Jarcho-Levin Syndrome

Contents

In 1938, Jarcho and Levin (1938) first described a syndrome of malformations with abnormal fusion of thoracic vertebrae and ribs associated with a short trunk and respiratory insufficiency. At present, Jarcho-Levin syndrome is an eponym used to describe a variety of clinical phenotypes, consisting of short-trunk dwarfism associated with rib and vertebral anomalies. Two phenotypic subtypes of spondylothoracic dysostosis and spondylocostal dysostosis have recently been proposed.

Synonyms and Related Disorders

Costovertebral dysplasia; Costovertebral segmentation anomalies; Spondylocostal dysostosis/dysplasia (Jarcho-Levin syndrome); Spondylothoracic dysostosis/dysplasia (Lavy-Moseley syndrome)

Genetics/Basic Defects

1. Inheritance and molecular defects (Cornier et al. 2003)
    1. The presence of considerable genetic heterogeneity with varied clinical presentations and associated abnormalities (Roberts et al. 1988)
    2. Spondylothoracic dysostosis or Lavy-Moseley syndrome
        1. Autosomal recessive inheritance (Romeo et al. 1991; Bautista et al. 1997)
        2. Linked to chromosome 2q32.1
        3. More severe respiratory compromise
        4. Largely linked to Puerto Rican cohorts and is thought to be associated to the *MESP2* gene, also a Notch pathway gene
    3. Spondylocostal dysostosis or Jarcho-Levin syndrome (Whittock et al. 2004; Turnpenny and Young 2013)
        1. Inheritance: either autosomal recessive (Turnpenny et al. 1991; Turnpenny and Young 2013) or autosomal dominant (Rimoin et al. 1968).
        2. Mutations in the delta-like three gene (*DLL3*) on chromosome 19q13.1-q13 (Bulman et al. 2000; Turnpenny et al. 1999, 2003; Bonafe et al. 2003).
            1. As the major cause of autosomal recessive spondylocostal dysostosis.

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2. *DLL3* (Dunwoodie et al. 2002) encodes a ligand in the Notch gene signal pathway. When mutated, defective somitogenesis occurs resulting in a consistent and distinctive pattern of abnormal vertebral segmentation affecting the entire spine.
3. Mutated mesoderm posterior two homolog gene (*MESP2*) that codes for a basic helix-loop-helix transcription factor was found to cause spondylocostal dysostosis in one consanguineous family with two affected children (linkage to 15q21.3-15q26.1) (Whittock et al. 2004; Cornier et al. 2008).
4. Mutation of the Lunatic Fringe gene in humans causes spondylocostal dysostosis with a severe vertebral phenotype (Sparrow et al. 2006).
5. Autosomal dominant spondylocostal dysostosis is caused by mutation in *TBX6* (Sparrow et al. 2013a).
6. Mutation of HES7 in a large extended family with spondylocostal dysostosis and dextrocardia with situs inversus (Sparrow et al. 2013b)

2. Pathogenesis
   1. Vertebral anomalies: probably attributed to defective segmentation of the somite at about the fourth or fifth week of intrauterine life.
   2. Costal anomalies: probably secondary to the vertebral anomalies.
   3. *Pax1* and *Pax9* might be required for the phenotypic expression of Jarcho-Levin syndrome (Bannykh et al. 2003).

Clinical Features

1. Spondylothoracic dysostosis (Herold et al. 1988; Karnes et al. 1991; Mortier et al. 1996; Cornier et al. 2004)
   1. Vertebral segmentation and formation defects throughout cervical, thoracic, and lumbar spine
      1. Hemivertebrae
      2. Block vertebrae
      3. Unsegmented bars
   2. Fusion of all the ribs at the costovertebral joints bilaterally
   3. Absence of intrinsic rib anomalies
   4. Other clinical features
      1. Short-trunk dwarfism
      2. Craniofacial features
         1. Brachycephaly
         2. Low posterior hairline
         3. Prominent nasal bridge
         4. High-arched palate
      3. Short and rigid neck
      4. Short thorax
      5. Protuberant abdomen
      6. Inguinal and umbilical hernias
      7. Urinary tract abnormalities
      8. Talipes equinovarus
   5. Prognosis: poor but not an invariably lethal condition with 56% of survival among the prospectively evaluated patients
      1. Normal intelligence
      2. Progressive kyphosis and neurologic compromise complicating spondylothoracic dysplasia in infancy (Jarcho-Levin syndrome) (Mooney and Emans 1995; Martinez-Frias and Urioste 1994)
      3. Respiratory complications such as pneumonia
      4. Congestive heart failure
      5. Pulmonary hypertension
2. Spondylocostal dysostosis (Karnes et al. 1991; Mortier et al. 1996)
   1. Constitutes a heterogeneous group of radiologic phenotypes with axial skeletal malformations
   2. Generally milder phenotype
   3. Multiple vertebral segmentation and formation defects
   4. Typical findings
      1. Intrinsic asymmetric rib anomalies
         1. Broadening
         2. Bifurcation
         3. Fusion
      2. No symmetric fusion of the ribs
      3. Do not display a fanlike configuration of the thorax
      4. No cervical spine anomalies in some patients

