A comparative study between preoperative and postoperative conventional autonomic functions in congenital craniovertebral junction anomalies

ABSTRACT

Background: Autonomic nervous system (ANS) is invariably affected by craniovertebral junction (CVJ) anomalies. The usual presentation is sudden after trivial trauma. When symptomatic, most of this autonomic dysfunction is clearly elicited clinically with bedside tests. Nonetheless, ANS functionality in relatively less symptomatic or asymptomatic patients is not known as no studies exist.

Methodology: We performed a longitudinal prospective study of 40 less symptomatic patients who underwent surgery with conventional autonomic function tests (AFT) in pre- and post-operative periods. Correlation of its association with such anomalies is studied.

Results: All 40 had both pre- and post-operative clinical follow-up, pre-operative AFT, whereas only 22 patients had follow-up AFT. The mean age for the group was 32 years and male: female ratio was 2.3:1. Mean Nurick's grade was 1.8, whereas Barthel's index was 83.75%. Clinical improvement was seen in almost 98% at follow-up. Orthostatic test showed a significant association with Nurick's grade. Barthel's index was significantly associated with degree of compression. The mean follow-up was 17.4 months. Most conventional AFTs were significantly decreased in the preoperative period ($P \leq 0.01$). Both parasympathetic and sympathetic tone improved on follow-up with better improvement later. Overall clinical involvement of ANS was seen in 22.5% whereas subclinical involvement in the form of AFT impairment was seen in 100%.

Conclusion: There is a definite involvement of subclinical ANS in all patients of CVJ anomalies irrespective of their symptomatology. Knowing the extent of involvement in the preoperative period can help prognosticate, prioritize regarding surgery as well as correlate with the extent of improvement.

Keywords: Congenital craniovertebral junction anomalies, parasympathetic and sympathetic dysfunction subclinical conventional autonomic dysfunction

INTRODUCTION

Craniovertebral junction (CVJ) anomalies are spectrum of developmental anomalies that encircle and enclose compact neurological structures of complex neurophysiology. Death in such cases may be either due to cardiovascular collapse following loss of proper coordination of autonomic functions or due to lung atelectasis secondary to compromised pulmonary functions. Overt autonomic dysfunction is not found in CVJ anomalies unless faced with trivial trauma and hence laboratory assessment of subclinical autonomic nervous system (ANS) is warranted. Conventional autonomic function test (AFT) has been used in multiple studies of compressive myelopathy to report subclinical respiratory and autonomic dysfunction.[1-4]

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There are no studies to demonstrate the same in relatively less symptomatic CVJ anomalies. Having documentation of subclinical autonomic dysfunction in early stages of the disease can guide regarding disease progression as well as prioritize regarding timing of surgery. So also prolonged ventilatory support which may be needed in delayed or late disease can be avoided if the progression of these subclinical dysfunctions is properly documented. Thus, serial watchful documentations of autonomic functioning is necessary. Additionally, study also hypothesizes that clinical improvement at follow-up should lead to equivalent improvement in ANS, thus helping predict prognosis in preoperative period.

METHODOLOGY

The span of study is from October 2015 to June 2020-6 years, and the study type is observational prospective study

All consecutive patients presenting to NIMHANS hospital with history, clinical findings, and imaging suggestive of craniovertebral junctional anomaly were included in the study. Patients with chronic clinical conditions like chronic kidney disease/chronic diabetes/cardiac disease which can alter autonomic functions were excluded. Additionally patients with history of trauma, worse clinical grades, on medications like sympathomimetic drugs/ B blockers etc which affect autonomic functions were also excluded to avoid bias and unnecessary skewing of results. A proper consent was taken before patient underwent the tests and patient/patient's relatives were explained in detail regarding the investigation. Furthermore, secret identification numbers were assigned to each patient so that none of their information is shared or leaked apart from the purpose of this study. A detailed clinical questionnaire [Appendix 1] was used for collecting data. Postoperative evaluation included only clinical examination in immediate postoperative period ranging from 1 to 7 days and delayed assessment minimum at 3 months and during subsequent follow-ups.

