One-stage sequential bilateral thoracic expansion for asphyxiating thoracic dystrophy (Jeune syndrome)

Nagarajan Muthialua,*, Shafi Mussa1, Catherine M. Owens1, Neil Bulstrodec and Martin J. Elliott1

a Department of Cardiothoracic Surgery, Great Ormond Street Hospital NHS Trust, London, UK
b Department of Radiology, Great Ormond Street Hospital NHS Trust, London, UK
c Department of Plastic and Reconstructive Surgery, Great Ormond Street Hospital NHS Trust, London, UK

* Corresponding author. Department of Cardiothoracic Surgery, Great Ormond Street Hospital, Great Ormond Street, London WC1N 3JH, UK.
Tel: +44-2074059200; fax: +44-2078298643; e-mail: prathnaga@gmail.com (N. Muthialu).

Received 27 August 2013; received in revised form 30 January 2014; accepted 3 February 2014

Abstract

OBJECTIVES: Jeune syndrome (asphyxiating thoracic dystrophy) is a rare disorder characterized by skeletal dysplasia, reduced diameter of the thoracic cage and extrathoracic organ involvement. Fatal, early respiratory insufficiency may occur. Two-stage lateral thoracic expansion has been reported, addressing each side sequentially over 3–12 months. While staged repair theoretically provides less invasive surgery in a small child with respiratory distress, we utilized a single stage, bilateral procedure aiming to rapidly maximize lung development. Combined bilateral surgery also offered the chance of rapid recovery, and reduced hospital stay. We present our early experience of this modification of existing surgical treatment for an extremely rare condition, thought to be generally fatal in early childhood.

METHODS: Nine children (6 males, 3 females; median age 30 months [3.5–75]) underwent thoracic expansion for Jeune syndrome in our centre. All patients required preoperative respiratory support (5 with tracheostomy, 8 requiring positive pressure ventilation regularly within each day/night cycle). Two children underwent sequential unilateral (2-month interval between stages) and 7 children bilateral thoracic expansion by means of staggered osteotomies of third to eighth ribs and plate fixation of fourth to fifth rib and sixth to seventh rib, leaving the remaining ribs floating.

RESULTS: There was no operative mortality. There were 2 deaths within 3 months of surgery, due to pulmonary hypertension (1 following two-stage and 1 following single-stage thoracic expansion). At the median follow-up of 11 months (1–15), 3 children have been discharged home from their referring unit and 2 have significantly reduced respiratory support. One child remains on non-invasive ventilation and another is still ventilated with a high oxygen requirement.

CONCLUSION: Jeune syndrome is a difficult condition to manage, but bilateral thoracic expansion offers an effective reduction in ventilator requirements in these children. While two-stage repair has been described previously, this is the first report of single-stage bilateral thoracic expansion. Single-stage repair is feasible and may offer better resource management and significant cost savings by potentially reducing theatre usage and overall length of stay (intensive care and hospital) without compromising clinical outcomes.

Keywords: Jeune syndrome • Chest expansion • Thoracic dystrophy

INTRODUCTION

Jeune syndrome, or asphyxiating thoracic dystrophy (ATD), is a rare genetic disorder transmitted as an autosomal recessive trait. It is characterized by an abnormal bone growth at the endochondrial level during foetal development [1]. Its clinical spectrum includes skeletal dysplasia, reduced diameter of the thoracic cage and extrathoracic organ involvement [1]. Though skeletal dysplasia is generalized, the natural history is often dictated by early respiratory insufficiency due to the restrictive chest cage. Ribs are classically horizontal and small, with dysplastic features affecting almost all ribs. This respiratory insufficiency may be fatal, and the child often succumbs to progressive respiratory failure before the age of 10. Treatment was purely palliative, until Davis et al. [2] reported a lateral thoracic expansion with promising early results. This procedure aimed to expand the chest cavity by staggered osteotomy of the ribs on each side, done in stages, and with consequent expansion of the chest volume. Once chest volume is expanded, the lungs have the opportunity to fill the enlarged chest cavity, resulting in transient amelioration of respiratory symptoms. However, these children are likely to need further surgeries of unknown frequency at unknown intervals further to increase chest cavity size as somatic growth proceeds. The ability of the lungs themselves to expand into the enlarged chest cavity, and to improve function (without alveolar distension or pulmonary hypertension), is difficult to determine before surgery. Thus, currently, surgical chest expansion is the only way we have to identify those patients whose lung function can be maximized to improve prognosis.

Davis’ method requires staged surgery (one side and weeks later, the other), increasing cost and delaying benefit to the second lung, if such benefit is achievable. We modified this staged approach to a combined single-stage expansion of both sides at the same sitting.
This aims to rapidly expand the chest cavity bilaterally both to maximize lung development and to potentially reduce hospital stay. We present our early experience of this modification.