5. Short-trunk dwarfism
5. Associated anomalies
    1. Congenital heart disease
    2. Urogenital and anal anomalies
    3. Limb abnormalities
    4. Torticollis
    5. Diaphragmatic, umbilical, and inguinal hernias
6. Prognosis (Hayek et al. 1999)
    1. A good prognosis, due in part to the asymmetry of the thoracic anomalies resulting in a less restrictive thorax
    2. Long survival
    3. Normal intelligence

Diagnostic Investigations

1. Radiography (Cornier et al. 2003)
    1. Spondylothoracic dysostosis
        1. Bilateral fanning of the ribs with posterior fusion, giving the appearance of a common origin of ribs at the posterior thoracic spine
        2. A decreased number of cervical, thoracic, and lumbar vertebrae
        3. Multiple vertebral segmentation and formation defects
            1. Block and wedge vertebrae
            2. Unsegmented bars
            3. Hemivertebrae
            4. Anterior-posterior-lateral failure of closure
        4. Symmetric posterior fusion of the ribs: characteristic radiographic finding (Berdon et al. 2011)
    2. Spondylocostal dysostosis
        1. Multiple vertebral formations and segmentation defects along the entire spine
            1. A decreased number of cervical, thoracic, and lumbar vertebrae
            2. Block and wedge vertebrae
            3. Agenesis of the coccygeal region
            4. Progressive scoliosis of the thoracic spine due to tethering effect secondary to the rib anomalies
        2. Asymmetric intrinsic rib malformations
            1. Broadening
            2. Bifurcation
            3. Fusion
            4. Do not display a fanlike configuration of the thorax as in spondylothoracic dysostosis
        3. Asymmetrical abnormalities of the vertebral bodies and ribs: characteristic radiographic finding (Berdon et al. 2011)
2. Reconstructed tridimensional CT scan of the chest
    1. Spondylothoracic dysostosis
        1. Bilateral rib fusion at the costovertebral junction.
        2. Segmentation and formation defects in all cervical, thoracic, and lumbar vertebrae. Sacrococcygeal regions are spared from any abnormality.
        3. Increase in the coronal diameter of the thoracic and lumbar vertebrae which acquire a sickle-like appearance.
    2. Spondylocostal dysostosis
        1. Varying extent of the thoracic fusion
        2. Thoracic fusion always asymmetric with respect to each side of the thorax
        3. Increase in the coronal diameter of the thoracic and lumbar vertebrae which acquire a sickle-like appearance
3. Pulmonary function tests for restrictive lung disease
4. Molecular genetic analysis (Turnpenny and Young 2013)
    1. *DLL3* mutations in spondylocostal dysostosis (homozygous or compound heterozygous mutations).
    2. Other subtypes are defined by identification of two mutant alleles in other three genes known to be associated with autosomal recessive spondylocostal dysostosis: *MESP2*, *LFNG*, and *HES7*.

