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Jarcho-Levin syndrome in Pakistan: a case report and review of 321 cases on the principles of diagnosis and management

Imran Asghar[1], Sheharyar Zameer[1*], Taimoor Ashraf Khan[2], Muhammad Abdullah Zahid[3], Muhammad Hamza Khan[4] and Noor Ul Ain Zameer[1]

Abstract

Background: Jarcho-Levin syndrome (JLS) is a genetic condition that constitutes specific vertebral anomalies combined with coastal or thoracic anomalies due to specific gene mutations. Although the condition is associated typically to Puerto-Ricans, we describe the novel case of JLS in a Pakistani family that presented with respiratory distress secondary to the condition.

Case presentation: The case is a full-term girl that had a webbed neck with an undefined chest deformity. Radiology showed kyphoscoliosis and a crablike chest. Early identification of these high morbidity conditions is key to allow for optimal treatment and improved outcomes.

Conclusions: We have provided a brief breakdown of the management principles of the condition and more than 80 years after the first case of Jarcho-Levin syndrome was reported, we present the diagnostic criterion for JLS.

Keywords: Spondylothoracic dysostosis, Spondylocoastal dysostosis, Thoracic insufficiency, Diagnostic criterion, Vertical expandable prosthetic titanium ribs

Background

In 1938, Saul Jarcho and Paul Levin first described two siblings with thoracic insufficiency due to vertebral and rib anomalies. The rare genetic condition came to be known as Jarcho-Levin Syndrome (JLS) and was found to be attributed to mutations in one of five genes, specifically: *DLL3* (most commonly involved), *MESP2*, *LFNG*, *HES7*, *or TBX6* genes. The condition typically has an autosomal recessive pattern of inheritance and is categorized into two types: spondylothoracic dysostosis (STD) and spondylocoastal dysostosis (SCD) [1].

Here, we present a case of a newborn girl diagnosed as spondylothoracic dysostosis based on clinical-radiological findings. To our knowledge, this is the first case of JLS from Pakistan.

Case presentation

A full-term girl born of cesarean section, after a non-consanguineous marriage cried immediately at birth but developed progressive acrocyanosis, tachypnea (80 breaths/min), chest retractions and nasal flaring (APGAR Score = 6/10) at the 5-min mark from birth. The lower segment cesarean section (LSCS) was planned due to maternal hypertension. The antenatal visits were all unremarkable. The newborn was immediate shifted to the neonatal intensive care unit (NICU) and put on breathing support with 3 L/min of high-flow oxygen. Due to the lack of sucking reflex, the child was maintained on intravenous dextrose-saline and prophylactic antibiotics.

Once stabilized, a set of baseline investigations were advised. The blood count, liver function tests, renal

*Correspondence: sheriyar55@gmail.com

[1] Combined Military Hospital, Rawalpindi, Pakistan
Full list of author information is available at the end of the article

function tests and serum electrolytes were all within normal limits. Over the course the next 24 h, the respiratory distress settled, and the child was gradually weaned off oxygen and put on oral feed.

On examination, the child had a short, webbed neck with a mild chest deformity (Fig. 1). The chest radiograph showed a 'crab-like' chest due to rib anomalies including irregular shape, mal-alignment, crowding, and fusion (Fig. 2). The whole spine radiograph showed kyphoscoliosis especially at the thoracolumbar region due to malformed vertebrae (Fig. 2).

No other defects were noted clinically or radiologically and hence a diagnosis of JLS/STD was made. The parents were counselled regarding the typical autosomal recessive nature of the disease for future pregnancies, development of infectious and non-infectious complications in the child and were advised follow up for these complications. Genetic testing was not done since in Pakistan, close to no set-up specifically offer the required genetic testing and the family themself was resource-stricken.

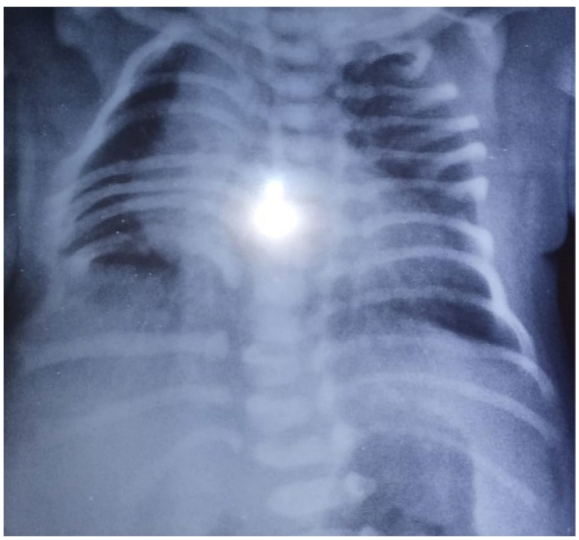

Fig. 2 Rib crowding, fanning, and fusion along with irregular shaped on chest radiograph with vertebral agenesis, hypoplasia, and fusion on whole spine radiograph

