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Mini-symposium: Chest Wall Disease

Chest Wall Hypoplasia - Principles and Treatment

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EDUCATIONAL AIMS

- Understand the significance of chest wall and spine growth on lung growth and respiration.
- Understand how abnormal spine growth can cause chest wall hypoplasia and the treatment options available.
- Understand how abnormal lateral chest wall growth can impact lung development and the options for therapy.

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SUMMARY

The chest is a dynamic structure. For normal movement it relies on a coordinated movement of the multiple bones, joints and muscles of the respiratory system. While muscle weakness can have clear impact on respiration by decreasing respiratory motion, so can conditions that cause chest wall hypoplasia and produce an immobile chest wall. These conditions, such as Jarcho-Levin and Jeune syndrome, present significantly different challenges than those faced with early onset scoliosis in which chest wall mechanics and thoracic volume may be much closer to normal. Because of this difference more aggressive approaches to clinical and surgical management are necessary.

INTRODUCTION

The ribs of the chest wall and the spine provide the skeletal structure from which respiration occurs. The thoracospinal unit is very dynamic with three-dimensional movement of the chest cephalad, anteriorly and laterally. This occurs in a complex interaction between the diaphragm contraction increasing the circumference of the lower rib cage and rotation at the costo-vertebral joints increasing the circumference of the upper rib cage in the transverse plane and elevating the rib cage. Additionally, contraction of the accessory muscles of the neck and anterior chest will further elevate the rib cage.

The bones of the thoracospinal unit should grow symmetrically with the rest of the body to support development and growth of the lungs to continue to meet the increasing metabolic demands. In normal circumstances this growth occurs symmetrically at over 130 separate growth plates in the spine and chest wall [1]. However, abnormal or asymmetric growth in even a small number these can cause non-syndromic early onset scoliosis (EOS) [1].

Compounding this issue of growth, however, is the actual formation of the spine and ribs and the complex signaling that directs the differentiation of the mesenchyme [2]. When this process does not occur properly there can be a variety of different formation or segmentation problems that can produce absent or incompletely formed or fused ribs [2]. When these defects are unilateral and localized to a relatively small portion of the chest wall and/or spine EOS is often produced, but when these defects are broader and effect a large portion if not all of the chest wall or spine chest wall hypoplasia can occur.

Many of these defects were described years ago and carry the name(s) of the clinicians who first defined the condition, e.g. Jeune, Jarcho-Levin, and Ellis-van Creveld syndrome. However, as the field of genetics has progressed the majority of these conditions have identified genes that help explain the onset of the condition itself and more broadly a better understanding of the formation of the spine and chest wall (Table 1).

These various conditions can be grouped genetically based on gene location, protein product, and inheritance [2]. The phenotype can be classified within the broader rubric of thoracic insufficiency

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Table 1
A description of the variety of different conditions causing chest wall hypoplasia including both primary rib and spine disease [1].