Genetic Counseling

1. Recurrence risk
    1. Autosomal recessive inheritance (spondylothoracic dysostosis and spondylocostal dysostosis)

1. Patient's sib: 25%
2. Patient's offspring: not increased unless the spouse is also a carrier; in which case, there is a 50% risk of having an affected offspring

2. Autosomal dominant inheritance (spondylocostal dysostosis)
   1. Patient's sib: not increased unless a parent is affected; in which case, there is a 50% risk of having an affected sibling
   2. Patient's offspring: 50%

2. Prenatal diagnosis by ultrasonography
   1. Ultrasonography (Tolmie et al. 1987; Marks et al. 1989; Eliyahu et al. 1997; Lawson et al. 1997; Kauffmann et al. 2003).
      1. Grossly distorted thoracic and lumbar spine
      2. Marked kyphoscoliosis
      3. Multiple vertebral segmentation anomalies
      4. Fanned ribs from fused thoracic vertebral bodies (Wong and Levine 1998)
      5. A small chest with foreshortened spine
      6. Increased fetal nuchal translucency thickness (Hull et al. 2001)
      7. Inguinoscrotal hernia in a fetus with vertebral anomalies: a clue for Jarcho-Levin syndrome and other pathologies that increase abdominal pressure (Basaran et al. 2010)
   2. Three-dimensional computed tomography of fetal spondylothoracic dysostosis at 23 weeks' gestation (Ranes et al. 2012).
   3. Prenatal diagnosis by molecular genetic analysis of *DLL3* (Whittock et al. 2003), *MESP2* (Whittock et al. 2004), *LFNG*, or *HES7* gene mutations by sequencing entire coding region of fetal DNA obtained from amniocentesis or CVS, provided the disease-causing allele has been previously identified.
   4. Preimplantation genetic diagnosis may be available for families in which the disease-causing mutations have identified previously.

3. Management (Cornier et al. 2003)
   1. Minimize positive end-expiratory pressure to avoid bronchopulmonary dysplasia.
   2. Continuous feeding instead of in boluses to avoid stomach distension that will lead to increase diaphragmatic pressure.
   3. Aggressive treatment of infections.
   4. Treat the spinal deformities.
   5. Management of thoracic insufficiency syndrome in patients with Jarcho-Levin syndrome using VEPTRs (vertical expandable prosthetic titanium ribs): improves thoracic symmetry, control spinal deformity, and was associated with improved clinical respiratory function (Karlin et al. 2014).

References

Bannykh, S. I., Emery, S. C., Gerber, J. K., et al. (2003). Aberrant Pax1 and Pax9 expression in Jarcho-Levin syndrome: Report of two Caucasian siblings and literature review. *American Journal of Medical Genetics, 120A*, 241–246.

Basaran, A., Deren, Ő., & Őnderoglu, L. S. (2010). Prenatal diagnosis of Jarcho-Levin syndrome in combination with inguinoscrotal hernia. *American Journal of Perinatology, 27*, 189–192.

Bautista, D. B., Kahlstrom, E. J., & Gozal, D. (1997). Recurrence of spondylothoracic dysplasia (Jarcho-Levin syndrome) in a family. *Southern Medical Journal, 90*, 1234–1237.

Berdon, W. E., Lampl, B. S., Cornier, A. S., et al. (2011). Clinical and radiological distinction between spondylothoracic dysostosis (Lavy-Moseley syndrome) and spondylocostal dysostosis (Jarcho-Levin syndrome). *Pediatric Radiology, 41*, 384–388.

Bonafe, L., Giunta, C., Gassner, M., et al. (2003). A cluster of autosomal recessive spondylocostal dysostosis caused by three identified DLL3 mutations segregating in a small village. *Clinical Genetics, 64*, 28–35.

Bulman, M. P., Kusumi, K., Frayling, T. M., et al. (2000). Mutations in the human delta homologue, *DLL3*, cause axial skeletal defects in spondylocostal dysostosis. *Nature Genetics, 24*, 438–441.

Cornier, A. S., Ramirez, N., Carlo, S., et al. (2003). Controversies surrounding Jarcho-Levin syndrome. *Current Opinion in Pediatrics, 15*, 614–620.

Cornier, A. S., Ramirez, N., Arroyo, S., et al. (2004). Phenotype characterization and natural history of spondylothoracic dysplasia syndrome: A series of 27 new cases. *American Journal of Medical Genetics Part A, 128*, 120–126.

Cornier, A. S., Staehling-Hampton, K., Delventhal, K. M., et al. (2008). Mutations in the MESP2 cause spondylothoracic dysostosis/Jarcho-Levin syndrome. *American Journal of Human Genetics, 82*, 1334–1341.