Discussion

The exact prevalence of JLS is unknown because of its rarity and repeated misdiagnosis [2]. We reviewed all cases of JLS described in literature since inception to February 2022. In our review, we assessed a total of 321 cases of JLS that were reported in literature. Twenty of these cases are of SCD and 301 cases of STD. A prenatal diagnostic criterion for the condition exists in literature [3]. Even though the condition had been first described more than eight decades ago, to our knowledge, there is still no formal diagnostic criteria for the condition at birth. Therefore, after an extensive review, we present our criterion for the diagnosis of JLS in Table 1. The criterion was developed from the 321 cases reviewed and each of these cases can be diagnosed via the criterion at birth. The criterion has the property of being utilized within resource-stricken healthcare set ups, even if genetic testing is not available. All cases reviewed to develop the criterion have been attached as a supplemental file.

The first step in the management of JLS is counselling of the parents regarding the condition of the child and genetic counselling for future pregnancies including prenatal diagnosis, termination of pregnancies and the option of adoption [4]. However, the definitive correction of the condition requires collaborative efforts from pediatric, orthopedic, and thoracic surgeons. Depending on the disability produced by the disease, multiple orthopedic procedures can be used for correcting the condition, most promising of which is vertical expandable prosthetic titanium ribs or VEPTRs that are known to improve thoracic symmetry, kypho-scoliotic curve

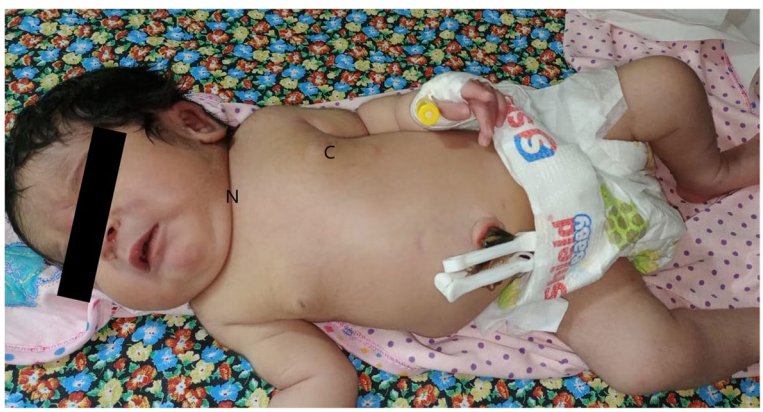

Fig. 1 The child with a visible short, webbed neck (N), and chest deformity (C)

Table 1 Asghar-Zameer criterion for the diagnosis of JLS at birth

Major criteria
1. Vertebral anomalies including hemivertebrae, vertebral agenesis, butterfly vertebrae, hypoplastic vertebrae, costovertebral fusion defects.
2. Rib anomalies including malalignment, crowding, fanning-out, fusion, absence.
3. Genetic evaluation showing mutation in *MESP2*, *DLL3*, *IFNG*, *HES7*, *or PSEN1* genes.
4. Prenatal sonographic features including costovertebral segmentation, indistinct or fused posterior ribs, irregularly shortened spine, short trunk, and short neck.
Minor criteria
1. Child born of a consanguineous marriage.
2. Having a sibling diagnosed with Jarcho-Lavin syndrome.
A definite diagnosis of JLS is made on the presence of two or more major criteria.
A diagnosis is probable in the presence of one major and two minor criteria.

correction, and markedly improve respiratory function. Furthermore, it has shown to improve capacity for physical activity, increase average lifespan, and improve psychosocial health [5].

VEPTRs are essentially curved rods that are surgically attached to a child's rib, spine, or pelvis and in doing so straightens the child's spine and separates ribs so their lungs can grow and expand as the child grows [5]. VEPTRs are indicated in a case of JLS if the child is more than 6 months but has not reached skeletal maturity, has adequately strong bones for the attachment of the device, a certain degree of diaphragmatic function, and adequate coverage for the device [6, 7].

With insertion of VEPTRs, follow-up care is essential involving multiple hospital returns typically at 6–9 months. Patients may also be given wound protective covers for the device to prevent rubbing and bumping. In certain cases, adjustment surgeries may be required to allow the VEPTRs to expand with respect to the child's development. Furthermore, once the child reaches skeletal maturity, spinal fusion surgery may be done to make the chest wall correction permanent [6]. A special consideration is lung herniation via the chest wall and accompanied paradoxical movements due to a lack of ribs. One treatment option in such a case would be a functional vascularized ipsilateral latissimus dorsi flap [8].