Category	Disorder	Major findings	Thoracic involvement	Respiratory complications	Inheritance pattern	Gene	Mutation
Dominant negative action	Osteogenesis imperfecta	Multiple fractures; joint laxity; blue sclera; dentinogenesis imperfecta	Rib fractures	Pulmonary hypoplasia in severe forms; unstable thorax after multiple rib fracture	Autosomal dominant	*COL1A1* or *COL1A2* (procollagen molecules)	Multiple
Dominant negative action	Marfan syndrome	Dolichostenomelia arachnodactyly; joint laxity; aortic dilatation	Scoliosis, kyphosis and pectus excavatum or carinatum	Rarely respiratory distress due to abnormal thorax	Autosomal dominant	*FBN1* (Fibrillin 1)	Multiple
Loss of function	Marfan syndrome 2 [1]	Dolichostenomelia arachnodactyly; joint laxity; aortic dilatation	Scoliosis, kyphosis and pectus excavatum or carinatum	Rarely respiratory distress due to abnormal thorax	Autosomal dominant	TGFBR2 (TGF-beta receptor 2)	Multiple
Loss of function	Loeys-Dietz syndrome [2]	joint laxity; aortic dilatation; hypertelorism; bifid uvula; micrognathia; patent ductus arteriosus; arachnodactyly;	Scoliosis, pectus excavatum or carinatum	Rarely respiratory distress due to abnormal thorax	Autosomal dominant	TGFBR1 or TGFBR 2 (TGF-beta receptor1, 2)	Multiple
Dominant negative action	Beals syndrome	Dolichostenomelia; camptodactyly; arachnodactyly; crumpled ears	Kyphoscoliosis	Rare	Autosomal dominant	*FBN2* (Fibrillin 2)	Multiple
Gain of function	Achondro-plasia	Rhizomelic dwarfism; macrocephaly	Small rib cage; kyphosis	May occur in infancy; upper airway obstruction possible	Autosomal dominant	*FGFR3* (Fibroblast growth factor receptor 3)	Gly380Arg
Gain of function	Thanatophoric dysplasia	Short limbs, lethal dwarfism	Narrow thorax due to shortened ribs; flat vertebral bodies	Lethal shortly after birth, often due to respiratory insufficiency	*Sporadic cases due to new mutation*	*FGFR3*	Arg248Cys; Lys650Glu; others
Haploinsufficiency	Campomelic Dysplasia	Bowing of long bones; male to female sex reversal; micrognathia	Small thoracic cage with slender ribs or decreased number of ribs. Kyphoscoliosis	Respiratory insufficiency may cause death in early infancy; failure to thrive in survivors.	Autosomal dominant	*SOX9* (transcription factor)	Multiple
Haploinsufficiency	Cleidocranial Dysplasia	Wide anterior fontanel with delayed closure; excess teeth; mild short stature	Partially or completely absent clavicle; narrow chest	Rare	Autosomal dominant	*CBFA1* (transcription factor)	Multiple
Loss of function	Ellis-van Creveld syndrome (Chondro-ectodermal dysplasia)	Short distal extremities; polydactyly; nail hypoplasia; cardiac defects	Small thoracic cage with short ribs	Respiratory distress may occur due to the small thorax or the cardiac defect	Autosomal recessive	*EVC*	Multiple
Loss of function	Hypophosphatasia (neonatal form)	Undermineralized, hypoplastic and fragile bones; rachitic rosary; hypercalcemia	Short ribs and small thoracic cage	Death due to respiratory insufficiency in neonatal period common	Autosomal recessive	*ALPL* (Alkaline phosphatase)	Multiple
Loss of function	Jarcho-Levin syndrome (Spondylothoracic dysplasia; Spondylocostal dysostosis)	Short neck; long digits with camptodactyly	Short thorax with multiple vertebral defects and abnormal ribs	Respiratory distress due to small thoracic volume causes death in infancy	Autosomal recessive; most cases of Puerto Rican ancestry	DLL3 (delta-like 3)	multiple
Unknown	Jeune syndrome (Asphyxiating thoracic dystrophy)	Short limbs; polydactyly; cystic renal lesions or chronic nephritis	Small, bell-shaped rib cage; hypoplastic lungs	Usually fatal neonatal asphyxia	Autosomal recessive	unknown	unknown
Unknown	Cerebro-Costo-Mandibular syndrome	Severe micrognathia; prenatal growth deficiency	Small, bell-shaped thorax; gaps between posterior ossified and anterior cartilagineous ribs	Respiratory insufficiency may cause neonatal death	Possibly autosomal recessive or autosomal dominant	Unknown	Unknown

Citations:
1. Mizuguchi, T., et al., *Heterozygous TGFBR2 mutations in Marfan syndrome.* Nat Genet, 2004. **36**(8): p. 855-60.
2. Loeys, B.L., et al., *A syndrome of altered cardiovascular, craniofacial, neurocognitive and skeletal development caused by mutations in TGFBR1 or TGFBR2.* Nat Genet, 2005. **37**(3): p. 275-81.

syndrome (TIS), which is the inability of the thorax to support normal growth and respiration [3]. Campbell described subcategories or volume depletion deformities, with types 1 and 2 representing asymmetric deformity from absent ribs or fused ribs, respectively, and type 3 being due to symmetric deformity in vertical thoracic and spine growth (type 3a) or in lateral chest wall growth (type 3b) [3].

