Original Article

# Craniovertebral junction instability in Larsen syndrome: An institutional series and review of literature


## ABSTRACT

**Objective:** Larsen syndrome (LS) is characterized by osteo-chondrodysplasia, multiple joint dislocations, and craniofacial abnormalities. Symptomatic myelopathy is attributed to C1–C2 instability and sub-axial cervical kyphosis. In this article, we have analyzed the surgical outcome after posterior fixation in LS with craniovertebral junction instability.

**Methods:** Ten symptomatic pediatric patients, operated between 2011 and 2019, were included, and the clinical outcome was assessed by Nurick grade, neurological improvement, and complications. The requirement of anti-spasticity drugs, the degree of bony fusion, and restriction of neck movement were also noted. At last follow-up, patient satisfaction score (PSS) and back to school status were studied. We also reviewed the literature and categorized two types of presentation of reported LS patients and discussed the pattern of disease progression among both.

**Results:** Ten patients, age range 1.5–16 years, underwent 12 surgeries (6 C1–C2 fixation, 4 long-segment posterior cervical fixation, and 2 trans-oral decompressions as the second stage); the mean follow-up was 23 (range, 6–86 months). All the ten patients in our study had the characteristic "dish-" like face and nine patients had acral anomalies. The median Nurick grade improved from preoperative (median = 4) to follow-up (median = 3). The requirement of anti-spasticity drugs decreased in seven patients and the neck-pain improved in nine patients. The median satisfaction at follow-up was good (median PSS = 2); five patients were going back to school.

**Conclusion:** Craniovertebral junction instability in LS is rare and surgically challenging. Early posterior fixation showed a promising outcome with a halt in the disease progression.


**Keywords:** Cervical kyphosis, cranio-vertebral junction anomalies, Larsen syndrome, long segment fusion, sub-axial compression, syndromic atlantoaxial dislocation

## INTRODUCTION

The syndromes involving craniovertebral junction (CVJ) instability have three types of the underlying mechanism (a) basioccipital dysgenesis, or proatlas anomalies, (b) odontoid dysgenesis, or os-odontoideum, (c) laxity of ligaments or some abnormal mucopolysaccharide deposition.[1,2] Out of nearly 84 syndromes associated with CVJ instability, Larsen syndrome (LS) is the most notorious and challenging to treat.[1] It is inherited as both autosomal dominant or recessive manner;[3] chromosome region as 3p21.1–14.1 and small in-frame deletions in the protein Filamin B – beta actin-binding protein (FLNB).[4,5] LS forms a rare subset of patients who manifests with either (a) atlantoaxial instability, sub-axial cervical kyphosis (CK), in poor Nurick grade, with or without any history of trivial trauma;


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**Submitted:** 02-Oct-20 **Accepted:** 05-Oct-20
**Published:** 26-Nov-20



**How to cite this article:** Singh S, Sardhara J, Raiyani V, Saxena D, Kumar A, Bhaisora KS, *et al.* Craniovertebral junction instability in Larsen syndrome: An institutional series and review of literature. J Craniovert Jun Spine 2020;11:276-86.

or (b) asymptomatic (in terms of compressive myelopathy) with facial dysmorphism (dish face) and forelimb deformity.[4] The triad of odontoid hypoplasia, small bullet-shaped vertebral bodies, and typical facies of "dish face" is diagnostic of LS. Other comorbidities include osteo-chondro-dysplasia, multiple joint dislocations, and craniofacial anomalies.[5] Progressive CK and CVJ instability are the two most crucial underlying etiologies for spastic quadriparesis. The natural course of the disease is unpredictable, and there is a lack of a consensus regarding the "timing" and "approach" of surgical management. In this study, we have shared our surgical outcome of 10 "symptomatic LS patients" and reviewed the available literature discussing the pattern of recovery among two different types of phenotypes.

## METHODS

In this retrospective, observational study, we studied the surgically managed pediatric patients (age less than 18 years of age) of LS with CVJ instability. These patients include either (a) asymptomatic children with facial or skeletal phenotypic features of LS, managed in the medical genetics department and subsequently referred to us after developing myelopathy ($n = 4$) and (b) symptomatic patients directly admitted from neurosurgery outpatient department with features of progressive, compressive, cervical myelopathy ($n = 6$). We analyzed our department's prospectively maintained database from 2011 to 2019 and ten patients of LS (out of 41 syndromic patients) were included in this study. We noted the age at admission, presence of associated syndromes with characteristic phenotypic features, clinical presentation, CVJ stigmata, and any other co-existing comorbidities.

The patients were contacted telephonically and called upon for an outpatient visit. Subsequently, these ten patients were further assessed for neck movement, clinical outcome, patient satisfaction score (PSS), and a subjective questionnaire including able to go back school (BTS), and status of their anti-spastic drugs. PSS was also analyzed using a 5-point Likert scale.[6] The parents were also asked Back-to school (BTS) questionnaires using a 5-point Likert scale (they were asked: "How safe you feel sending your child to school" Response categories included the following: 1 = they feel safe with all precautions; 2 = safe but worried after trauma; 3 = not sure, its duty so they don't think on that much; 4 = unsafe and send their child irregularly, and 5 = very unsafe do not send their child to school).