Pretesting preparation

The tests were carried out in AFTs laboratory in the department of neurophysiology under all standardized conditions. As there are geographical, racial, gender, age differences, and occupation, we took age-adjusted controls from same geographical region for comparison. Forty patients with congenital CVJ anomalies and relatively asymptomatic or mildly symptomatic were selected for the study. Only 22 patients were available for follow-up in person. Rest was present for follow only on telephone. Hence, preoperative autonomic functions were compared with 40 age-matched normal controls; whereas pre- and post-operative autonomic functions were compared for 22 patients available for follow-up. Clinical comparison between preoperative and postoperative follow-ups was done for 40 patients either in person or telephonically in consultation with local physician. We included 5 conventional autonomic tests for our study based on the protocol of Ewing and Clarke.[5]

Deep breathing difference test

Deep breathing difference (DBD) shows the respiratory sinus arrhythmia, which is a function of the vagus nerve (parasympathetic). It is usually calculated from the
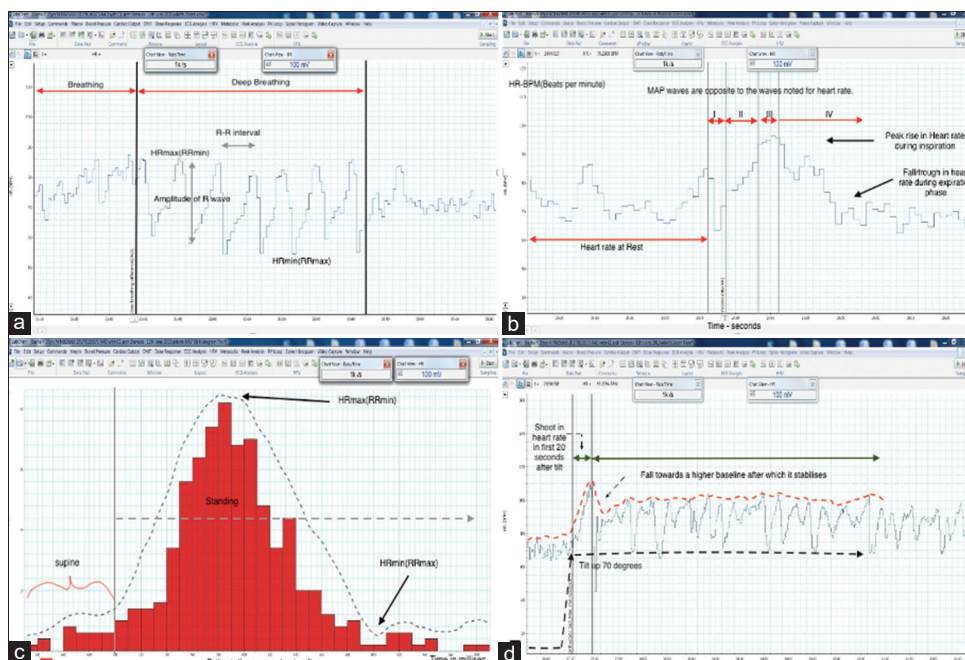

Figure 1: (a) A normal Patient performing Deep breathing manoeuvre. In above patient Vagal tone is intact, (b) Patient performing Valsalva manoeuvre, VR showing various phases (I to IV), c) and d) Normal patient's Heart rate recording during orthostatic test. VR: Valsalva ratio

average or mean of the differences between maximum heart rate during inspiration and minimum heart rate during expiration of six cycles [Figure 1a]. To rule out bias or shifts from outliers such as ventricular ectopics, median, and interquartile ranges were used in our study to signify true association. Values: >15 normal, 11–14 borderline, <10 abnormal.

Valsalva maneuver
Patients were asked to blow out and maintain the intrathoracic pressure at 45 mmHg for 15 s [Figure 1b]. The ratio between the highest heart rate (HR_{max}-reflecting the result of strain) generated during the maneuverer and slowest heart rate (HR min-reflecting the bradycardia response to overshoot) with 30 s of highest peak was taken as Valsalva ratio (VR). The highest of three trials is usually taken as VR; ≥1.21-normal, 1.11–1.20-mild stress and ≤1.10-severe stress. Higher the stress, more is the sympathetic surge signifying either parasympathetic paralysis, sympathetic oversurge or sympatho-vagal imbalance.

Isometric handgrip test
Patients were asked to maintain the handgrip at one-third of maximal voluntary contraction (30%) for up to 5 min, and the heart rate and blood pressure changes at prerelease were compared with the baseline values. The diastolic blood pressure (DBP) should rise more than 15 mm Hg. Persistent muscle contraction causes blood pressure and heart rate to increase → exercise reflex → parasympathetic activity decreases → increased sympathetic activity.[6] Values: >15 normal, 11–15 borderline, <10 abnormal.

Orthostatic test/tilt table test (OST)
It records heart rate and blood pressure variability of patients during postural changes [Figure 1c and Figure 1d]. Initially, 5–10 min baseline HR and BP were recorded in supine position. Then, the patient was tilted slowly in 70° position over a period of 10 s after which BP was recorded continuously till 5 min in the brachial artery. Any systolic blood pressure (SBP) fall more than 20 mm hg or DBP >20 mmhg over 3 min of tilt was considered abnormal. A heart rate increase of more than 30 bpm (beats per minute) or total heart rate more than 120 bpm was also considered abnormal. values: <10 normal, 11–29 borderline, and >30 abnormal

OST ratio
30:15 ratio is ratio of RR interval at 30th beat and 15th beat. OST generally involves ratio of either maximum to minimum RR intervals or maximum to minimum heart rates in 1st 3 min after tilt. This is to bypass inter-operator variability which can occur in 30:15 ratio and also confounding that occurs with ventricular ectopics. Like 30.15 ratio, generally, values more than 1 are considered normal, whereas values <1 are considered to have affected sympathovagal tone.

