# A child with Jarcho-levin syndrome

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In 1938, Jarcho and Levin[1] first described a syndrome of congenital abnormalities affecting the spine and the thorax. The syndrome described a spectrum of radiological and skeletal anomalies including abnormal vertebral segmentation or formation defects, rib deformities and short trunk dwarfism. In 1978, Solomon et al[2] subdivided patients with the above features into 2 distinct phenotypes: spondylothoracic and spondylocostal dysostosis. The patients in the former phenotype had bilateral fusion of the ribs at the costal vertebral joints, segmentation and formation vertebral defects throughout the spine without intrinsic rib anomalies. The patients in the other phenotype were characterized by intrinsic rib anomalies such as broadening, bifurcation, and fusion but no symmetric fusion of the ribs. In 1996, Mortier et al[3] analysed 141 cases of short trunk dwarfism and further classified the syndrome into three distinct clinical presentations: Jarcho-levin as the lethal autosomal recessive form with a symmetric crab-like chest; spondylothoracic dysostosis for the autosomal recessive usually less severe phenotype; and spondylocostal dysostosis for the autosomal dominant or recessive condition with intrinsic rib anomalies, usually without severe thoracic impairment and better prognosis.

Jarcho-levin syndrome had high prevalence among Puerto Ricans population and was relatively rare in other parts of the world. The mortality rate within 6 months of life was up to 44%. Cause of death was respiratory insufficiency secondary to pneumonia and pulmonary restriction.[4] Autopsy finding of a newborn with the syndrome revealed pulmonary hypoplasia.[5] The longest survival had been up to 33 to 47 years.[4,6]

In this report, we described an infant from a non-consanguineous Chinese family with the syndrome.

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The child had very borderline respiratory status since birth, and has multiple episodes of chest infection necessitating invasive ventilator support. Tracheostomy was performed to ease the clearance of secretion and sputum, and to decrease the airway resistance. However, the vertebral and rib cage anomalies continued to impair the lung growth and the normal respiration. Finally the child underwent the surgery of expansion thoracoplasty with implantation of Vertebral Expandable Prosthetic Titanium Rib (VEPTR) in view of the thoracic insufficiency syndrome.

## Report of case

HM was the first child of a non-consanguineous Cantonese family. He was born full term by spontaneous vaginal delivery. Apgar score was normal. Birth weight was 2,385 gram. Antenatal history was un-remarkable and there was no family history of inherited skeletal dwarfism. HM was noticed to have short neck / trunk and abdominal distension. He developed respiratory distress soon after birth and was transferred to our Special Care Baby Unit for further management. CPAP was initiated with clinical improvement. Pre- and post-ductal $SaO_2$ discrepancy was noticed suggestive of transient pulmonary hypertension. HM's appearance was striking in that his neck was short and immobile and the trunk was markedly shortened. There was a prominent thoraco-lumbar lordosis and the abdomen was protuberant. The extremities were long and thin with normal limb lengths. The vertex-to-heel length was 42 cm (<3%). Head circumference was 32 cm (<3%). He was also noticed to have bilateral un-descended testes.

Plain radiographs showing the chest, abdomen and long bones of patients (Figures 1a & 1b) showed small thorax, distended abdomen and normal bone density.