We believe that the Nurick grading system is not suitable for the pediatric population and is difficult to comment upon "improvement" or "same status" using the same. Grade 2 is difficulty with walking but fully employed (or employable), but these terms do not apply to the pediatric population, so the examiner used "2- to 3 scores." However, being a retrospective study, we noted the available pre- and post-operative Nurick grade, level of compression (CVJ or sub-axial), and other osseous, vascular or co-existing soft-tissue anomalies. We excluded all the patients with less than 6-months of follow-up ($n = 2$).

Posterior fixation was done using Goel and Harm's technique of posterior fixation (C1 lateral mass, C2 pars interarticularis ± C1-C2 joint distraction). Some patients ($n = 4$) also required simultaneous sub-axial kyphosis correction. Inter-laminar distraction followed by manual compression was the technique we used in these patients. Titanium horizontal connecter rod was applied at C1-2 level in the cases of the anterior or posterior bifid arch and C3 or C4 level while performing long segment fusion to prevent lateral instability.

Institutional ethical board approval was obtained to review the medical records and neuroimaging studies of these patients (IEC code number: 2013-08-MCH-67). Patient data were analyzed using SPSS software version 24 (IBM Corp., Chicago, IL, USA), and a $P < 0.05$ was considered statistically significant.

## RESULTS

A total of 550 patients with nontraumatic CVJ anomalies were operated from 2011 to 2019 in our department; out of whom, 180 patients belonged to the pediatric age group (<18 years). Ten patients of LS with CVJ instability, with a median age of 4-years (range 1.5–16 years) (M: F = 8:2), were included in our study (incidence 5.5%). Four patients (out of seven in their follow-up) referred from medical genetics department were initially asymptomatic, but subsequently developed myelopathy during follow-up or evaluation. A summary of the clinical characteristics, radiological features, systemic abnormalities, and surgical outcome of the study population is shown in Table 1. Seven patients were presented before 5 years of age with moderate-to-severe cervical myelopathy. All the ten patients in our study had the characteristic "dish-" like face and nine patients had acral anomalies. All of them had atlantoaxial dislocation (AAD) (reducible AAD, $n = 8$; irreducible AAD, $n = 2$). All ten patients had sub-axial vertebral body hypoplasia with or without clinically obvious kyphosis. Six of them (60%) had a beak-shaped vertebral body with congenital wedging, while two patients had hypoplasia of one or more vertebral bodies [Figure 1]. Bifid atlas arch was seen in one patient of LS, and bifid axis was seen in two patients.

**Table 1: Clinical and radiological details of patients with Larsen syndrome ($n=10$) in our study**

| Case number | Age (years) | Sex | Preoperative Nurick grade | Clinical association | | | Radiological association | | | | | Postoperative Nurick grade | Follow-up Nurick grade | Follow-up (months) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Facial anomaly | Acral anomaly | Others | Clivus | Odontoid | Atlas | Axis | Sub-axial | | | |
| **Group 1: Patients operated by C1-C2 lateral mass screw and rod fixation with C1-C2 joint distraction (Goel's and Harm's technique)** | | | | | | | | | | | | | | |
| 1 | 5 | Male | 2 | + | + | HMD, CDH, hydro-nephrosis | - | Hypoplasia | - | - | Beak shaped with C5 hypoplasia | 2 | 2 | 86 |
| 2 | 4 | Male | 3 | + | + | - | - | Hyper-mobile AAD Partial agenesis | - | Partial agenesis | Beak shaped with C2-C7 hypoplasia | 3 | 3 | 6 |
| 3 | 1.5 | Male | 5 | + | + | - | - | Os-odon | - | - | C6 hypoplasia | 4 | 4 | 6 |
| 4 | 2.5 | Male | 4 | + | + | Polymicrogyria with seizure disorder | - | Os-odon | - | - | Beak shaped with C2-C7 hypoplasia | 4 | 3 | 6 |
| **Group 2: long-segment fixation and cervical kyphosis correction** | | | | | | | | | | | | | | |
| 5 | 16 | Male | 4 | + | + | - | Platy-basia | Os-odon | - | Bifid body | C6 hypoplasia | 4 | 3 | 18 |
| 6 | 16 | Female | 3 | + | + | - | - | Os-ter | Bifid | Partial agene-sis | C4-C5 hypoplasia | 3 | 3 | 8 |
| 7 | 8 | Male | 5 | + | + | Polymicrogyria | - | Os-odon | - | Bifid body | Beak shaped with C2-C7 hypoplasia | 5 | 5 | 33 |
| 8 | 4 | Male | 3 | + | + | - | - | Os-odon | - | C2 VB hypoplasia | Beak shaped with C2-C7 hypoplasia | 3 | 3 | 9 |
| **Group 3: Others** | | | | | | | | | | | | | | |
| 9 | 4 | Female | 4 | + | - | CHD | - | Hypoplasia | - | Hypoplasia | Beak shaped with C2-C7 hypoplasia | 4 | 3 | 50 |
| 10 | 3 | Male | 5 | + | + | - | - | Hypoplasia of dens | - | C2 VB hypoplasia | Beak shaped with C2-C7 hypoplasia | 4 | 5 | 8 |