Dunwoodie, S. L., Clements, M., Duncan, S., et al. (2002). Axial skeletal defects caused by mutation in the

spondylocostal dysplasia/pudgy gene DLL3 are associated with disruption of the segmentation clock within the presomitic mesoderm. *Development, 129*, 1795–1806.

Eliyahu, S., Weiner, E., Lahav, D., et al. (1997). Early sonographic diagnosis of Jarcho-Levin syndrome: A prospective screening program in one family. *Ultrasound in Obstetrics & Gynecology, 9*, 314–318.

Hayek, S., Burke, S. W., Boachie-Adjei, O., et al. (1999). Jarcho-Levin syndrome: Report on a long-term follow-up of an untreated patient. *Journal of Pediatric Orthopaedics. Part B, 8*, 150–153.

Herold, H. Z., Edlitz, M., & Baruchin, A. (1988). Spondylothoracic dysplasia. A report of ten cases with follow-up. *Spine, 13*, 478–481.

Hull, A. D., James, G., & Pretorius, D. H. (2001). Detection of Jarcho-Levin syndrome at 12 weeks' gestation by nuchal translucency screening and three-dimensional ultrasound. *Prenatal Diagnosis, 21*, 390–394.

Jarcho, S., & Levin, P. M. (1938). Hereditary malformation of the vertebral bodies. *Bulletin of the Johns Hopkins Hospital, 62*, 216–226.

Karlin, J. G., Roth, M. K., Patil, V., et al. (2014). Management of thoracic insufficiency syndrome in patients with Jarcho-Levin syndrome using VEPTRs (vertical expandable prosthetic titanium ribs). *Journal of Bone and Joint Surgery (American Volume), 96*, 1–8.

Karnes, P., Day, D., Berry, S., et al. (1991). Jarcho-Levin syndrome: Four new cases and classification of subtypes. *American Journal of Medical Genetics, 40*, 264–270.

Kauffmann, E., Roman, H., Barau, G., et al. (2003). Case report: A prenatal case of Jarcho-Levin syndrome diagnosed during the first trimester of pregnancy. *Prenatal Diagnosis, 23*, 163–165.

Lawson, M. E., Share, J., Benacerraf, B., et al. (1997). Jarcho-Levin syndrome: Prenatal diagnosis, perinatal care, and follow-up of siblings. *Journal of Perinatology, 17*, 407–409.

Marks, F., Hernanz-Schulman, M., Horii, S., et al. (1989). Spondylothoracic dysplasia. Clinical and sonographic diagnosis. *Journal of Ultrasound in Medicine, 8*, 1–5.

Martinez-Frias, M. L., & Urioste, M. (1994). Segmentation anomalies of the vertebras and ribs: A developmental field defect: Epidemiologic evidence. *American Journal of Medical Genetics*, *49*, 36–44.

Mooney, J. F., 3rd, & Emans, J. B. (1995). Progressive kyphosis and neurologic compromise complicating spondylothoracic dysplasia in infancy (Jarcho-Levin syndrome). *Spine, 20*, 1938–1942.

Mortier, G. R., Lachman, R. S., Maureen, B., et al. (1996). Multiple vertebral segmentation defects: Analysis of 26 new patients and review of the literature. *American Journal of Medical Genetics, 61*, 310–319.

Ranes, M., Carlan, S. J., Perez, J., et al. (2012). Three-dimensional computed tomography of fetal spondylothoracic dysostosis at 23 weeks' gestation. *Prenatal Diagnosis, 32*, 604–606.

Rimoin, D. L., Fletcher, B. D., & McKusick, V. A. (1968). Spondylocostal dysplasia. A dominantly inherited form of short-trunked dwarfism. *American Journal of Medicine, 45*, 948–953.

Roberts, A. P., Neurol, C. A., Tolmie, J. L., et al. (1988). Spondylothoracic and spondylocostal dysostosis. *Journal of Bone and Joint Surgery, 70-B*, 123–126.

Romeo, M. G., Distefano, G., Di Bella, D., et al. (1991). Familial Jarcho-Levin syndrome. *Clinical Genetics, 39*, 253–259.

Sparrow, D. B., Chapman, G., Wouters, M. A., et al. (2006). Mutation of the LUNATIC FRINGE gene in humans causes spondylocostal dysostosis with a severe vertebral phenotype. *American Journal of Human Genetics, 78*, 28–37.