Statistics (SPSS 26.0 IBM Corp. Released 2019, Armonk, NY: IBM Corp, Stata 15.0, MedCalc 19.1.6, and Systat 13.0)
Descriptive statistical analyses were carried out in the present study. Results on continuous measurements were presented in mean standard deviation and results on categorical measurements were presented in number (%). Significance was assessed at 5% level and 95% confidence intervals. Mean, median, and interquartile range all were used wherever appropriate to find association between variables. Nonparametric tests (Kruskal–Wallis Test and Wilcoxon-Mann–Whitney U Test) were used to make group comparisons where data were not normally distributed. Chi-square test was used to explore the association between various clinical and autonomic subgroups along with age and gender. Parametric tests such as *t*-test and Paired sample *t*-test were used to make group comparisons and explore the difference at the two-time points in normally distributed data. Paired Wilcoxon test was used to explore the difference at the two-time points. Stuart–Maxwell test was used to assess the change in Nurick's Grade between the two-time points. To test for the strength of association between various groups Kendall's Tau, Cramer's V, and Bias Corrected Cramer's V were used. Only DBD variables were normally distributed whereas all other groups were not.

RESULTS

A total of 70 patients were screened for the study. Out of which 20 patients had a definite history of trauma, hence were excluded. Out of 50 patients, 10 were not included as they were lost to follow-up. Of 40 patients studied, 22 patients underwent both preoperative and postoperative conventional AFT with minimum follow-up of 3 months.

Demographic characteristics of patients
Twenty-eight patients were male. The mean age for the group was 32 years with least age being 8 years and maximum age being 75 years old [Table 1]. Only 3 patients were below the age of 16 years (2 were 11 years old and one was 8-year-old). Preoperative sphincter disturbances were present in 9 (22.5%) patients of which 5 improved at follow-up, 2 remained same and 2 deteriorated.

Nurick's grade and Barthel's index
Seventy-five percent (30 patients) had improved in both Nurick's and Barthel's Index at follow-up [Figure 2]. 17.5% (7 patients) showed immediate improvement in the postoperative period. As shown in [Table 2], the degree of Nurick's grade was not strongly associated with AFT dysfunction. In fact apart from grade 0, all were significantly affected. Even the degree of compression did not play a significant role in ANS signifying an early development of subclinical ANS

Table 1: Demographic characteristics of patients (n=40)

	n/frequency (%)
Occupation	
Student	5 (12.5)
Labourer/farmer	12 (30.0)
Private employee	18 (45.0)
Unemployed	5 (12.5)
Total	40 (100.0)
Symptoms	
Neck pain	31 (77.5)
Neck tilt	8 (20)
Neck movement restriction	24 (60)
Difficulty walking	25 (62.5)
Stiffness of limbs	21 (52.5)
Weakness of limbs	29 (72.5)
Progressive weakness	24 (60)
Sensory symptoms	23 (57.5)
Signs	
Head tilt	9 (22.5)
Short neck	32 (80)
Low hairline	26 (65)
Neck movement restriction	24 (60)
Papilledema	0
Nystagmus	3 (7.5)
Sensory	17 (42.5)
Posterior column involvement	20 (50)
Ataxia	16 (40)
Hand muscle involvement	12 (30)
Increased tone	29 (72.5)
Increased DTR's	38 (95)
Plantars	35 (87.5)
C2 Sensory Involvement/neuralgia	5 (12.5)

DTR's - Deep tendon reflexes

dysfunction irrespective of grade or stage (Barthel's index) of disease. As opposed to above, follow-up improvement in ANS was noted maximum in Grade 1 and Grade 2 as compared to Grade 3 and Grade 4 with improvement in orthostatic test showing significant association for Nurick's grades ($\chi2 = 11.975, P = 0.018$), reporting least improvement in Grade 4 group (Kendall's Tau = 0.22).

Radiological features

All the patients in our group had atlantoaxial instability. Thirty-five patients had both anterior and posterior compression, four patients had nonreducible and 36 patients had reducible AAD. C1 assimilation and basilar invagination were the most common CVJ anomalies associated with AAD. Thirty had severe and 8 had moderate canal stenosis.