The remainder of this manuscript will be a discussion on specific representative examples of volume depletion deformity type 3a, Jarcho-Levin syndrome, and type 3b, Jeune syndrome, the clinical presentation, progression, and options for medical and surgical intervention.

JARCHO-LEVIN SYNDROME

Jarcho and Levin originally described the syndrome that now bears their name in 1938 while at Johns Hopkins Hospital [4]. The two patients they described both had a shortened trunk, reduced number of vertebrae, with vertebral segmentation and formation defects and asymmetric rib malformation [4]. Over the next 60 years a variety of different phenotypic presentations were identified that were originally all under the broad category of Jarcho-Levin syndrome [5], but were recognized in having similarities in having a malformed shortened spine, but differed significantly in other ways [5–9].

Two separate diagnoses have been defined: spondylocostal dysostosis (SCD) (Figure 1a) and spondylothoracic dysplasia (STD) (Figure 2a) and while they share some features, such as multiple vertebral segmentation and formation defects and rib anomalies, there are many radiographic features that distinguish the two [10]. Furthermore, they each have been linked to two completely different genes [5,9], and not surprisingly are concentrated in two different ethnic groups [10].

Spondylocostal dysostosis is most similar to the original condition that was described by Jarcho and Levin [5]. It is an autosomal dominant condition affecting about 1 in 40,000 live births [10] and has been linked to a gene on Chromosome 19q13 that has been identified as Delta-like 3 (DLL3) protein, which is involved in signaling the epithelial-mesenchymal transition during spine formation [5]. SCD is always asymmetric and as such often causes progressive scoliosis [5,10] in as many as 75% of patients [3]. The rib anomalies can range from rib absence to rib fusion and the spine abnormalities include hemivertebrae, block vertebrae, and fusion [10]. The overall prognosis is substantially better than STD, and chest wall reconstruction surgery is widely felt to be an appropriate option [3,5,10,11].

Spondylothoracic dysplasia is an autosomal recessive condition with a linkage to the MESP2 gene on chromosome 2q32.1 that appears to impact the same spinal development pathway that the DLL3 gene [10]. The incidence is unknown. STD is a bilateral process and as such coincident scoliosis is exceptionally rare, unlike in SCD [5]. In addition to substantial spinal segmentation and formation defects such as hemivertebra, block vertebra, and unsegmented bars, there can be substantial rib fusion that starts from the spine and extends radially to take up as much as 60% of the rib cage circumference in extreme cases [5]. The ribs typically radiate superiorly and inferiorly from a short rib mass in an orientation has been described as being fan- or crab-like [5,12]. This causes a major growth asymmetry between the spine and posterior portion of the rib cage and the anterior rib cage that causes a lordotic posture with a protuberant anterior chest and abdomen. While the abdomen is "protruberant" there is no organomegaly and it is entirely from the anatomic distortion from the abdomen due to the spondylothoracic deformity [5].

The prognosis has been poor for patients with STD and historically the mortality has been between 80 and 100% [3]. In a Puerto Rican cohort of 27 with longitudinal data the mortality rate was shown to be much lower at 45% [13]. Interestingly there was no difference in the chest circumference relative to normal for the survivors compared to those who died [13]. 28% survived into adulthood and were able to work and exercise without major pulmonary problems [13].

Surgical Approach

In SCD proactive surgical intervention early in life to treat the progressive restrictive respiratory disease requires a growth preserving surgical procedure. The Vertical Expandable Prosthetic Titanium Rib (VEPTR) has been shown to be quite effective (Figures 1a & b) [3,11,14]. The approach depends on the specific defect and usually involves a rib to spine VEPTR between T2-3 and L1-2 and a more lateral VEPTR between T2-3 and T9-10 followed by 6 monthly lengthening(11). Ramirez, *et.al.* reviewed 2 year post-operative data on 20 patients and demonstrated a preservation of respiratory status in 14 and an improvement in 5, with a significant decline in respiratory rate in the entire group [14].