Sparrow, D. B., Mcinerney-Leo, A., Gucev, Z. S., et al. (2013a). Autosomal dominant spondylocostal dysostosis is caused by mutation in *TBX6. Human Molecular Genetics, 22*, 1625–1631.

Sparrow, D. B., Faqeih, E. A., Sallout, B., et al. (2013b). Mutation of *HES7* in a large extended family with spondylocostal dysostosis and dextrocardia with situs inversus. *American Journal of Medical Genetics Part A, 161A*, 2244–2249.

Tolmie, J. L., Whittle, M. J., McNay, M. B., et al. (1987). Second trimester prenatal diagnosis of the Jarcho-Levin syndrome. *Prenatal Diagnosis, 7*, 129–134.

Turnpenny, P. D., Thwaites, R. J., Boulos, F. N., et al. (1991). Evidence for variable gene expression in a large inbred kindred with autosomal recessive spondylocostal dysostosis. *Journal of Medical Genetics, 28*, 27–33.

Turnpenny, P. D., Bulman, M. P., Frayling, T. M., et al. (1999). A gene for autosomal recessive spondylocostal dysostosis maps to 19q13.1-q13.3. *American Journal of Human Genetics, 65*, 175–182.

Turnpenny, P. D., Whittock, N., Duncan, J., et al. (2003). Novel mutations in *DLL3*, a somitogenesis gene encoding a ligand for the Notch signaling pathway, cause a consistent pattern of abnormal vertebral segmentation in spondylocostal dysostosis. *Journal of Medical Genetics, 40*, 333–339.

Turnpenny, P. D., & Young, E. (2013). Spondylocostal dysostosis, autosomal recessive. *GeneReviews*. Retrieved January 17, 2013. Available at: http://www.ncbi.nlm.nih.gov/books/NBK8828/

Whittock, N. V., Turnpenny, P. D., Tuerlings, J., et al. (2003). Molecular genetic prenatal diagnosis for a case of autosomal recessive spondylocostal dysostosis. *Prenatal Diagnosis, 23*, 575–579.

Whittock, N. V., Sparrow, D. B., Wouters, M. A., et al. (2004). Mutated MESP2 causes spondylocostal dysostosis in humans. *American Journal of Human Genetics, 74*, 1249–1254.

Wong, G., & Levine, D. (1998). Jarcho-Levin syndrome: Two consecutive pregnancies in a Puerto Rican couple. *Ultrasound in Obstetrics & Gynecology, 12*, 70–73.