HMD - Hyaline membrane disease; CDH - Congenital dysplaisa of hip; CHD - Congenital heart disease; Os-odon - Os Odontoideium; Os ter - Os tertium; AAD - Atlantoaxial dislocation; O - Occipital; VB - Vertebral body; TOD - Trans-oral decompression or odontoidectomy

Four patients (cases 1–4) underwent C1–C2 lateral mass screw and rod fixation with C1–C2 joint distraction (Goel's and Harm's technique). These four patients showed an arrest in their symptom progression as a delayed outcome, with the cessation of anti-spasticity drugs, improvement in neck pain among all four of them. All the four patients had sub-axial hypoplasia (either single vertebrae or multiple) but did not have CK or sub-axial compression that warranted surgical intervention.

Four patients (cases 5–8) had sub-axial cervical cord compression with myelopathy [Figure 2], and underwent long-segment fixation and CK correction (either occipital plate – C1 (lateral mass) – C2 (pars) – C3 downward pedicle fixation in $n = 3$; or C1 (lateral mass) – C2 (pars) – C3 downward pedicle fixation in $n = 1$). One of them had associated platybasia, Goel's type II basilar invagination, and retroverted odontoid. This patient needed simultaneous trans-oral odontoidectomy (TOD); surgical outcome (Nurick grade) showed an arrest in clinical progression but no functional improvement.

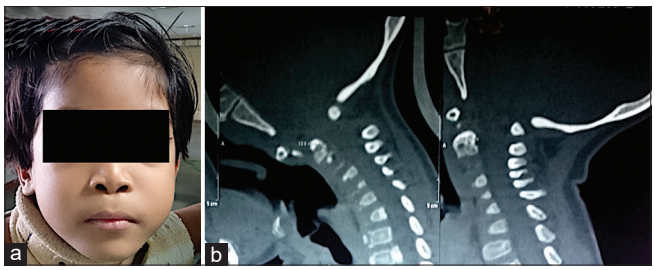

**Figure 1: A patient of Larsen syndrome (a) with computed tomography sagittal view showing bullet-shaped subaxial vertebral bodies (b)**

One patient (case 9) underwent C1 (pars) – C2 (lateral mass) (Goel's and Harm's technique) without C1-C2 distraction. This patient needed TOD after 3 months for postoperative respiratory distress and long-term ventilator requirement. In his initial course of hospital stay, the ventilator requirement decreased gradually. Hence, we waited for recovery, but the child was not able to weaned off completely and had intermittent ventilator requirements. After TOD, the child had remarkable improvement and was discharged after 16-days. In the follow-up, the tracheostomy site was closed (3 months after discharge), and the child is doing well.

Our last patient (case 10) (operated at age 3 years) with odontoid hypoplasia and mobile AAD, who underwent C1–C2 (lateral mass) (Goel's and Harm's technique) without C1-C2 joint distraction, needed a second-stage long-segment fixation for progressive CK and clinical deterioration.