Degree of compression

Most of the patients had severe decompression (80%) as per the classification given by Muhle *et al.*[7] and Kang *et al.*[8] into none, mild, moderate, and severe. There was nil significant association

between Nurick's grade and degree of compression [Table 3]; whereas a significant difference between the four groups in terms of Barthel's Index ($\chi2 = 12.098, P = 0.007$) was seen, with the mean Barthel's Index being highest in the degree of compression: none and mild group (Kendall's Tau = 0.48). As far as, AFT tests are concerned, none had a significant association with degree of compression.

Management

Ninety-eight percent (39 patients) underwent posterior decompression with fusion. None deteriorated in the immediate postoperative period of 7 days, 7 had improved in the immediate postoperative period. Ninety percent of the patients had improved both radiologically and clinically on minimum follow-up of 3 months whereas 5 had deteriorated out of which 3 underwent redo surgery and 2 refused redo surgery.

Preoperative traction

Eleven patients underwent preoperative traction, though 9 showed radiological reduction, clinical improvement occurred only in 2 patients.

Intraoperative vertebral artery injury

Eleven patients had intraoperative vertebral artery injury, 5 on left and 5 on the right side, whereas 1 patient had bilateral injury. None of these patients did poorly on follow-up as compared to other patients in the cohort. Even bilateral vertebral artery injury did well for 2 years after which she died due to unknown reasons.

Follow-up in months

All 40 patients had follow with mean follow-up being 17.4 months with 40% patients having follow-up of more than 12 months and 32% having more than 2 years.