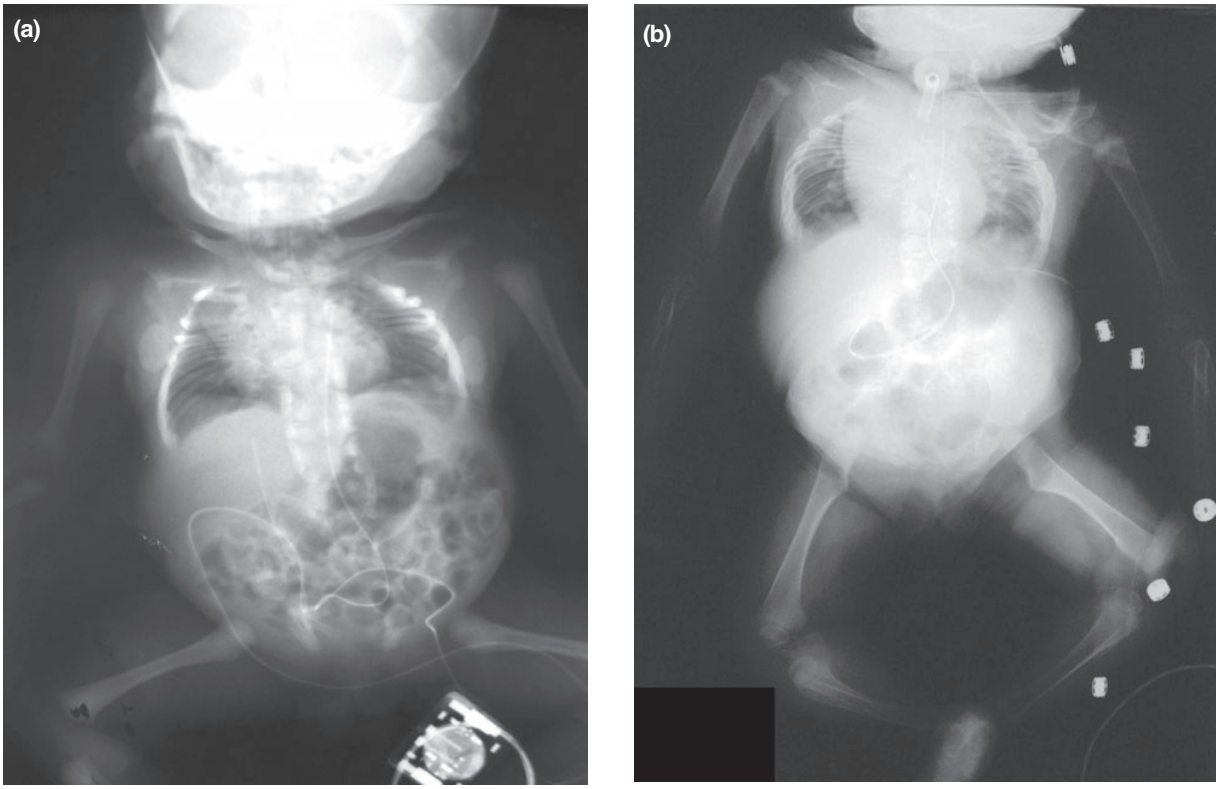


**Figure 1.** (a) CXR and AXR of HM soon after birth. He was receiving oxygen supply from the nasal cannula and he also had umbilical arterial and venous catheter inserted. His thoracic cage is very small with bilateral crowding of ribs giving a crab-like appearance. Butterfly and hemivertebrae are also observed. There is no scoliosis. (b) No structural abnormalities seen in the long bones.

Skull shape and craniofacial proportion appeared normal. Multiple hemi-vertebrae and fusion between some of the hemi-vertebrae were noted along the thoracic and lumbar spine, suggestive of generalized segmentation and formation anomalies of the vertebral column. The coronal diameter of the vertebrae was also widened. Diminished thoracic cavity as a result of abnormal rib cage was observed. Relatively symmetrical crowding of the ribs with possible costo-vertebral fusion resulting in crab-like appearance was noted. Abdomen appeared slightly protuberant in contour. No hepatosplenomegaly was seen and the bowel shadows appeared normal. The long bones of upper and lower limbs appeared not shortened and there was no focal bony abnormality noted along the long bones. 3D resconstructed CT thorax at 13 months (Figures 2a & 2b) showed a small thoracic cavity. Multiple segmentation and formation defects through the cervical, thoracic, and lumbar spine were noted. There was also bilateral symmetric fusion of the ribs at the costo-vertebral junction. The radiological features were compatible with Jarcho-levin syndrome of the phenotype of spondylothoracic dysostosis.

HM was able to take off the CPAP by day 3. However, he developed recurrent chest infection requiring back to CPAP repeatedly. There were also multiple episodes of deterioration with lung atelectasis and pneumonia requiring repeated intubation and ventilator support. Problems were encountered in weaning off HM from ventilator support despite very low ventilator settings and vigorous adjunctive therapy including chest physiotherapy and aggressive antibiotics treatment of pneumonia. Finally HM underwent tracheostomy at 6.5 months of age. Support was weaned down to CPAP soon after the operation. He was able to wean down to tracheostomy mask at 11 months of age.