With STD the recommendation for surgery is not as universal as for SCD likely due to the substantial spine fusion that many patients with STD have. However, Campbell, *et.al.* demonstrated that they could restore spine growth in patients with past spine fusion using the VEPTR for distraction across the fused segment (Figure 2 a & b) [15]. The approach involves a V-shaped osteotomy through the rib mass and placing bilateral VEPTR devices between T2-3 and T9-11 [11] (Dr. Robert Campbell, personal communication). There are not enough published data on this approach to clearly demonstrate success or failure, though there is a manuscript in press (Dr. Robert Campbell, Personal Communication).

JEUNE SYNDROME

Jeune syndrome was first described in 1956 as asphyxiating thoracic dystrophy [16] and that descriptor is used interchangeably with Jeune syndrome. The incidence is between 1 in 100,000 and 130,000 live births [17]. The inheritance is autosomal recessive and the causal gene was localized to Chromosome 15q13 [18,19] and 3q24 [19], and has been identified as the IFT80 gene which produces an intraflagellar transport protein [18,19].

The majority of patients with Jeune syndrome develop chronic respiratory failure and without support will die within the first few years of life [17], most of whom have respiratory failure within the first year of life [19]. For those patients who survive through the first year of life, some will have renal dysfunction starting with a concentration defect and progressing to failure [17,19]. In addition occasional patients can have bile duct proliferation leading to portal fibrosis and cirrhosis [19].

The affected ribs are significantly shorter and have a smaller radius of curvature than normal and in some situations the thoracic and cranial circumferences can be very similar. After infancy, however, patients will have more rapid rib growth [19] and thoracic circumference will become larger than that of the cranium. similarly, the cardiothoracic ratio, from an AP radiograph, is elevated above the normal value of 0.50 in the majority of patients [19]. In some patients with there can be atlantoaxial instability [18], which can cause significant spinal compression if not recognized and managed early [3].

The primary presentation of Jeune syndrome is in the severely hypoplastic chest that can be oriented in a narrow cylindrical pattern (Figure 3a) or in a bell-shaped pattern with more prominent hypoplasia superiorly than inferiorly [18,19]. The end of the ribs have a typical broad, flared appearance [17], and the ribs are horizontal in infancy, as is normal, and they remain so with growth [19]. These two factors prevent and significant outward

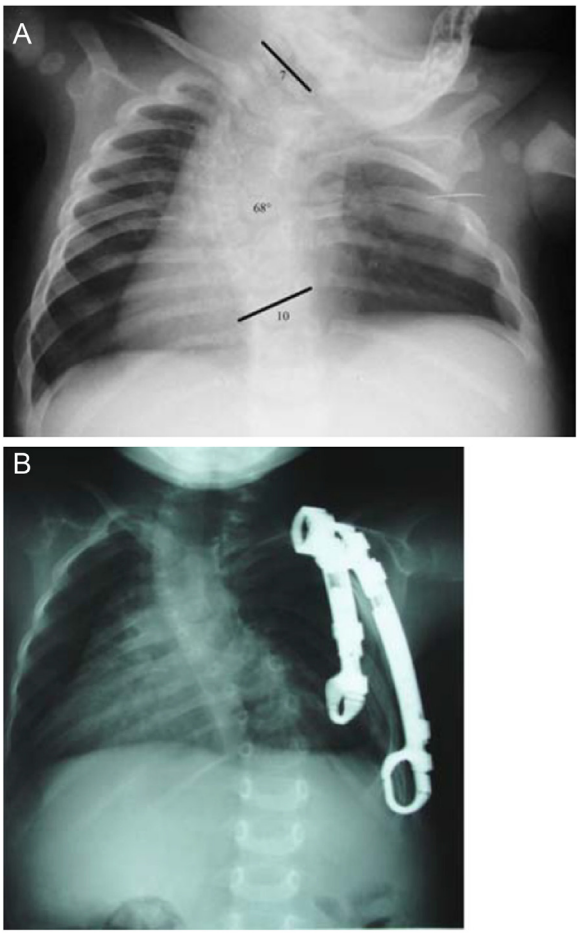

Figure 1. (a) 2 year old male with spondylocostal dysostosis pre-operatively; (b) 1 year post-VEPTR insertion [2].

chest wall motion and render the chest wall completely immobile. Therefore, the lungs are left to expand only inferiorly.