Autonomic function tests
Deep breathing difference test

DBD, which signifies parasympathetic activity, was significantly decreased in all patients as compared to controls ($P = 0.015$) [Table 4]. During the postoperative follow-up period of 3 months, it showed improvement, but it was not significant ($P = 0.321$). It signifies that the parasympathetic tone related to respiratory rhythm is significantly affected as compared to age-matched controls. This parasympathetic tonal disarray is mostly subclinical as most of the patients remained largely less symptomatic. As shown in Figure 3, we report 2 patients having grossly high DBD values.It may suggest that few of these patients have an alerted respiratory dysfunction which is subclinical. As respiratory rhythm influences parasympathetic functioning, higher than normal values could well be encountered [Figure 3] but not
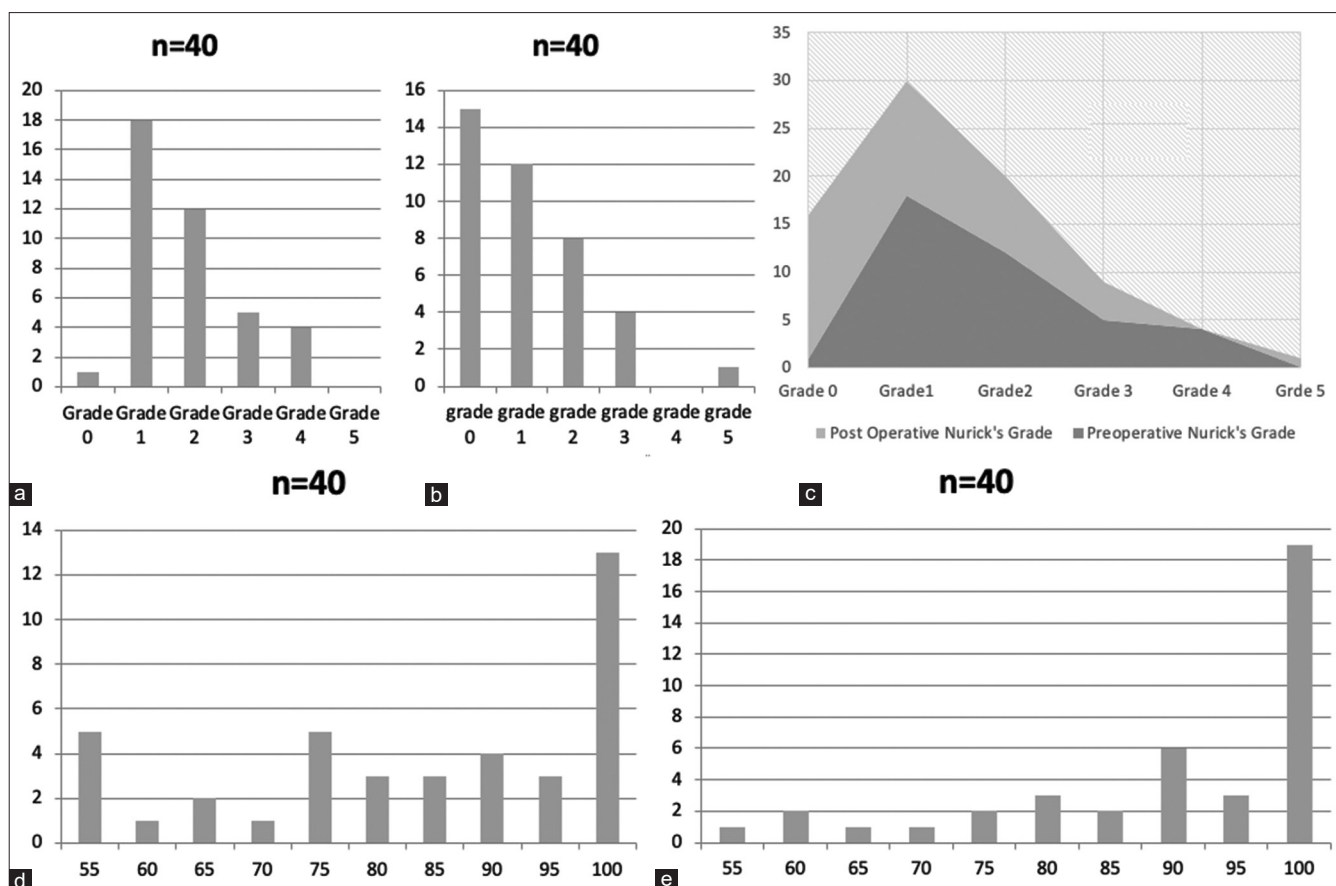
Figure 2: (a) 45% (18 patients) had a preoperative Nurick's grade 1 and 30% (12 patients) were grade 2, (b) shows Follow-up Nurick's grade at 3–6 months - 37.5% (15 patients) had grade 0, 30% (12 patients) - Grade 1, (c) depicts clinical improvement in 98% (39 patients), (d) 32.5% (13 patients) had preoperative Barthel's Index of 100, (e) follow-up Barthel's index at 3–6 months: 47.5% (19 patients) had 100 score
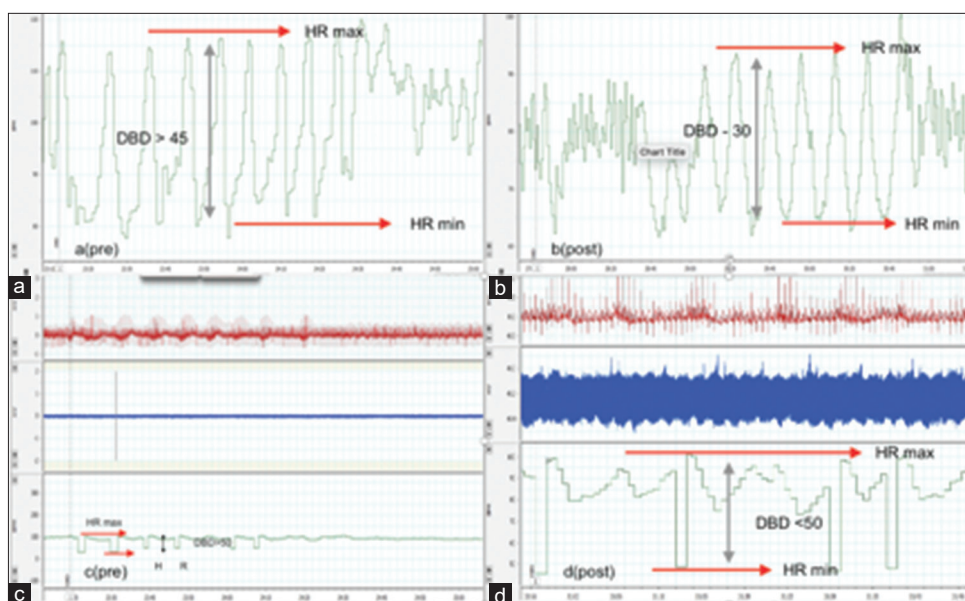
Figure 3: (a) shows DBD- shoot in heart rate and fall to be significantly higher as compared to in the follow up period (b). This suggests sympathovagal imbalance. Similar picture is noted in another patient (c). DBD to almost 50 with persistent higher values even in follow up period (d). Such overshoot can be explained with loss of parasympathetic contribution. DBD - Deep breathing difference

reliable. This may alter the dynamics of respiratory effect on parasympathetic tone causing spuriously high values which are maintained even in postoperative follow-up period. Furthermore, since there may be combined involvement of

Table 2: Association of Nurick's grade with various clinical and autonomic parameters