**MATERIALS AND METHODS**

This is a retrospective review of the records of 9 children who had undergone surgery for ATD in our centre between July 2010 and March 2013. Institutional ethical committee approval was obtained before commencement of the treatment programme for this extremely rare, and usually fatal, condition and for this chart review.

A total of 9 children were managed with lateral thoracic expansion during the study period. Six of them were males and 3 were females. Their age ranged from 3.5 to 75 months (median 30 months). None had received an antenatal diagnosis nor any of them were offered any counselling against therapy.

The initial diagnosis of ATD had been made by the referring team (neonatologist or paediatrician), and a genetic consultation was sought. The predominant reason for referral was respiratory distress, and all of them needed respiratory support of some kind. Eight of the 9 children had invasive ventilator support via endotracheal tube before surgery, and 1 child was on biphasic non-invasive ventilation (BiPAP) during day/night cycle. Five children had already received a tracheostomy. One child (age 4 months) was transferred to high-frequency ventilation.

All children underwent chest radiography (Fig. 1) to rule out any segmental or lobar collapse. They also underwent a computerized tomographic (CT) scan of chest, which was the primary imaging modality (Fig. 2), to show the nature of rib anomalies and the quality of the underlying lung. An estimated lung volume was assessed in all these individuals bilaterally (Table 1), and an airway reconstruction was performed to rule out dysplastic or cystic changes in the lungs (Figs. 3 and 4). The presence of either of these changes in the lung would have excluded them from surgical management to expand their chest, on the basis that if the lungs were already dysplastic, the chances of clinical improvement with chest expansion and a good quality of life would be quite poor.

Full renal, hepatic and cardiac (especially searching for pulmonary hypertension after 2 deaths from this condition vide infra) functional assessments were carried out.

All patients were considered for chest expansion, and the exclusion criteria were severe pulmonary hypertension with or without right ventricular failure and/or the presence of dysplastic changes in the underlying lung.

There were a total of 11 chest expansions in 9 children during the study period. Figure 5 shows the chronology of these children through the course of surgical treatment. The initial 2 children had unilateral chest expansion as described above, but subsequently the remaining 7 children had bilateral single-stage expansion. Two children presented with a severe form of asphyxiating dystrophy in the neonatal period, and they needed respiratory support in the form of high-frequency oscillatory ventilation during admission to our unit. Both of them had had median sternotomy with sternal separation and stabilization for widening the chest cavity as initial palliation. This had provided good clinical improvement, and subsequent management in these 2 children was by conventional respiratory support with semielective tracheostomy and periodic assessment. Both these children subsequently underwent bilateral single-stage chest expansion at 9 and 11 months of age, respectively. While 1 child remains on a nocturnal biphasic non-invasive ventilator support, the other child is increasingly symptomatic, warranting a further chest expansion in the near future.

The remaining 7 children presented at varying age groups with progressive respiratory impairment, though the diagnosis of Jeune’s asphyxiating dystrophy was made either soon after birth or at some stage at neonatal period by the referring paediatricians. The youngest age at presentation in this group of 7 children was 4 months (n = 2), and both of them had a rapid decline in respiratory function following an episode of respiratory infection. This warranted a transient management using high-frequency oscillation, while an attempt was made to stabilize and transport these sick children to our tertiary centre, and surgery was offered following a complete assessment.

**Operative treatment**

Surgery for chest expansion was performed through a lateral decubitus position as for a thoracotomy and a curvilinear incision just below the angle of scapula. A mixture of adrenaline and bupivacaine in saline was injected subcutaneously to help in delineating a surgical plane for dissection during muscle-sparing thoracotomy, and also for a bloodless field of dissection of this plane throughout surgery. A subcutaneous plane was raised both superiorly and inferiorly, and a muscle-sparing approach was used wherein both latissimus dorsi and serratus anterior muscles were dissected and freed completely and retracted laterally on either side to expose the ribs from second rib onwards. Once identified, a staggered osteotomy was used to divide the fourth to seventh ribs, and a mid-level osteotomy was performed at third and eighth rib. Intercostal muscle was separated, and the fourth rib was divided anteriorly close to its costo-chondral junction, and the fifth rib posteriorly close to its junction to transverse process of spine. Similarly, the sixth rib was divided anteriorly and the seventh posteriorly. The long end of the fourth rib was united to the long end of the fifth rib to produce a consequent lengthened rib in its place, while leaving a stump of residual fourth rib anteri- orly and fifth posteriorly. This results in dimensional volume expansion, as described previously by Davis et al. [2, 3]. The sixth rib...
was joined similarly to the seventh rib, and fixations were performed with plate and screws to ensure proper bone union. The mid-level osteotomies of the third and eighth ribs were left widened with consequent gap between the bone ends, maintaining the (wider) contour of the chest wall.