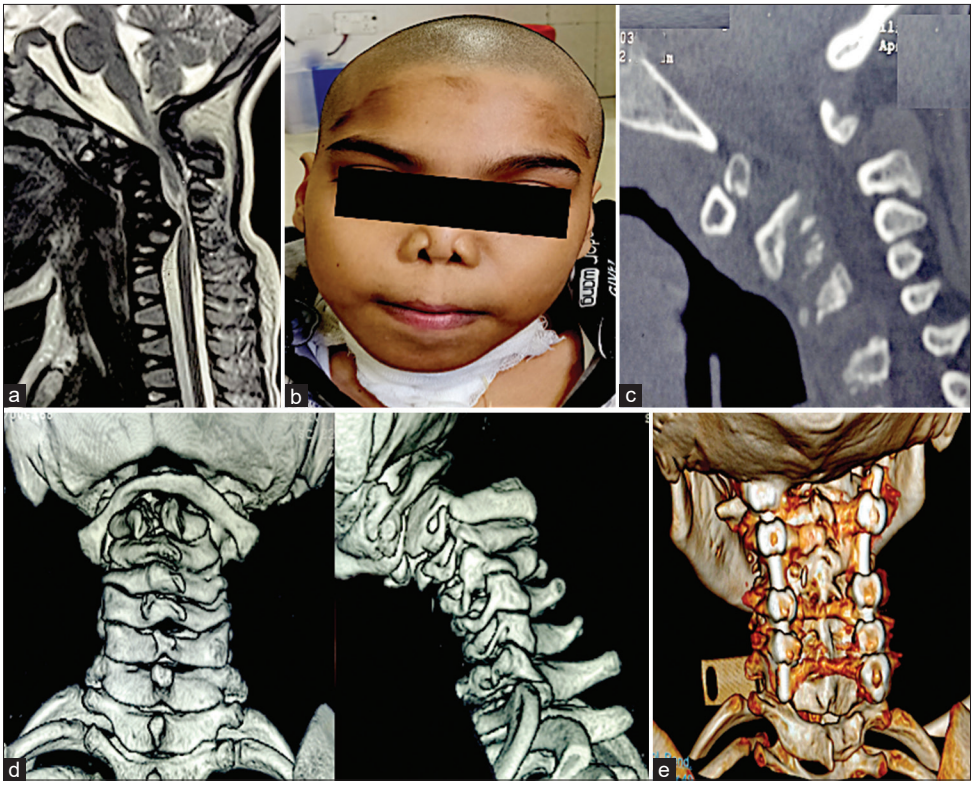

**Figure 2: Magnetic resonance imaging sagittal T2-weigted imaging (a) of a patient with "dish facies (b); the sagittal computed tomography showing os odontoidium and bullet shaped subaxial vertebral bodies (c). The three-dimensional computed tomography show facetal dislocation and bifid posterior arch of axis (d). Postoperative three-dimensional computed tomography scan showing long long-segment fixation (e)**

### Surgical outcome

The mean follow-up in our study was 23 (range 3–84)-months. The median Nurick grade did not change from preoperative to postoperative (i.e., median = 4), but it improved to "3" at last follow-up. Seven patients did not show improvement in Nurick grading and three of them improved by grade 1 (case no. 4, 5, and 9). We were successful in achieving subjective straightening of the spine (exact Cobb's angles are difficult to quote because of simultaneous CVJ and subaxial pathologies, and also that the vertebral bodies were bullet shaped). The requirement of anti-spasticity drugs decreased in seven patients (five patients who were on Baclofen [30 mg/day] at the time of discharge, does not need the drug any more; two patients who were on baclofen [60-mg/day] and tizanidine [6-mg/day], needed only baclofen [20-mg/day]). Three patients were continuing on the same dosage prescribed at the time of discharge (case no. 3, 4, and 6 [follow-up of fewer than 8 months]). One point needs to be emphasized herein is that three patients showed improvement in the power of distal extremities, but it was not significant to change their Nurick grading as an overall functional outcome. Neck pain improved in nine patients (as compared to preoperative status) except in case no. 10 who had persistent mild to moderate pain. Moreover, it is difficult to comment upon the neurological improvement in toddlers (as five of our patients were operated at the age of 1.5, 2.5, 3, 4, and 4-years, respectively).

Two patients (follow-up 50 months and 86 months) with C1–C2 posterior fixation had nearly 60° flexion, 15° of extension, 45° of lateral bending, and 30° of rotation each side on long-term follow-up in cervical neck movement examination. The other two patients showed a restriction in neck movement. Among the four patients of long-segment fixation, one patient (follow-up 33 months) showed 30° flexion, 15° of extension, 15° of lateral bending, and 15° of rotation each side; while the other three patients had severe restriction of neck movements. Case no. 9 and 10 had nearly 45° flexion, 15° of extension, 30° of lateral bending, and 30° of rotation each side. Complete bony fusion was evident among three patients (out of the four who underwent radiological evaluation) and none of the four radiographs showed any evidence of adjacent segment disease.

### Patient-related outcome measures

Despite intact pre- and post-operative Nurick grade, the median satisfaction at follow-up was good (median PSS = 2). Four patients (case no. 2, 3, 4 and 6) were less satisfied (median PSS = 3), which could because of operative site pain, difficulty to ambulate, and comparatively lesser follow-up. None of the patients in our study was dissatisfied after surgery. These results may be confounded by the educational and socio-economic status of patients. We also inquired about the educational status of these children; out of seven patients (who had Nurick grade of 3 or less), only one patient (case no. 1) had BTS score of 2 (safe but worried after trauma) and was able to go school regularly. Four patients (case no. 2, 4, 5, and 6) had BTS score of 4 (parents think that sending school is unsafe and send their child irregularly); while two patients had BTS of 5 (case no. 8 and 9) and were not sent to school at all. Three patients were bedridden and could not perform even their daily routine activities. We did not perform comparative assessments of height measurements but all the parents told subjectively that height is not stunted and growth is equivalent to their peer group.