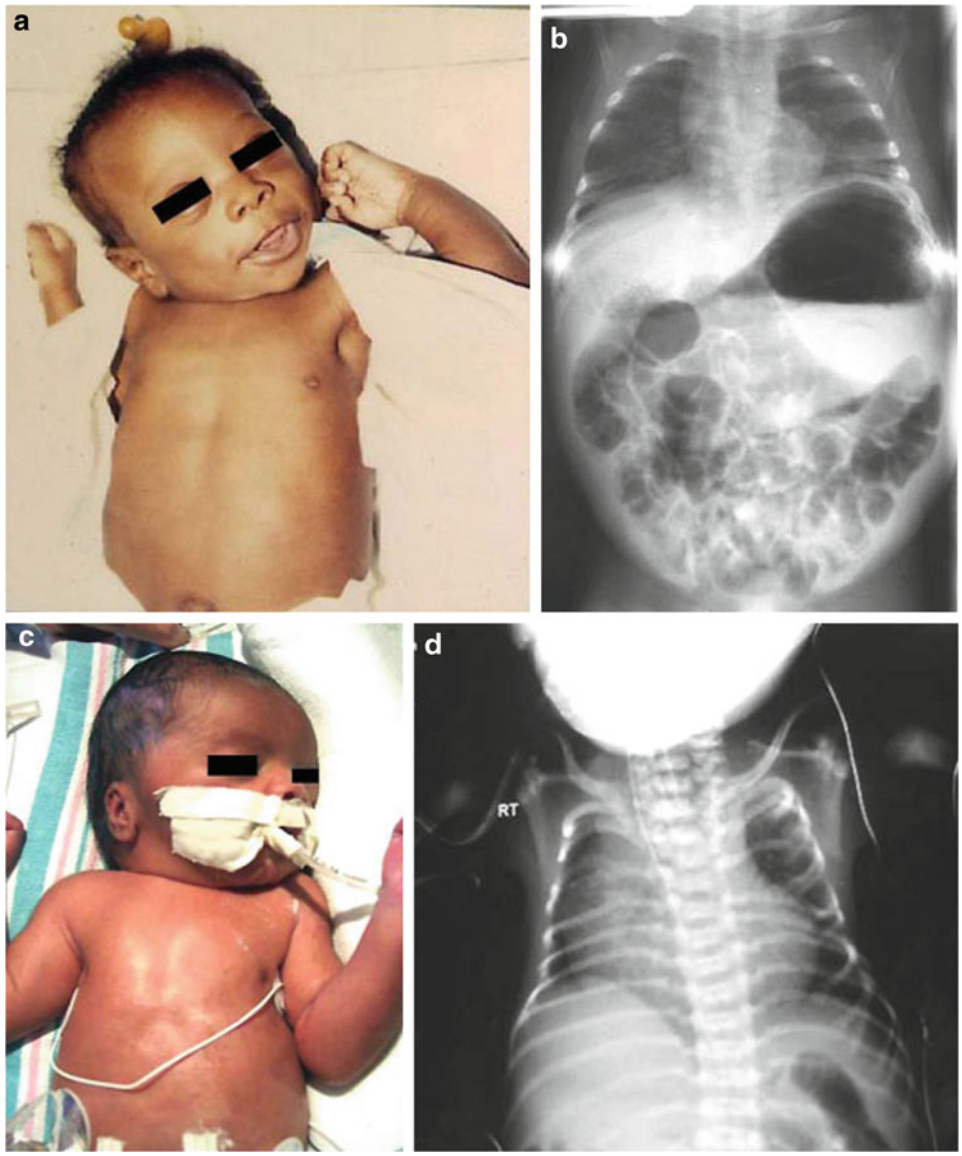

Fig. 1 (**a**–**d**) Two infants (**a**, **c**) with spondylocostal dysostosis with typical crablike deformities of the chest with fused ribs (radiographs) (**b**, **d**)

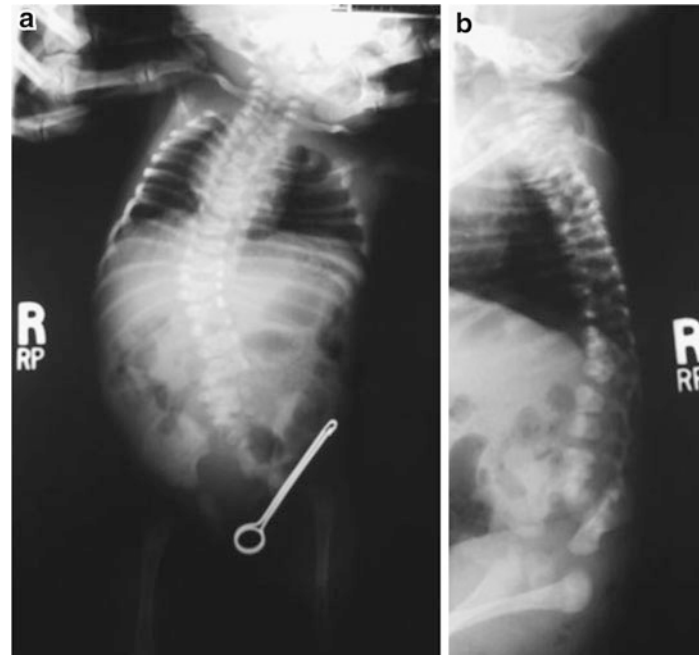

Fig. 2 (**a**, **b**) Radiographs of another infant with spondylocostal dysostosis showing fused ribs and fused vertebrae

