costal involvement* and includes SCD types 1, 2, 3 and dominant, JLS, Currarino syndrome, cerebro-costo-mandibular syndrome, ischio-spinal dysostosis and Klippel–Feil anomaly.

The first second trimester prenatal diagnosis case was described in 1987 [10], followed by first trimester and three-dimensional ultrasound descriptions [11, 16]. There are very few cases of prenatal detection in low-risk patients [17]. del Rio et al. [18] describe a lethal JL/STD type I case in a low-risk patient. Our patient presents an also sporadic but non-lethal case of STD.

Imaging and clinical data on the present case suggests a mild form of the syndrome that can be labeled under sporadic STD. These are characterized by multiple thoracic vertebral segmentation defects and symmetric rib anomalies (see Cornier et al. [2] for a diagnostic algorithm).

What this paper adds is the correlation of images in 2-D and 3-D ultrasound, newborn X-Ray and photography, the

evolution of the MRI and X-Ray imaging, and a new non-lethal sporadic case of STD.

In a tertiary medical center in Israel [19], the authors describe 26 cases of hemivertebrae but more than 80% had associated malformations. If isolated, hemivertebrae can be a casual finding in routine X-Ray in children [20].

Aneuploidies have not been associated with hemivertebrae as an isolated finding [19] neither in STD nor SCD; only in some cases translocations, deletions or placental mosaicisms have been described [21]. The worst prognosis is seen when oligoamnios is present, as was not in the present case. The prognosis of this disorder depends on respiratory complications, and spine surgery and physiotherapy can provide a normal life span [4].

Careful scanning for cardiac, intestinal, renal, intracranial, and limb anomalies must follow the diagnosis of any skeletal dysplasia. Fetal MRI mainly aims at pregnancies in the third trimester where ultrasound imaging is impaired (obesity, oligohydramnios, etc.). We recommend performing only 2-D and 3-D fetal ultrasound scan, as they should suffice for the diagnosis of hemivertebrae. Postnatal MRI showed rib fusion that was missed in utero. Bidimensional ultrasound can fail to diagnose kyphosis versus scoliosis; therefore, we recommend 3-D ultrasound to clarify the diagnosis of fetal skeletal disorders.

In our case, first trimester scan did not detect the vertebral anomaly, probably as it was not associated to other major anomalies. Early and accurate diagnosis showing the span of the syndrome and associated anomalies can anticipate prognosis and help parental decision on the fate of pregnancy. There is a lack of evidence on the benefit of an elective cesarean section, although Wax et al. [22] found high rates of cesarean deliveries as well as preterm deliveries and small for gestational age babies in affected pregnancies. We believe that the mode of delivery has to be discussed with the parents as we did in the present case.

The differential diagnosis among SCD, STD and JLS is shown on Table 1. For a complete table on syndromes featuring vertebral segmentation anomalies we refer the reader to the paper by Turnpenny et al. [3].

In the present case, vertebral segmentation anomalies and rib deformities causing congenital scoliosis were suspected in utero at a gestational age where pregnancy termination was not legally allowed in our country. Lethality depends on respiratory complications and associated malformations. As stated by Ayme et al. [23] in 1986 “one must be cautious in advising families of the prognosis for a child with severe structural chest deformity since it may not be severe from a functional point of view”. Inheritance pattern is difficult to elucidate based only on vertebral anomalies. When thoracic anomalies

Table 1 Abnormal vertebral segmentation: differential diagnosis

	Clinical features	Prenatal ultrasound features	Inheritance	Prognosis
Spondylocostal dysostosis (SCD)	Reduced number of ribs Asymmetric rib fusion Hemivertebrae Short neck Short stature Short thorax Protuberant abdomen	Abnormal fetal spinal curvature Rib fusion Hemivertebrae Normal amniotic fluid volume Normal skull and long-bone biometry Possible associated anomalies [2, 11]	Usually family history. Notch signaling pathway. Recessive of dominant (milder)	Depends upon severity
Spondylothoracic dysostosis	Phenotype milder than SCD. Short neck Short stature Symmetric rib fusion Fan-like thoracic configuration Symmetric crab chest	Abnormal fetal spinal curvature. Vertebral anomalies. Posterior convergence of ribs with anterior gradual widening. Possible associated anomalies [2] Lung restriction by severely deformed and fused ribs [18]	Underlying cause not known	Lethal when severe (respiratory failure)
Jarcho-Levin Syndrome (known also as spondylothoracic dysostosis type I)			Autosomal recessive	Lethal
Hemivertebrae isolated	Can be accidental finding in a routine X-ray	Abnormal vertebral segmentation Need to rule out cardiac, intestinal, renal, intracranial, neural tube or limb anomalies in 60% of case [4]	Sporadic	Survival reduced 50% if associated with anomalies

are not severe and in the absence of associated malformations, we can inform the parents that life span can be almost normal although spine surgery will be needed.

We believe that molecular diagnosis will provide a new classification for this extensive group of disorders. Therefore, chromosome mapping and prenatal molecular diagnosis could be offered upon ultrasonography findings to predict prognosis.

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Conflict of interest statement None.