## DISCUSSION

LS is characterized by facial dysmorphic anomalies, multiple joint dislocations, spinal segmentation, or kyphotic anomalies. The presence of CK and multiple large joint pathology further complicates the management and depreciates the surgical outcome. CVJ instability in LS (LS) needs surgical fixation. However, it is still debatable, whether asymptomatic pediatric patients should be offered surgical fixation or not. The association of cervical instability has been variably quoted in the literature;[1-3,7-10] and in our experience the incidence is 5.5%. Nearly 12% of the patients of LS show associated cervical spine involvement.[11] Considering the rarity of disease, very few articles in the literature have focused exclusively on the surgical outcome of CVJ instability in LS.

There are two types of clinical presentation in LS (a) first, without features of cervical myelopathy, but patients have a "dish" face or multiple joints involvements; (b) secondly, a child presenting with cervical myelopathy with or without facial or joint involvement. Symptomatic patients certainly need surgical fixation but the postoperative course does not depend solely on cervical involvement, but also on the associated knee, ankle, hip, or other joint pathologies. Asymptomatic patients may be followed radiologically but surgical fixation seems imperative and inevitable. The asymptomatic patients, who were initially followed radiologically, may need surgery for progressive CK (as in four of the patient in our experience). In a study by Crostelli *et al*., only one patient (age 17 months) needed surgical management (sublaminar wiring) out of 31 reported.[7]

The association of CK with LS, is known for decades (Larsen *et al*., 1950), but the nature of the disease remains a conundrum.[9] In a series by Laville *et al*., 38 patients of LS were studied, but they could not found a single case of CK.[8]

Four of our patients had simultaneous CK and underwent long-segment cervical fixation. None of these four patients' complaint of kyphosis progression in follow-up but there are studies showing CK progressing after surgical fixation. The patients who had progressive kyphosis after surgical fixation underwent anterior or posterior or both fixations. However, none of the authors had addressed simultaneous CVJ instability. It is difficult to diagnose the instability radiological because CVJ ossification is yet to complete.[10] Therefore, a high index of suspicion for CVJ instability must be kept in the patients of LS. Another interesting observation was that 80% of our patients were male. This predisposition has never been discussed in the literature but paves a food for thought for further genetic translational research in the subject. Our data showed that though the surgical fixation is not promising in terms of improvement in Nurick grade, surgery can (a) halt the progression of the disease, (b) parents were satisfied as these children have crippling preoperative course, and (c) long-term follow-up showed that height is not restricted and neck movements remain uncompromised after Goel and Harms' technique.

### Conservative management with radiological follow-up versus prophylactic surgery

In our literature review, we found a silent consensus on prophylactic fixation of these patients.[9-11] Forese *et al*. managed these children conservatively, with traction and bracing, and concluded that surgical intervention would be required in future.[12] Sahoo *et al*. reported a case of adult LS and proposed that treating adult kyphosis is not necessary as the disease becomes nonprogressive.[13] In his series of four patients, Johnston *et al*. found that the CK kept on progressing, even after posterior fixation.[14] In another review of ten cases, Madera *et al*. proposed that conservative management should be avoided because prognosis remains guarded.[15] In our experience, four out of seven asymptomatic patients subsequently became symptomatic and therefore we agree with Madera *et al*.'s hypothesis.

In our series, all the patients were symptomatic and that too in poor Nurick grade. The etiology of the cervical myelopathy could be reducible AAD, in which frequent minor trauma to the spinal cord by the tip of odontoid during the flexion movement of the child leads to permanent damage.[15] None of the patients had a prior history of trivial trauma, sudden onset deterioration, or features suggestive of recent onset lower cranial nerve involvement.

The timing of surgical intervention depends on the degree of kyphosis, presence, or absence of C1–C2 instability and neurological status of the patient. Some authors also have shown that prophylactic fusion has better neurologic consequences compared with fusions performed after neural compromise.[16] Ain *et al*. recommended instrumentation even for the asymptomatic patient, if the spinal cord space is 8 mm and for patients with 5 to 8 mm of cervical instability with evidence of spinal cord impingement or damage on flexion-extension radiographic imaging and magnetic resonance imaging.[17]

Our results show that the progression of disease halted upon, after surgical intervention. In a median follow-up of 8.5 months, with four patients of follow-up 18–86 months, we did not found the progression of either kyphosis or spasticity. Only one of our patient required kyphosis correction after 1 year due to the progress of compression. Hence, we recommend early fixation of the cervical spine to avoid the ill effect of trivial trauma, as the majority of cases in the literature show an acute-onset quadriparesis after the history of fall.