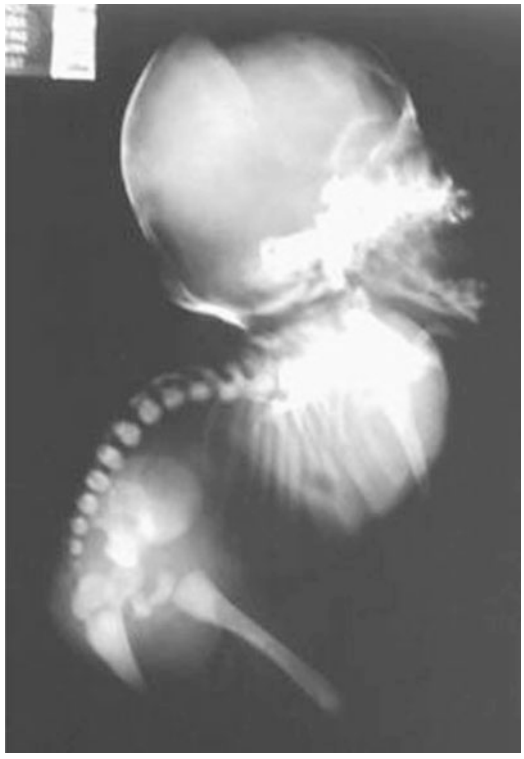

Fig. 3 Radiographs of another infant with spondylothoracic dysostosis showing severe chest deformity