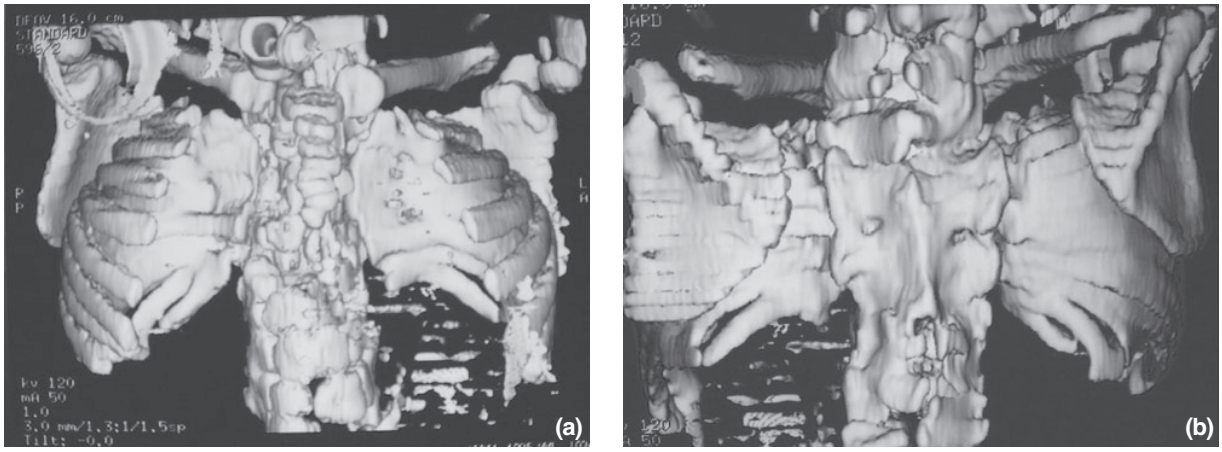


**Figure 2.** (a) 3D reconstructed CT thorax, anterior view showing small thoracic cage with crab-like appearance. (b) 3D reconstructed CT, posterior view showing symmetrical fusion of the posterior ribs at the costovertebral junctions. No scoliosis was detected.

Karyotype of peripheral blood leukocyte revealed normal number and morphology of chromosomes with an XY pattern. Delta-like 3 (DLL3) gene was negative.

Pulmonary assessment at 24 months of age showed that his body weight and height were markedly below 3rd percentiles. The respiration was mainly abdominal breathing with very little chest movement. Respiratory rate was 45 to 60 per minute. Daytime $SaO_2$ was around 93% and he needed nocturnal oxygen supplement and BiPAP. Venous blood gas did not revealed any $CO_2$ retention. Computed tomography of the thorax showed that the lung volume was 197 ml, which was even less than the functional residual capacity of children with similar height. The clinical situation was compatible with thoracic insufficiency syndrome, which was defined as inability of the thorax to support normal respiration and lung growth. In Jarcho-levin syndrome, the fused ribs and shortening of the thoracic spines were factors contributing in the development of this problem. In order to lengthen the foreshortening rib cage and allow the unrestricted growth of thoracic spine to address the problem of primary thoracic insufficiency, expansion thoracoplasty with implantation of VEPTR were subsequently performed on both sides in 38 months and 59 months of ages (Figure 3). HM was doing well after the operations and was able to wean off the oxygen during daytime after the 1st operation. Repeated computed tomography of the thorax showed much improved lung volume of 335 ml after the 2nd operation.

## Discussion

Jarcho-levin syndrome is a heterogeneous group of inherited skeletal disease with variable inheritance and prognosis, which were characterized by short-trunk dwarfism with associated rib and vertebral anomalies.