### Posterior fixation only versus 360° approach for sub-axial cervical kyphosis

Single-stage 360° fixation (corpectomy with implant or graft anteriorly along with C1/occipital plate to C6 fixation) is a popular option, tailored to the complexity of cervical sub-axial spinal involvement.[18] Moreover, the choice of approach depends on the familiarity of a surgeon with a corridor, the extent of radiological involvement, availability of pediatric intensivist, and age of the child. In a 360° approach, which corridor should be taken first is again a matter of debate. The proponents of the posterior-only approach showed that pedicle fixation provides the best stabilization biomechanically.[19] However, the success rate of posterior fusion is nearly 50% after 2 years of age.[20] Our surgical experience and review of the literature show a promising result after posterior fixation. Sakaura *et al*. proposed that an anterior approach entails the risk of spinal cord injury, especially during decompression maneuvers.[5] Even the authors who recommend 360° fixation, failed to demonstrate any substantial improvement.[18,21] Anterior spinal fusions alone are not advised in young children with LS, owing to high risk for spinal cord injury and an arrest of anterior growth.[5] Exceptionally, in patients with severe CK with fixed variety and myelopathic symptoms, an anterior decompression along with circumferential fusion is beneficial. The sub-axial vertebrae in LS are bullet-shaped, comparatively thin, and have large intervertebral spaces. If surgical intervention is done at an early age and considering the need for long-segment fixation, then and there, we believe that the progression of CK may stop.[20,22,23] In two of their three patients, Johnston *et al*. reported that kyphosis transformed into cervical lordosis after 6 years.[14] In our series, only one patient has such long-term

follow-up (7-years), so such reported transformation is still a possibility [Figure 3].

### Literature review of all Larsen syndrome with cervical or craniovertebral junction instability

We reviewed nearly all the cases reported in the literature and found that the patients of LS invariably present as two types.[22-30] The first group of patients present early (at birth or neonatal period) and has as typical facies, multiple joint anomalies or cleft lip, while the cervical or thoracic kyphosis is noticed in clinical evaluation. The kyphosis may subsequently progress and warrants surgical intervention [Table 2]. The second group of patients present in adolescent or adult age, with quadriparesis and required surgical intervention [Table 3]. These patients may or may not have a history of trivial trauma. The patients presenting in early age, irrespective of the severity of myelopathy or an early surgical fixation, usually show disease progression. Their surgical outcome is not good due to multiple system comorbidities. On the other hand, the patients who presented late [as in Table 3] and were operated in poorer Nurick grade after surgery, but show a halt in their disease progression. The outcome was good, may be due to a lack of systemic abnormalities. It means that the prognosis depended on not only the timing of surgery but also on the co-existing systemic pathologies affecting the child's functionality. Although the median Nurick grade did not change, the requirement of anti-spasticity drugs, neck pa, and self- care was improved.

### Functional outcome of these patients

Patients with LS and their parents suffer significant psychological stress. The children require repeated hospital visits, are bedridden and are always susceptible to death. Surgical fixation removes danger of trivial trauma and ensures a halt in progression of myelopathy. In our study, all the parents were satisfied after surgery with the median satisfaction score of two, at follow-up. Four patients (case no. 2, 3, 4 and 6) were less satisfied (median PSS = 3), which could because of operative site pain, difficulty to ambulate, and comparatively lesser follow-up. Schooling is disturbed among these patients and social involvement gradually deteriorates. We are assessing these children with psychological counseling and vocational training modules but results are still not promising. None of our patients had mental retardation and growth is also unrestricted. Therefore, we believe that a preoperative psychological counseling may be helpful.

### Limitations of the study

Being a rare subset, the sample size of the study was less. Detailed genetic assessment for each child could not be possible due to their low socioeconomic condition. A longer follow-up to access the disease progression may provide a better meaningful conclusion.

## CONCLUSION

CVJ instability in LS is rare and surgically challenging. The syndrome may present with or without cervical myelopathy,