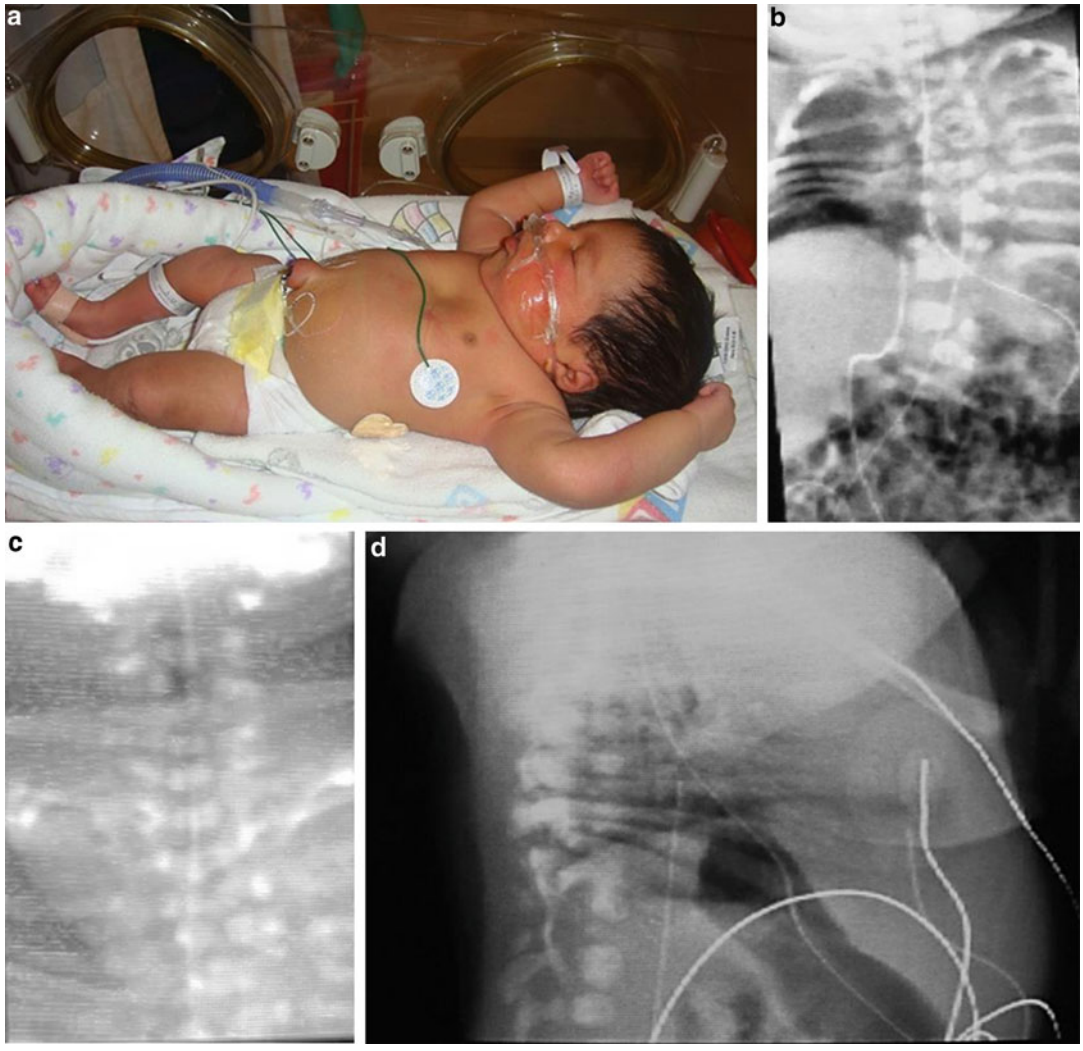

Fig. 4 (**a**–**d**) An Arabic female newborn (**a**) was evaluated for multiple vertebral and rib anomalies. Her prenatal ultrasound showed vertebral anomalies, hydramnios, and possible TE fistula. Postnatally, she was noted to have short neck, short chest, and protuberant abdomen. The postnatal radiographs (**b**–**d**) showed vertebral segmentation and formation defects throughout cervical, thoracic, and lumbar spine. Fusion of the ribs was present. Clinical diagnosis of Jarcho-Levin syndrome was made. The parents are first cousins. Molecular genetic diagnosis showed positive *DLL3* mutation. This patient is apparently homozygous in the *DLL3* gene for a frameshift mutation defined as c.329delT which is predicted to result in premature protein termination (p.Val110GlyfsStope22). This particular mutation has not been reported previously. However, it is the type expected to be pathogenic (e.g., Turnpenny et al. 2003). The homozygous c.329delT mutation is very likely the cause of recessive spondylocostal dysostosis

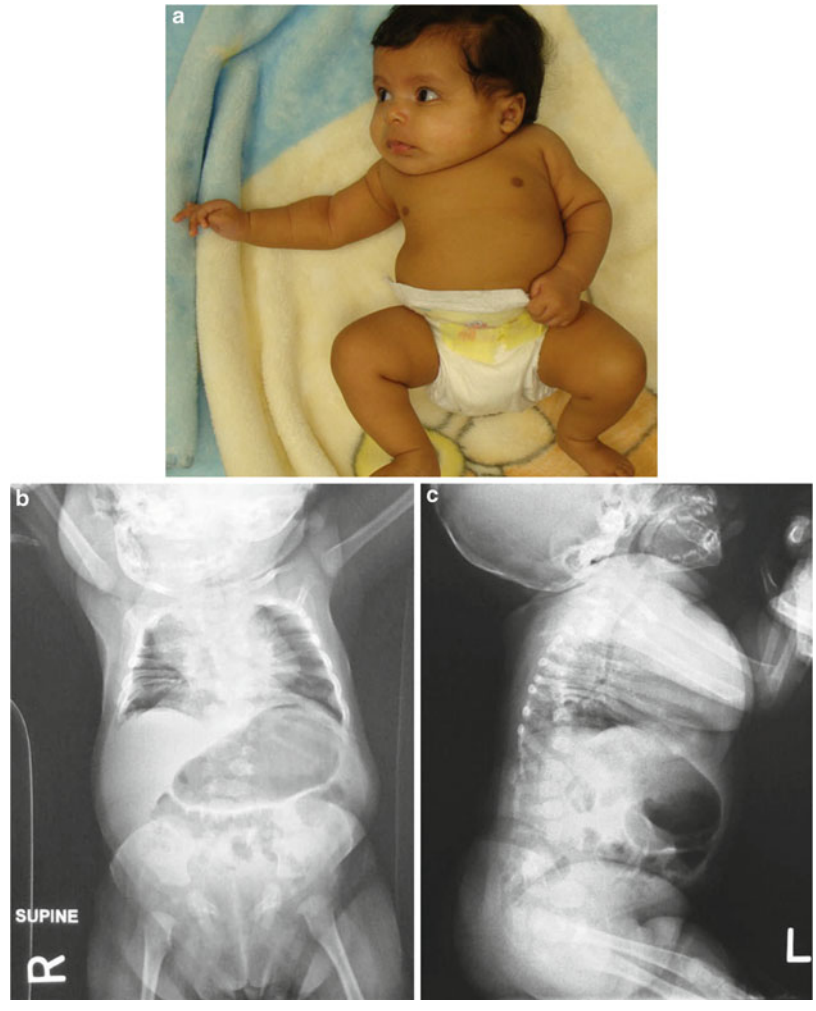

Fig. 5 (**a**–**c**) The previous infant (**a**) at 3 months of age with follow-up X-rays (**b**, **c**)