Two distinct clinical and radiological patterns are recognized.[7] In spondylothoracic dysostosis, patients have vertebral segmentation and formation defects throughout the spine, including hemivertebrae, blocked vertebrae and unsegmented bars. These are associated with bilateral posterior fusion of ribs at the costovertebral joints, but not intrinsic rib anomalies. They display a fan-like configuration of the thorax radiologically. The vertebral defects and the rib fusion contribute to the poor ventilatory function and predispose the patients to recurrent pneumonia, congestive heart failure and pulmonary hypertension. In spondylocostal dysostosis, patients generally have milder phenotype. The vertebral segmentation and formation defects are variable. They do not have symmetric posterior fusion of the ribs. Intrinsic and asymmetric rib anomalies are present including

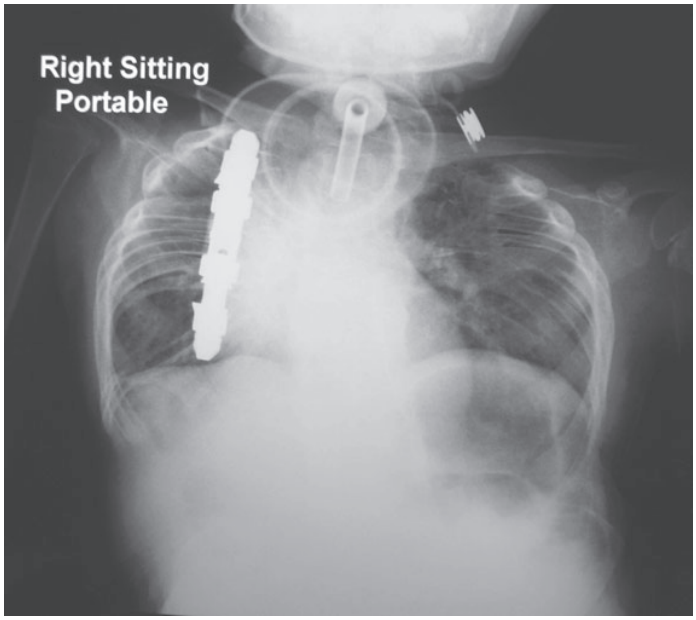


**Figure 3.** CXR taken at 3-year-old. Vertical expandable prosthetic titanium rib was inserted onto the right side of the thoracic cage. Note that there is increase distance between the right second and third, and the ninth and tenth ribs.

broadening, bifurcation and fusion. The patients have less restrictive thorax due to asymmetry of thoracic anomalies and hence better prognosis. Both are them are of normal intelligence. Associated anomalies are common with both phenotypes, including undescended testes, hydronephrosis, hernia (inguinal, umbilical and diaphragmatic), patent foramen ovale, renal anomalies, impeforate anus, high arch palate and cleft palate.

Radiologically, both phenotypes show a decreased in number of cervical, thoracic and lumbar vertebrae and there are multiple vertebral segmentation and formation defects along the entire spine such as block and wedge vertebrae, unsegmented bars, hemivertebrae and anterior-posterior-lateral failure of closure. In spondylothoracic dysostosis, patients show bilateral fanning of ribs with posterior fusion, giving the appearance of a common origin of ribs at the posterior thoracic spine. In spondylocostal dysostosis, patients may have agenesis of the coccygeal region. They may develop progressive scoliosis of the thoracic spine due to the tethering effect of secondary to the rib fusion (Table 1).

3D reconstructed CT thorax shows variable segmentation and formation defects in all the cervical, thoracic and lumbar vertebrae. Thoracic and lumbar vertebral shape present an increase of at least twice in the coronal diameter compared with the sagittal diameter. These abnormalities give the vertebrae a sickle shape appearance. In patients with spondylothoracic dysostosis, computed tomography

**Table 1.** Typical radiological features to differentiate spondylothoracic and spondylocostal dysostosis

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| **Sponylothoracic dysostosis** |
| • Vertebral segmentation and formation defects |
| – Hemivertebrae |
| – Block vertebrae |
| – Unsegmentation |
| • Sacrococcygeal region spared |
| • Fusion of all ribs at costovertebral joints bilaterally |
| – Resulted in crablike thoracic cage |
| – No intrinsic structural abnormality in the ribs |
| **Spondylocostal dysostosis** |
| • Vertebral segmentation and formation defects |
| • Agenesis of coccygeal region |
| • Intrinsic asymmetric rib anomalies |
| –Broadening |
| –Bifid |
| –Fusion |
| • Asymmetric fusion resulted in scoliosis |

show bilateral rib fusion at the costovertebral junction. The extent of fusion ranged from 30% to 60% of the thorax circumference. In patients with spondylocostal dysostosis, computed tomography may show sacrococcygeal abnormalities.