Once completed, two chest drains were left in the pleural cavity for both air and blood, and muscles were brought back anatomically to ensure proper cover to the skeletal fixation. The patient was subsequently repositioned for similar surgery on the opposite side, during the same anaesthetic.

RESULTS

There were no intraoperative difficulties in the surgical technique related to size of the ribs, even in small children. The mean operative time was 3 h for single-stage bilateral thoracic expansion and no adverse respiratory compromise was encountered at any stage during surgery.

There was no operative mortality. The conventional postoperative management in these children included leaving the chest drain on suction in the first 48 h after surgery, to ensure not only an adequate drainage of pleural cavity, but also to keep the lung well expanded during recovery from surgery. Ventilation was weaned as tolerated to an optimal level, and the children were usually sedated without the use for muscle relaxants. Blood losses were minimal and chest drains were removed at 48 h. No prolonged air leak was noted in any of these children. The length of intensive care unit stay postoperatively in our unit ranged between 4 and 8 days (mean duration of 5 days), and usually these children were transported to the referring centre for further management. The criteria to transport these children included stable but weaning parameters of ventilation, low oxygen requirement, no concerns about infection or any other surgery-related complications. The ventilator parameters were within a range of acceptable values (FiO2: 30–50%; peak inspiratory pressure: 20–26; positive end-expiratory pressure: 3–5) in all these children. The median length of further intensive care stay in the referral hospital was 171 days (range 81–312 days).

Further course included improvement of ventilatory requirements in the referral hospital (5 children) with an effective change to nocturnal biphasic non-invasive form of support and they were usually nursed at a ward environment (n = 3) or home care with frequent community visits (n = 2). There were 2 overseas patients who returned to their native countries following a well-improved respiratory parameter.

There were 2 deaths during the follow-up. One child died at 4 months following single-stage lateral expansion due to persistence of severe pulmonary hypertension, and progressive respiratory failure. Worsening respiratory status soon after expansion in this child indicated the need for palliative care. The second child was one of the youngest to undergo surgery (at 4 months of age), and

<table>
<thead>
<tr>
<th>Patient</th>
<th>Right</th>
<th>Left</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Height (cm)</td>
<td>Width (cm)</td>
</tr>
<tr>
<td>1</td>
<td>10.25</td>
<td>6.05</td>
</tr>
<tr>
<td>2</td>
<td>11.1</td>
<td>8.87</td>
</tr>
<tr>
<td>3</td>
<td>13.33</td>
<td>7.03</td>
</tr>
<tr>
<td>4</td>
<td>12.16</td>
<td>5.84</td>
</tr>
<tr>
<td>5</td>
<td>15.04</td>
<td>7.11</td>
</tr>
</tbody>
</table>

The volumes are measured from CT scan, and have no normograms to assess their clinical relevance.

SD: standard deviation.
died at 3 months following single-stage surgery with a similar feature of severe pulmonary hypertension. Following these two, a change in protocol of including presence of severe pulmonary hypertension as one of the exclusion criteria for surgical management was made. The follow-up was 100% complete in the remaining 7 children at 18 months. Three of the 7 children had worsening respiratory parameters, and these served as the warning signs showing disparity of lung growth against restriction of chest wall. One child aged 3 years showed dysplastic changes in the lungs on the follow-up CT scan with worsened respiratory function. It was decided at this stage that further surgery may be futile, and a re-expansion was not offered. The remaining 2 children had further re-expansion of both chest cavities (as single stage) similar to first surgery, but further separation of the bone ends needed synthetic bone grafts to join the ribs. There were bony unions at the site of osteotomies, indicating a new bone formation in this group, which was encouraging.

Apart from the fact that the surgery was a reoperation, the postoperative care was similar in line, and recovery was almost similar to previous ones. Their respiratory parameters had improved, and were at baseline ventilator support equivalent to their preworsening stage, and back to ward environment.

**DISCUSSION**

Jeune’s syndrome or ATD is a fatal condition, manifesting very early in childhood. Jeune et al. [4] originally described this extremely rare syndrome in 1955, and it has since been delineated clearly by various reports. ATD is thought to be genetically mediated, with an autosomal recessive inheritance and variable penetrance.

Various genetic mutations have been implicated in the causation of this syndrome, and homozygous and compound-heterozygous mutations in the retrograde dynein motor DYNC2H1 have been specifically identified in cases of ATD [5]. These also show the correlation between the extents of genetic component to that of primary ciliary abnormalities, known to be a feature of all these skeletal dysplasias, thereby influencing their clinical presentation. There is a variable incidence of 1 in 70,000 to 1 in 150,000, with very few surviving infants beyond certain age to pass on the disease in the same family [1, 6].