Surgical Approach

The approach to surgical management of Jeune syndrome has always started with the acknowledgement of these problems and has been focussed on the only viable option of making the thorax larger. The two general approaches have been sternal based and rib based.

The documented successful thoracic reconstruction was by Barnes, *et.al.* in which a 7 month old who was invasively ventilated had a sternotomy performed with 2.5 cm distraction and insertion of autologous rib grafts harvested using a subperiosteal resection, leaving the capacity for regrowth [20]. There were initial problems with the viability of the rib grafts requiring regrafting, and with lung herniation through the sternotomy for which Dacron patches were placed [20]. This approach was then simplified with the use of a 2.5 cm pre-formed acrylic sternal prosthesis that was placed in substantially less time [21]. Preformed tibial grafts have also been used [22].

A dynamic approach was developed using a modified pediatric sternal spreader that was externalized and the sternal cleft was expanded from 3 cm to 6 cm over a period of 8 months [23].

Davis, *et.al.* developed a lateral thoracic expansion in which a series of 3 pairs of adjacent offset rib osteotomies were performed, the periosteum was stripped and the long ends of each were fused with titanium plates to expand the thorax [24]. The short ends were left free with the periosteum put in place between the rib ends of the to allow for bone regrowth [25]. Within 12 months lung

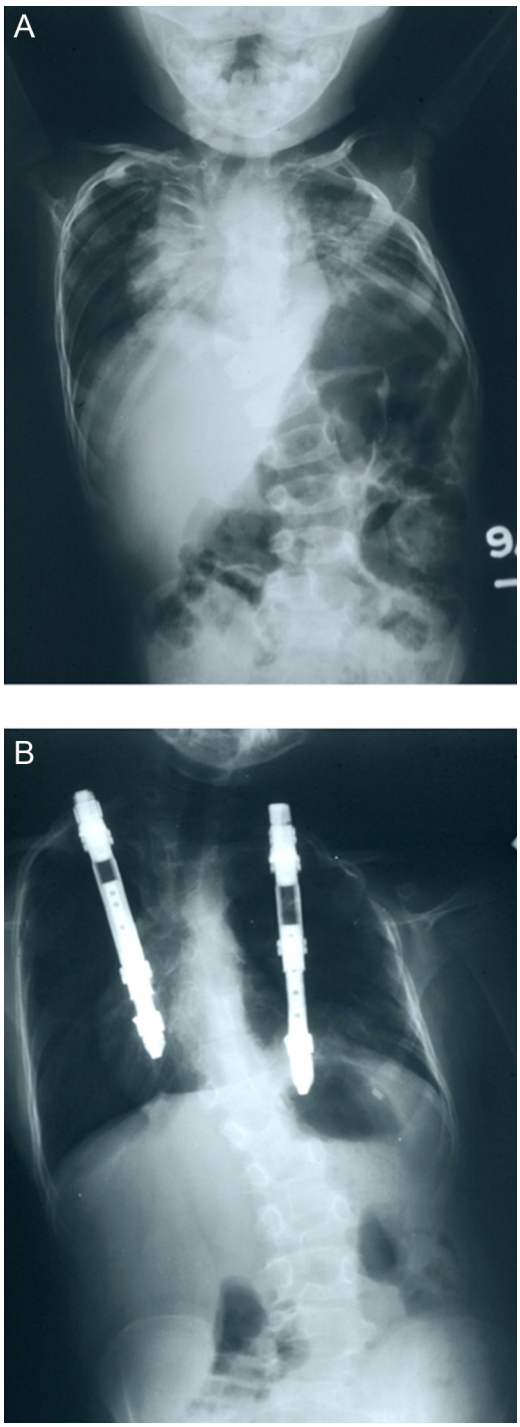

Figure 2. (a) 3 year old with spondylothoracic dysplasia pre-operatively; (b) 6 years post-VEPTR insertion [3].

volume by infant lung function testing and chest CT improves [26]. However, one limit of the procedure is that it can be performed only once and there are no data to demonstrate that the short term improvement is maintained.