Parameters	Nurick Grade (baseline)					P
	Grade 0 (*n*=1)	Grade 1 (*n*=18)	Grade 2 (*n*=12)	Grade 3 (*n*=5)	Grade 4 (*n*=4)	
Age (years)	15.00±0	38.72±15.94	37.92±19.12	22.00±9.14	34.75±14.50	0.163[a]
Barthels index (baseline)	100.00±0	95.83±6.91	77.92±13.05	74.00±7.42	55.00±0.00	<0.001[a]
Degree of compression, *n* (%)						
None	1 (100.0)	0	0	0	0	0.189[b]
Mild	0	1 (5.6)	0	0	0	
Moderate	0	5 (27.8)	3 (25.0)	0	0	
Severe	0	12 (66.7)	9 (75.0)	5 (100.0)	4 (100.0)	
Clincial status (follow-up), *n* (%)						
Improved	0	15 (83.3)	8 (66.7)	3 (60.0)	4 (100.0)	0.366[b]
Status Quo	1 (100.0)	1 (5.6)	2 (16.7)	1 (20.0)	0	
Deteriorated	0	2 (11.1)	2 (16.7)	1 (20.0)	0	
Deep breathing difference (baseline)	46.60±0	18.55±7.64	19.66±10.14	29.23±14.54	20.77±10.84	0.220[a]
Valsalva ratio (baseline)	1.47±0	1.26±0.36	1.32±0.22	1.47±0.33	1.29±0.26	0.667[a]
Isometric handgrip test (Δ ↑DP) (mmHg) (baseline)	26.00±0	8.39±5.60	5.33±7.44	7.60±6.02	5.25±7.09	0.189[a]
Orthostatic test (maximum: minimum ratio) (baseline)	0.86±0	1.20±0.22	1.13±0.15	1.27±0.17	1.04±0.09	0.068[a]
Orthostatic Test (Δ ↓SP) (mmHg) (baseline)	−5.00±0	−0.44±8.61	−3.33±14.77	1.00±5.24	6.25±6.65	0.535[a]
Deep breathing difference (postoperative)	22.00±0	21.88±6.27	19.68±12.47	30.65±0.92	24.60±9.15	0.603[a]
Valsalva ratio (postoperative)	1.22±0	1.33±0.09	1.31±0.24	1.35±0.07	1.39±0.25	0.764[a]
Isometric handgrip test (Δ ↑DP) (mmHg) (postoperative)	0.00±0	11.58±3.03	11.50±9.04	6.50±9.19	10.33±8.96	0.590[a]
Orthostatic test (maximum: minimum ratio) (postoperative)	1.21±0	1.26±0.22	1.18±0.26	1.24±0.03	1.34±0.19	0.704[a]
Orthostatic test (Δ ↓SP) (mmHg) (postoperative)***	−6.00±0	−0.50±5.57	−13.00±10.89	5.50±3.54	8.67±5.86	0.018[a]

Significant at *P*<0.05, [a]Kruskal-Wallis Test, [b]Fisher's exact test. DP - Diastolic pressure; SP - Systolic blood pressure

sympathetic system, these values may not be reliable, and it may be more appropriate to confirm with other tests. Nonetheless, it proves sympathovagal imbalance.

Valsalva ratio test

This test assesses the functional integrity of afferent limb (vagus nerve), central processing, and efferent limb of the baroreflex (mainly sympathetic).[9,10] Valsalva maneuver itself does not specifically point out disturbance of sympathetic or parasympathetic tone. An adrenergic score comprising of Valsalva maneuver, orthostatic test usually forms a complete basis for delineating any sympathetic disturbance whereas parasympathetic disturbance is quite obvious on VR scores. In usual scenarios of gross autonomic dysfunction, sympathetic disturbances are evaluated by the tachycardia response during overshoot of phase 2 and withdrawal of this raised heart rate transitioning into bradycardia in phase 4. In our study, 12 patients lacked this or had a blunted response. During their mean blood pressure reading, they failed to show recovery (absent) of blood pressure at the end of phase 2 and phase 4 suggesting impaired vasoconstriction response in relation to respiration. Although it is not a conclusive test to demonstrate sympathetic activity, it does help to find out whether sympathetic function is affected qualitatively. VR was significantly decreased as compared to age-matched controls signifying moderate-to-severe stress [Figure 4], highlighting parasympathetic involvement. Follow-up VR showed some

improvement but was not significant (*P* = 0.523) [Table 4], although it remained to be significantly low than the control values (*P* = 0.001).

Isometric handgrip test

This test assesses the sympathetic activity.[9,10] A generalized increase in sympathetic activity as a result of the isometric exercise causes vasoconstriction which in turn causes an increase in diastolic pressure. There was a significant decrease in preoperative isometric handgrip values as compared to controls (*P* < 0.001). Isometric handgrip showed maximal improvement in follow-up period [Figure 5], but still remained significantly low than control values (*P* < 0.001) [Table 4]. These findings highlight that even though sympathetic functions are affected significantly in the preoperative period, they remain to be affected at follow-up of 3 months.