Clinical presentation is variable, and is usually characterized by variable respiratory illness, starting from profound and severe respiratory failure in the neonatal period in extreme cases, to milder form of distress needing ventilatory support in some. The respiratory failure is akin to a restrictive type of ventilatory defect, with retention of carbon dioxide and progressive worsening of parameters with infants continuing to grow otherwise. Transient relief is often obtained with ventilatory support, and a definitive relief has to come in the form of a chest expansion to provide additional space for lung expansion.

Children, who survive the neonatal period or infantile period, continue to have progressive respiratory impairment due to restrictive chest wall. However, extrathoracic features predominate in later childhood in less severe variants, with hepatic or renal
cysts and degeneration complicating the clinical presentation [7] and contributing to ultimate death in this uniformly fatal condition, if untreated.

Radiology remains the mainstay in diagnosing the extent of skeletal dysplasia in this condition. Chest X-ray is quite characteristic, with shortened ribs placed horizontally and a bell-shaped chest, which is progressively narrow apically [1]. CT scans are very useful in showing the quality of underlying lungs, and calculating the estimated chest volumes on each side. A calculated improvement of volume can be predicted based on surgical expansion, which may potentially serve for future advances.

Although assessments were in line as explained in the section on materials, we employed a conventional way to calculate the lung volumes in these children before surgery. The lung volumes may serve as a baseline for any future comparison, but lack of normograms for this age group or disease process does not help in any decision-making on them at this stage. They may also serve to guide future directed therapy if a normogram based on growth in these children can be established.

Surgery to the chest wall early in life is known to postpone or palliate the respiratory compromise seen at presentation. Historical attempts at releasing a number of ribs at costo-chondral junction were universally unsuccessful in relieving the respiratory compromise [8]. The first surgical success dates back to 1971, when Barnes et al. [9] did a sternotomy and fixation by bone grafts in a 4-month old child, with an estimated 25% increase in thoracic volume. This led to further advances in initial midline approach for this condition. Subsequent attempts were in the form of refinement of various materials used to bridge the split sternum in midline, and Todd et al. [10] used methyl methacrylate to main this separation between sternal edges with its advantage being less anaesthesia time for the procedure, and an excellent bony support without any risk of local dehiscence.

A significant advance came in the form of lateral expansion of the chest, as reported by Davis et al. [2, 3] in 1995. The procedure involved, as in our series, a staggered osteotomy of consecutive ribs and a rigid titanium fixation and primary skin closure. Davis reported a sub-periosteal osteotomy for an effective bone formation, which was proven in subsequent series [11], but as seen in our reoperation, new bone formation is not seen to be an issue in this group in spite of being part of skeletal dysplasia syndromes. Further advances in the form of dynamic thoracoplasty, as reported by Kaddoura et al. [12], are quite appealing to clinical set-up, but limited by its hardware components.

The advantage of lateral chest expansion is primarily to maintain the protection of anterior mediastinal structures while allowing significant bone growth all around the chest, and maintaining the contour of the chest. The procedure is entirely safe, and there is no frail component that needs to have significant ventilatory support longer than needed for recovery from underlying compromise, with a rigid fixation of all divided rib ends.

While we maintained the advantages of Davis’ lateral thoracic expansion, we further modified this to allow for a shortened, yet a more clinically appealing, bilateral surgery with no additional risk. This offers a rapid chest expansion on the whole for both sides, with marked clinical recovery, less combined hospital stay and morbidity. There is also an indirect benefit from a combined lower cost on the health sector in managing these difficult children who will need a very prolonged ventilatory and hospital stay in any case for continued management.

There are various limitations to treatment of this extremely rare syndrome. Against a popular concept of offering treatment to a sick neonate with profound respiratory failure due to ATD, we offered treatment to all children who satisfied our criteria. The recent improvements in perioperative and intensive care managements permit indefinite survival of these children even with severely restrictive chest cavities, and sometimes with damaged lungs. These may raise social, ethical and economical problems to the health sector, but in retrospect, we feel that though there is an enormous amount of time and money involved in this, at no time, the situation looked difficult or hopeless to withdraw treatment on any of the children treated in our series. Moreover, by modifying to bilateral surgery, the cost is further reduced with rapid improvement in terms of recovery to a level that can be managed optimally for further care in secondary level care units.

In summary, ATD is a difficult condition to treat, but a bilateral expansion offers a rapid solution to improve prognosis, and achieve a stable respiratory parameter in a difficult child. Single-stage repair is feasible with a very low morbidity and offers advantages not only to the patient, but also to the national health service in terms of cost, hospital stay and projected need for lesser number of procedures overall, while ethical component and inclusion criteria still remain controversial.

Conflict of interest: none declared.

REFERENCES