Although a lot of research has not been done on developing the anesthetic principles of the patients; however, as with all patients at risk or with pulmonary hypoplasia and/or respiratory distress, isoflurane or sevoflurane are utilized as the major anesthetic agents with laryngeal mask airway (LMA) as the preferred airway, both of which have shown to limit post-operative respiratory complications [9].

We noted in our review that in multiple cases, JLS presents with multiple other concurrent anomalies including neural tube defects, caudal regression, congenital heart defects, abnormal airways, diaphragmatic hernias, and renal anomalies. The most common of these anomalies were neural tube defects (50 of 321 confirmed cases). The literature also reports multiple complications associated with JLS. These most commonly include airway compression [10], respiratory distress [11], pulmonary hypoplasia [11], thoracic insufficiency [2, 11], and abdominal wall hernias [12]. It also produces the appearance of a small 'crab-like' chest with long limbs [2].

Airway compression typically occurs secondary to kyphoscoliosis and may require urgent intubation [10]. Respiratory distress in these children will require immediate ventilatory support ranging anywhere from high-flow oxygen to continuous ventilation [11]. Most infants die due to respiratory and/or airway compromise at this stage [11, 13]. In most cases, the surviving infants will require oxygen supplementation at home suggesting varying degrees of respiratory compromise in survivors. Since this is a developmental disorder, the thorax is restricted from fetal life leading to pulmonary hypoplasia. In such cases, only supportive treatment is available; however, if detected in fetal life, certain fetal surgeries can improve outcomes [14].

Thoracic insufficiency develops when the abnormal thorax is unable to support lung growth leading to progressive respiratory compromise as the child grows. The prevention and correction of the condition maybe done conservatively via physiotherapy however results are not promising. This is where expansion thoracoplasty via vertical rib expansion and rib implants can help treat the condition [12]. Those that survive into adolescence can develop hernias, typically inguinoscrotal due to lax abdominal wall. This can be corrected by the standard mesh hernioplasty [12].

The detailed surgical technique for VEPTR insertion is to place the patient in lateral decubitus

position with shoulder extended not more than 90º (to prevent brachia plexus injury). Make the standard J-shaped thoracotomy incision and retract skin flaps. Continue the dissection and elevate the scapula and paraspinal muscles to expose the middle posterior scalene muscle. Make a small incision in the intercoastal muscles above and below the selected rib and gently elevate the periosteum from the inner surface of the rib. Select the proper cranial rib support of appropriate size and angulation and the seat it into the space crated next to the rib. Insert the closing half rib into the intercoastal space above and adjust it to mate with the cranial support rib. Insert the lock for the rib support to seal it. Here, additional rib retraction, wedge thoracotomy, and osteotomies may be done as per the case. With the help of an appropriate extension bar, measure the distance to the caudal rib and select an appropriate extension rod. Properly insert either the Lamina hook (for rib-to-lumber construct), the Ala hook (for rib-to-ilium construct), or a rib hook (for rib-to-rib construct). Now, align both sides via the extension rod and lock the construct with the inserter. Extend or tighten the implant as per the need [6, 7].

Conclusions

Conclusively, since the condition has no cure, the management is mainly centered around surgically correcting the developmental anomalies. The study also emphasizes the establishment of diagnostic and treating principles for JLS.

Abbreviations

LSCS: Lower segment cesarean section; JLS: Jarcho-Levin syndrome; STD: Spondylothoracic dysostosis; SCD: Spondylocoastal dysostosis; NICU: Neonatal intensive care unit; VEPTRs: Vertical expandable prosthetic titanium ribs.

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None to declare.

Authors' contributions

IA and TAK were core members of the primary treating team of the patient and selected the case report. SZ did the extensive literature review and interpreted the patient data. SZ, MHK, and NUZ wrote the first draft. IA, TAK, and MAZ critically reviewed the draft and corrected the manuscript for the final version. All authors approved of the final paper and take accountability for all aspects of the report.

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Availability of data and materials

The dataset generated or analyzed during the current study are not publicly available due to patient confidentiality but are available from the corresponding author on reasonable request. Supplemental data utilized in the literature review has been submitted to the journal with the case report.

Declarations

Ethics approval and consent to participate

An informed written consent to participate in the study was taken from the parents of the patient who are his legal guardians. Confidentiality was maintained at all levels of the study. Ethical approval was also obtained from the Hospital Ethics Review Committee.

Consent for publication

An informed written consent for publication was taken from the parents of the patient who are his legal guardians.

Competing interests

The authors declare that they have no competing interests.

Author details

[1]Combined Military Hospital, Rawalpindi, Pakistan. [2]Armed Forces Institute of Ophthalmology, Rawalpindi, Pakistan. [3]Monash Health, Monash, VIC, Australia. [4]Army Medical College, Rawalpindi, Pakistan.

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