OST test

It has an afferent baroreceptor arm and efferent vasoconstrictor/vasopressor arm signifying parasympathetic and sympathetic functioning, respectively. No significance was noted in either preoperative or follow-up OST [Table 4] suggesting nil overt sympathetic failure. The fall in SBP more than 30 mm hg was present in 2 patients whereas more than 20 mmhg was present in 1 patient [Figure 6]. Total 3 patients were categorized of having orthostatic hypotension when compared to controls. On follow-up, only 1 patient had

Table 3: Association of degree of compression with various clinical and autonomic parameters

Parameters	Degree of compression				P
	None (*n*=1)	Mild (partial obliteration of the anterior or posterior subarachnoid space or >50% obliteration) (*n*=1)	Moderate (central canal stenosis with cord deformity but without spinal cord signal change) (*n*=8)	Severe (cervical cord compression or displacement or presence of spinal cord signal change near the compressed level on T2-weighted images) (*n*=30)	
Age (years)	15.00±0	11.00±0	36.50±14.00	36.60±17.08	0.203[a]
Nurick grade (baseline)					
Grade 0	1 (100.0)	0	0	0	0.189[b]
Grade 1	0	1 (100.0)	5 (62.5)	12 (40.0)	
Grade 2	0	0	3 (37.5)	9 (30.0)	
Grade 3	0	0	0	5 (16.7)	
Grade 4	0	0	0	4 (13.3)	
Barthels index (baseline)	100.00±0	100.00±0	96.88±5.94	79.17±15.76	0.007[a]
Clincial status (follow-up)					
Improved	0	1 (100.0)	6 (75.0)	23 (76.7)	0.270[b]
Status Quo	1 (100.0)	0	0	4 (13.3)	
Deteriorated	0	0	2 (25.0)	3 (10.0)	
Deep breathing difference (baseline)	46.60±0	20.00±0	20.75±9.80	20.43±10.35	0.457[a]
Valsalva ratio (baseline)	1.47±0	1.37±0	1.22±0.56	1.34±0.21	0.740[a]
Isometric handgrip test (Δ↑DP) (mmHg) (baseline)	26.00±0	3.00±0	4.88±5.17	7.73±6.60	0.222[a]
Orthostatic test (maximum: minimum ratio) (baseline)	0.86±0	1.91±0	1.14±0.10	1.16±0.16	0.132[a]
Orthostatic test (Δ↓SP) (mmHg) (baseline)	−5.00±0	12.00±0	−2.00±8.64	−0.47±10.98	0.330[a]
Deep breathing difference (postoperative)	22.00±0	13.00±0	23.13±7.39	23.18±8.16	0.658[a]
Valsalva ratio (postoperative)	1.22±0	1.22±0	1.36±0.09	1.34±0.16	0.448[a]
Isometric handgrip test (Δ↑DP) (mmHg) (postoperative)	0.00±0	8.00±0	13.60±4.04	10.20±6.10	0.326[a]
Orthostatic test (maximum: minimum ratio) (postoperative)	1.21±0	1.80±0	1.29±0.22	1.20±0.15	0.303[a]
Orthostatic Test (Δ↓SP) (mmHg) (postoperative)	−6.00±0	8.00±0	−3.80±5.54	−0.67±10.27	0.309[a]

Significant at $P<0.05$, [a]Kruskal-Wallis test, [b]Fisher's exact test. DP - Diastolic pressure; SP - Systolic blood pressure
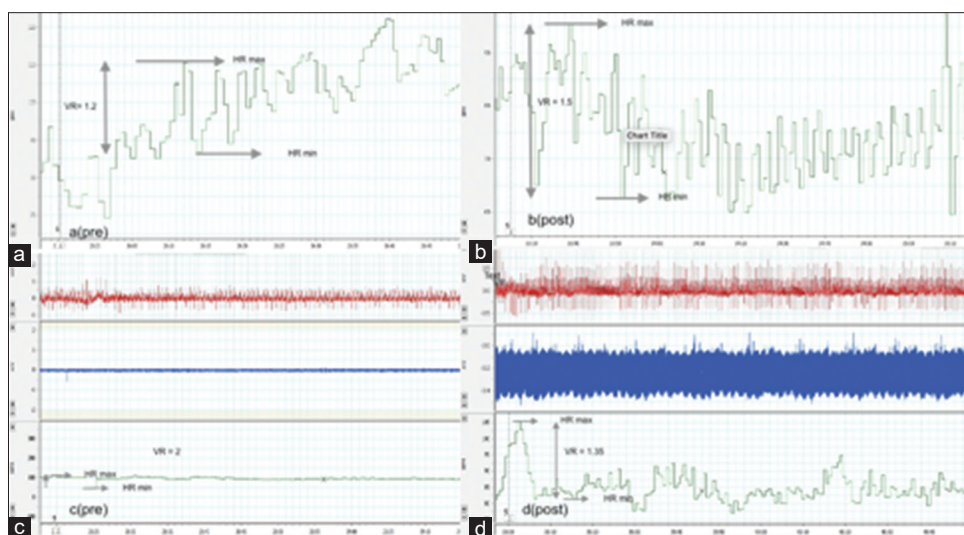