References

- Rimoin DL, Cohn D, Krakow D, Wilcox W, Lachman RS, Alanay Y (2007) The skeletal dysplasias: clinical-molecular correlations. *Ann N Y Acad Sci* 1117:302–309. doi:10.1196/annals.1402.072
- Cornier AS, Ramirez N, Carlo S, Reiss A (2003) Controversies surrounding Jarcho–Levin syndrome. *Curr Opin Pediatr* 15(6):614–620. doi:10.1097/00008480-200312000-00012
- Turnpenny PD, Whittock N, Duncan J, Dunwoodie S, Kusumi K, Ellard S (2003) Novel mutations in *DLL3*, a somitogenesis gene encoding a ligand for the Notch signalling pathway, cause a consistent pattern of abnormal vertebral segmentation in spondylocostal dysostosis. *J Med Genet* 40(5):333–339. doi:10.1136/jmg.40.5.333
- Zelop CM, Pretorius DH, Benacerraf BR (1993) Fetal hemivertebrae: associated anomalies, significance, and outcome. *Obstet Gynecol* 81(3):412–416
- Turnpenny PD, Alman B, Cornier AS, Giampietro PF, Offiah A, Tassy O et al (2007) Abnormal vertebral segmentation and the notch signaling pathway in man. *Dev Dyn* 236(6):1456–1474. doi:10.1002/dvdy.21182
- Mortier GR, Lachman RS, Bocian M, Rimoin DL (1996) Multiple vertebral segmentation defects: analysis of 26 new patients and review of the literature. *Am J Med Genet* 61(4):310–319. doi:10.1002/(SICI)1096-8628(19960202)61:4<310::AID-AJMG3>3.0.CO;2-Y
- Martinez-Frias ML, Urioste M (1994) Segmentation anomalies of the vertebrae and ribs: a developmental field defect: epidemiologic evidence. *Am J Med Genet* 49(1):36–44. doi:10.1002/ajmg.1320490109
- Whittock NV, Turnpenny PD, Tuerlings J, Ellard S (2003) Molecular genetic prenatal diagnosis for a case of autosomal recessive spondylocostal dysostosis. *Prenat Diagn* 23(7):575–579. doi:10.1002/pd.643
- Lavy NW, Palmer CG, Merritt AD (1966) A syndrome of bizarre vertebral anomalies. *J Pediatr* 69:1121–1125. doi:10.1016/S0022-3476(66)80304-9
- Apuzzio JJ, Diamond N, Ganesh V, Desposito F (1987) Difficulties in the prenatal diagnosis of Jarcho–Levin syndrome. *Am J Obstet Gynecol* 156(4):916–918
- Wong GY, Wong SF, Chan WP, Ng WF (2006) Three-dimensional ultrasound findings of spondylocostal dysostosis in the second trimester of pregnancy. *Ultrasound Obstet Gynecol* 27(5):580–582. doi:10.1002/uog.2769
- Kulkarni ML, Navaz SR, Vani HN, Manjunath KS, Matani D (2006) Jarcho–Levin syndrome. *Indian J Pediatr* 73(3):245–247. doi:10.1007/BF02825493
- Lawson ME, Share J, Benacerraf B, Krauss CM (1997) Jarcho–Levin syndrome: prenatal diagnosis, perinatal care, and follow-up of siblings. *J Perinatol* 17(5):407–409
- Solomon L, Jimenez RB, Reiner L (1978) Spondylothoracic dysostosis: report of two cases and review of the literature. *Arch Pathol Lab Med* 102(4):201–205
- Superti-Furga A, Unger S (2007) Nosology and classification of genetic skeletal disorders: 2006 revision. *Am J Med Genet A* 143(1):1–18. doi:10.1002/ajmg.a.31483
- Hull AD, James G, Pretorius DH (2001) Detection of Jarcho–Levin syndrome at 12 weeks' gestation by nuchal translucency screening and three-dimensional ultrasound. *Prenat Diagn* 21(5):390–394. doi:10.1002/pd.67
- Marks F, Hernanz-Schulman M, Horii S, Greenland VC, Lustig I, Snyder J et al (1989) Spondylothoracic dysplasia. Clinical and sonographic diagnosis. *J Ultrasound Med* 8(1):1–5
- del Rio Holgado M, Martinez JM, Gomez O, Casals G, Bargallo N, Fortuny A et al (2005) Ultrasonographic diagnosis of Jarcho–Levin syndrome at 20 weeks' gestation in a fetus without previous family history. *Fetal Diagn Ther* 20(2):136–140. doi:10.1159/000082438
- Goldstein I, Makhoul IR, Weissman A, Drugan A (2005) Hemivertebra: prenatal diagnosis, incidence and characteristics. *Fetal Diagn Ther* 20(2):121–126. doi:10.1159/000082435
- Teli M, Hosalkar H, Gill I, Noordeen H (2004) Spondylocostal dysostosis: thirteen new cases treated by conservative and surgical means. *Spine* 29(13):1447–1451. doi:10.1097/01.BRS.0000128761.72844.AB
- Imaizumi K, Masuno M, Ishii T, Kuroki Y, Okuzumi N, Nakamura Y (1997) Congenital scoliosis (hemivertebra) associated with de novo balanced reciprocal translocation, 46,XX, t(13;17)(q34;p11.2). *Am J Med Genet* 73(3):244–246. doi:10.1002/(SICI)1096-8628(19971219)73:3<244::AID-AJMG2>3.0.CO;2-S
- Wax JR, Watson WJ, Miller RC, Ingardia CJ, Pinette MG, Cartin A et al (2008) Prenatal sonographic diagnosis of hemivertebrae: associations and outcomes. *J Ultrasound Med* 27(7):1023–1027
- Ayme S, Preus M (1986) Spondylocostal/spondylothoracic dysostosis: the clinical basis for prognosticating and genetic counseling. *Am J Med Genet* 24(4):599–606. doi:10.1002/ajmg.1320240403