Campbell, *et.al.* developed an alternate lateral rib cage approach in which a series of posterior osteotomies are performed to create a free block of 6-7 ribs that are then distracted laterally and kept in place with a VEPTR [3]. The periosteum was then stripped off and placed in the open area in between the rib ends and new rib eventually regrows to fill the defect [3]. The procedure is initially

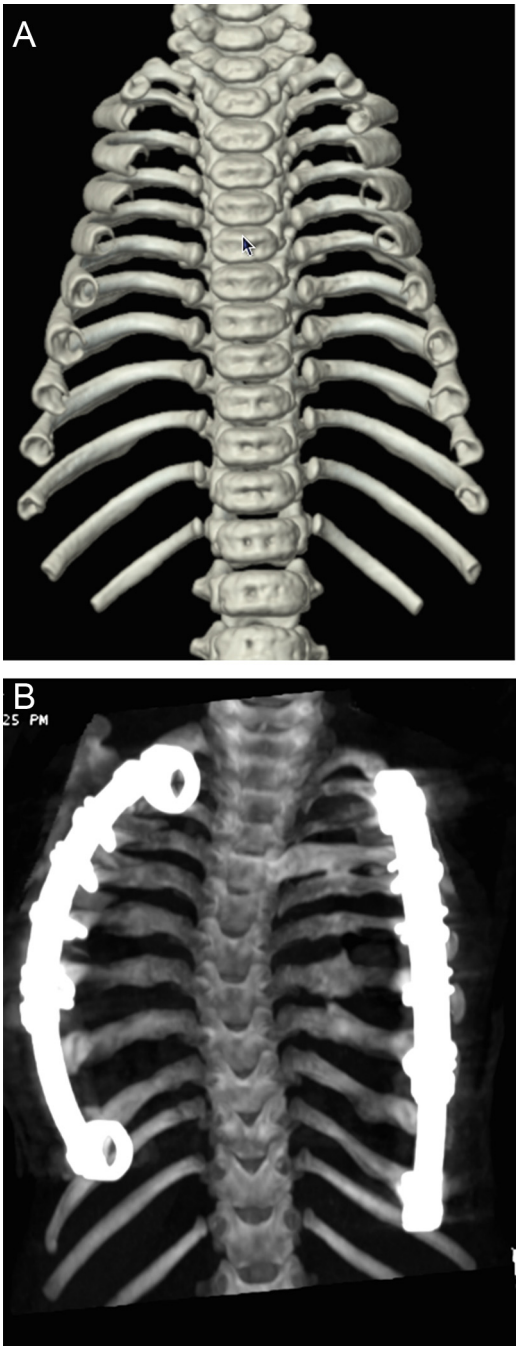

Figure 3. (a) 7 month old with Jeune Syndrome pre-operatively; (b) 18 months post-VEPTR insertion [2,14,27].

performed in the left chest and then 3 months later on the right chest, and from that point on the VEPTR devices are expanded every 4-6 months to maintain long term chest wall growth [3]. Long term outcome data are currently in press (Dr. Robert M Campbell, personal communication)

CONCLUSION

The development of the respiratory system over time is dependent on normal lung parenchymal development and growth in volume that is critically reliant on chest wall and spine growth. While the conditions described above are relatively uncommon, they present unique challenges that require approaches different than those used for more standard scoliosis

FUTURE DIRECTIONS AND CLINICAL RESEARCH

- Determine the optimal approach to addressing the chest wall hypoplasia and maximizing the growth potential of the lungs
- Identify the optimal time to intervene to minimize respiratory morbidity and maximize growth potential
- Better identify criteria for determining a successful repair both in respiratory and more broad quality of life outcomes.

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