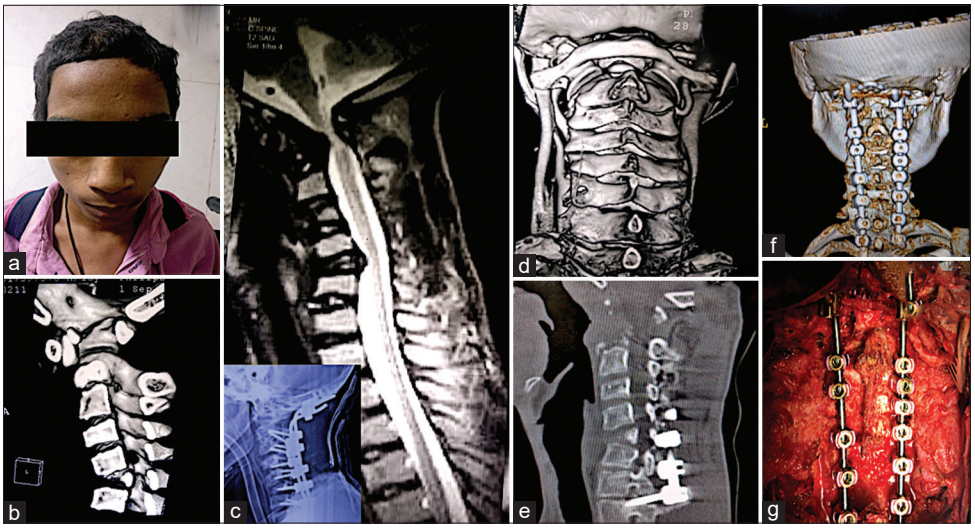


**Figure 3: A patient of Larsen syndrome with "dish-like" facial features (a); three-dimensional computed tomography sagittal view (b) and preoperative magnetic resonance imaging sagittal view (b) showing os-odontoidium with subaxial (C-6) vertebral body collapse with compression at craniovertebral junction; three-dimensional computed tomography reflected vertebral artery anomaly (right side vertebral artery hypoplasia with black arrow) (d); the postoperative CT scan showing long-segment cervical fixation with correction of cervical kyphosis and widened canal diameter at C6 level (e and f), and intra-operative photograph (g) showing long-segment fixation. The picture-in-picture shows X-ray immediately after surgery showing straightening of cervical spine**

**Table 2: Review of all surgically-managed, adolescent or adult-onset cases of Larsen syndrome with cervical kyphosis (*n*=9)**

| Author (year) | Age in years/sex | Syndromic feature | Preoperative | Surgery | Postoperative | Follow-up |
|---|---|---|---|---|---|---|
| Muzumdar *et al*. (1977)[28] | 13.5/NA | NA | History of fall<br>Bilateral numbness and weakness of all four limbs | Cervical decompression | NA | Minimal improvement later deteriorated |
| Johnston *et al*. (1996)[14] | 12/NA | NP | Myelopathy<br>Weakness | 360° fusion | NA | No improvement |
| Banks *et al*. (2003)[29] | 13/NA | NA | History of fall<br>Myelopathy<br>Quadriparesis | Posterior C1-T1 fusion, anterior cervical decompression and fusion 4 days later | | Halo vest and then hard cervical collar, no improvement |
| Menezes and Vogel (2008)[27] | 17/female | NP | Intermittent occipital headaches<br>Paresthesias in her upper extremities<br>Radiographs revealed Atlantoaxial instability with abnormal odontoid process with Os Odontoideum | Occipital to C3 fusion | NA | NA |
| Mohindra and Savardekar (2012)[26] | 17/male | Previously treated for right elbow dislocation and cubitus valgus deformity<br>"Facies scaphoidea" or "Dish faces" | Bedridden with spastic quadriparesis | Ventral decompression (trans-oral route) - Lower third of C2 body and complete C3 body was drilled away<br>Followed by rigid bony union, using screws in occipital squama, left pedicle of axis, and both the pedicles of the fourth cervical vertebra | Improved to ambulatory state | At 18 months of follow-up, patient has normal power in all four limbs, minimal spasticity and normal bladder control |
| Roopesh Kumar *et al*. (2013)[25] | 36/female | NP | Progressive stiffness of limbs during the past 6 months<br>Clawlike deformity of both hands with nontapering fingers<br>Frontal bossing<br>Hypertelorism<br>Widened nasal bridge<br>Kyphotic deformity at C2-C3<br>Increased atlantodental interval | Two stage surgery<br>First-stage via an anterior cervical approach - C3, C4 corpectomy<br>AAD corrected - The C1-C2 joint capsule was opened | Uneventful and patient was mobilized on the second postoperative day | At 6th month, remains neurologically intact |
| Yonekura *et al*. (2015)[30] | 18/- | Postcervical arthrodesis at age of 3 years | Airway obstruction and repeated aspiration pneumonia | Anterior mediastinal approach, tracheostomy | Uneventful | No deficit |
| Sahoo *et al*. (2016)[13] | 56/male | NP | Neck pain radiating to occiput<br>Progressive spastic quadriparesis for last 12 months | Posterior reduction with fusion of C1-2 (C1 lateral mass and C2 pedicle screw) | Uneventful | At a 12 months-follow-up, able to carry out his daily activities independently |
| Deora *et al*. (2020)[21] | 15/male | NP | Neck pain<br>Spastic quadriparesis | Transoral decompression followed by Occipital-T1 fusion | Uneventful with Hard cervical collar | Improvement in power and spasticity |

but an early surgical fixation shows better clinical outcome outcomes in the disease progression. In the preoperative planning, one should consider sub-axial kyphosis and the site of maximum cord compression.

## Financial support and sponsorship

Nil.

## Conflicts of interest

There are no conflicts of interest.