In our patient, he was probably having the spondylothoraic dysostosis because of the presence of costochrondral fusion resulting in crab-like appearance of the ribs and without any intrinsic rib anomalies.

For the genetic etiology of these syndromes, spondylocostal dysostosis arise during embryonic development by a disruption of somatogenesis. A few genes have been implicated in the causation of the disorders: Delta-like 3 (Dll3) gene (chromosome 19q13.1-q13.3); Mesoderm posterior-2 (MESP2) gene (chromosome 15q21.3-q26.1) and Lunatic Fringe Gene (LFNG). These genes are all important components of the Notch signaling pathway, which has multiple roles in development and diseases. The Notch signaling pathway[8] is an evolutionarily conserved, intercellular signaling mechanism essential for proper embryonic development in all metazoan organisms in the animal kingdom. Perturbations in the Notch signaling pathway contribute to the pathogenesis of spondylocostal dysostosis. Dll3[9] encodes a ligand for the Notch receptor and, when mutated, defective somitogenesis occurs resulting in a consistent and distinctive pattern of abnormal vertebral segmentation affecting the entire spine. MESP2[10] encodes for a basic helix-loop-helix transcription factor which has a key role in establishing rostrocaudal polarity by participating in distinct Notch-signaling pathways. LFNG[11] encodes a glycosyltransferase that modifies the Notch family of cell-surface receptors, a key step in the regulation of this signaling pathway. For spondylothoracic dysostosis, genetic linkage has been established to chromosome 2q32.1, no mutations in Dll3 gene has been found.[12]

In our patient, the borderline respiratory function of the child was reflected by the need of tracheostomy in the early neonatal period and poor somatic and lung growth at 24 months of age. He was diagnosed to have the thoracic insufficiency syndrome. Thoracic insufficiency syndrome[13] is the inability of the thorax to support normal respiration or lung growth. The normal thorax is defined by two characteristics, namely, normal, stable volume and the ability to change that volume. The volume depends on the width and depth of the rib cage while the thoracic spine provides the height. The ability to change volume, termed thoracic function, is provided by the diaphragm and the secondary muscles of respiration. Clinical indicators suggestive of thoracic insufficiency syndrome include abnormal respiratory examination with decreased chest excursion, oxygen dependency, need for ventilator support, failure to gain weight and pulmonary functions studies roughly below the 50th percentile. In Jarcho-levin syndrome, there are vertebral segmentation and formation defects throughout the spine, as well fusion of ribs at costovertebral joint bilaterally and intrinsic rib anomalies with the consequences of global foreshortening of the thorax as well as restrictive lung expansion. The features of our patient that were compatible with the thoracic insufficiency syndrome would include: 1) little chest movement on breathing; 2) tachypnoea at rest with borderline oxygen saturation on daytime requiring oxygen supplement during night time; 3) restrictive lung volume as demonstrated by CT thorax.

VEPTR is a form of expansion thoracoplasty, which is a surgical procedure to expand the 3 dimensional volume of a constricted hemi-thorax.[14] The goal of the treatment is to promote the growth and function of immature lung. The operation addresses thoracic insufficiency syndrome by lengthening and expanding the constricted hemithorax and allowing growth of the thoracic spine and the rib cage.

In summary, we discussed a case with Jarcho-levin syndrome of the phenotype of spondylothoracic dysostosis with thoracic insufficiency syndrome. The child was successfully managed by tracheostomy and subsequently Vertical Expandable Prosthetic Titanium Rib which improve his lung growth and thoracic function.

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