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**Table 3: Review of all surgically-managed, early-onset cases of Larsen syndrome with cervical kyphosis (*n*=15)**

| Author (year) | Age in months/sex | Disease progression | | Preoperative | Surgery | Postoperative | Follow-up |
|---|---|---|---|---|---|---|---|
| Johnston *et al*. (1996)[14] | 10/NA | NA | NA | No deficit | Postcervical fusion, patient fall, Second anterior decompression and fusion | Minerva jacket and halo vest | Improvement to walking |
| | 14/NA | NA | NA | No deficit | Posterior fusion | Halo vest | No deficit |
| | 14/NA | NA | NA | No deficit | Posterior fusion | Minerva jacket | No deficit |
| | 16/NA | NA | NA | No deficit | Posterior fusion | Minerva jacket | No deficit |
| Luk and Yip (2002)[31] | 96/NA | NA | NA | No deficit | Anterior T12-L3 fusion and anterior decompression and fusion, patient fall in follow-up, then posterior fusion | Halo vest | Transient weakness, later no deficit |
| | 72/NA | NA | NA | Myelopathy | Posterior C1-T1 fusion, anterior cervical fusion | Halo vest | Myelopathy resolved after 1st anterior cervical fusion |
| Katz *et al*. (2005)[23] | Birth/male | In neonatal period - globally hypotonic Required ventilator support and tracheostomy MRI - cervical kyphosis for which child was put on traction | Traction continued upto age of 2 years At age 13 months, child was bed ridden traction continued upto 3 years age | No further information | No further information | NA | NA |
| | 24/male | Diagnosed with Larsen's syndrome shortly after birth | At 2 years age, cervical kyphosis worsened, child developed spastic quadriparesis | | At 2 years age, posterior spine fusion from C4 to T1 - unsuccessful - continued on halo vest for 8 months - C2 to T3 decompression and fixation | | Improved dramatically in the lower but weakness persisted in C5 and C6 |
| Kaya *et al*. (2006)[24] | 72/female | Operated nine times on multiple deformities of extremities | | Progressive paraparesis, urinary incontinence and difficulty in swallowing | Pedicle screws into the C2, C4, C6, T1, and T3 vertebrae | Uneventful | After 3 months, she was able to walk and had full control of urination |
| Sakaura *et al*. (2007)[5] | 34/male | At birth, bilateral dislocations of the hips and knees, equinovarus deformities of the feet and typical face | At 9 months age, Minerva brace was given for progressive cervical kyphosis and quadriparesis | Child became severe quadriparetic with sleep apnea and recurrent respiratory infections by 2 years age | Anterior decompression with corpectomies of C4 and C5, and arthrodesis from C3-C6 using tibial strut bone grafts was performed *via* a lateral approach | Posterior dislodgement of bone grafts on postoperative day 4 Anterior revision surgery was done with posterior spinal fusion | NA |
| | 58/female | At birth, dislocations of both knees, equinovarus deformities of the feet, thoracolumbar kyphoscoliosis, and a "Dish face" | At the age of 1 year and 5 months, 51° cervical kyphosis from C3-C5 with hypoplastic C4 vertebra was identified | Radiography at 4 years 10 months revealed progression of the kyphosis to 60°, motor weakness was not present | PSF from C3-C5 was performed using tibial bone grafts | NA | NA |
| | 10/male | At birth, bilateral dislocations of the elbows, hips and knees, equinovarus deformities of the feet and typical face | At 10 months of age, posterior arthrodesis from C2-C7 was performed but kyphosis progressively worsened | Despite immobilization, the patient deteriorated with sleep apnea | Anterior decompression by C4-C5 corpectomy and fixation by lateral approach | NA | NA |

*Contd...*

**Table 3: Contd...**

| Author (year) | Age in months/sex | Disease progression | | Preoperative | Surgery | Postoperative | Follow-up |
|---|---|---|---|---|---|---|---|
| Madera *et al*. (2008)[15] | 30/male | Subglottic stenosis, capsulotomy for bilateral skew foot deformities | Worsening of cervical kyphosis but child was asymptomatic | Followed for 2 years; kyphosis worsened | C-3 and C-4 corpectomies and C1-C6 fixation with cross links posteriorly | Horner syndrome; Halo vest for 18 weeks; then Minerva brace for 4 weeks | Improvement |
| Crostelli *et al*. (2009)[7] | 17/male | NA | NA | NA | NA | NA | NA |
| Kaissi *et al*. (2016)[11] | 30/male | bilateral dislocation of the hips associated with massive acetabulo-femoral dysplasia<br>Genetic tests showed mutation of the *FLNB*-gene, typical facies, cleft lip | Orthopaedic intervention has been started at age of 2 months<br>At age of 8 months, a percutaneous dorsal release of the Achilles tendon was performed | Cervical kyphosis worsened progressively | Laminectomy of C5-C7 with dorsal spinal fusion (spondylodesis) of C3-7 | NA | NA |
| Ameri *et al*. (2016)[18] | 12/male | Undergone several corrective surgeries for knee, hip and foot deformities | At 2 years, scoliosis was surgically managed<br>At the same time, cervical kyphosis was observed and monitored | At 4-5 years, child developed motor deficit | C4-5 corpectomy and the C3-C6 posterior rod-hook fixation | During posterior approach the anterior allograft was failed, then a fibular strut graft was adjusted again | Initiation of neurological symptoms led to the subsequent C6-T2 cervico-thoracic fusion surgery |

MRI - Magnetic resonance imaging; NA - Not available; PSF - Posterior fixation


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