Figure 4: (a) VVR of 1.2 - severe stress, (b) VR of same patient at follow up is normal (1.5) i.e., no stress. This suggests gross parasympathetic paralysis. In 2nd patient the preoperative VR is 2.0 (c) which is normal, (d) Post-operative VR has decreased but still lies in normal range. This suggests no parasympathetic involvement. VR - Valsalva ratio

Table 4: Comparison of conventional autonomic function tests between controls versus preoperative values versus postoperative values

Autonomic function tests	Control values, mean±SD	Median (IQR)	Minimum–maximum	Patients (preoperative n=40) mean±SD	Median (IQR)	Minimum–maximum	P	Postoperative mean follow up at 3 months (n=22) (P value as compared to controls), mean±SD	Median (IQR)	Minimum–maximum	P
Deep breathing difference	26.73±9.45	24.04 (20.4-31.93)	9.68-54.02	21.14±10.68	20.40 (11.45-26.70)	3.4-47.0	0.015[b],***	22.65±7.72 (P=0.072[b])	22.00 (17.85-29.58)	6.3-35.0	0.321[b]
Valsalva ratio	1.52±0.25	1.46 (1.35-1.57)	1.21-2.16	1.32±0.30	1.32 (1.16-1.45)	0.0-2.0	0.001[a],***	1.33±0.14 (P=0.001[a])***	1.30 (1.23-1.39)	1.1-1.7	0.523[a]
Isometric handgrip test (Δ↑DP) (mmHg)	18.05±8.05	18 (11.75-23.25)	0-32	7.50±6.92	6.00 (0.75-11.25)	0.0-26.0	<0.001[a],***	10.41±5.98 (P<0.001[a])***	11.50 (7.25-14.50)	0.0-20.0	0.112[a]
Orthostatic test (maximum: minimum ratio)	1.48±0.25	1.48 (1.28-1.57)	1.07-2.16	1.17±0.19	1.12 (1.05-1.24)	0.9-1.9	<0.001[a],***	1.25±0.20 (P<0.001[a])***	1.21 (1.11-1.35)	0.9-1.8	0.404[a]
Orthostatic test (Δ↓SP) (mmHg)	3.12±5.30	3.5 (−0.25-7)	−9-16	−0.58±10.39	2.00 (−4.25-5.00)	−41.0-16.0	0.094[a]	−1.23±9.12 (P=0.049[a])***	−1.50 (−5.75-4.50)	−28.0-13.0	0.466[a]

***Significant at P<0.05, [a]Wilcoxon-Mann-Whitney U-test, [b]t-test, (−) negative denotes fall in SP. IQR was used for calculating significance due to negative values in mean and median. DP - Diastolic pressure; SP - Systolic blood pressure; IQR - Interquartile range; SD - Standard deviation

orthostatic hypotension. This suggests that most of the patients had subclinical autonomic dysfunction.

OST ratio (modification of 30:15 ratio) (sympathovagal balance)
Preoperative OST ratio was significantly affected (*P* < 0.001) [Table 4] as compared to controls. Although convincing improvement (*P* = 0.4) was noted, it remained significantly low (*P* < 0.001) than the control values. This shows that both sympathetic and parasympathetic improvement may occur with longer follow-ups following decompression.

Summary
Inference
Clinical involvement of ANS was seen in 22.5% (9 patients) of our patients whereas subclinical involvement in the form of AFT impairment was seen in 100%. Both sympathetic (Adrenergic score) and parasympathetic tone (Cardiovagal score-DBD + VR) were significantly affected in preoperative period. As OST was not affected significantly, it portends to lesser sympathetic dysfunction (Adrenergic score– OST + Isometric Handgrip Test [IHG]). Follow-up AFT demonstrated better gain in sympathetic parameters, although both reported early improvement.

DISCUSSION

The respiratory and autonomic dysfunction are considered to be the result of either repeated trauma to CVJ or by the pincer action on the cord by the bony anomalies.[4] Acute trauma may sometimes highlight the condition and present the patient to the clinician. Sudden death is known in such patients before they present to the clinician.[4] Postural hypotension is another manifestation that is quite common. Spinal cord injury is known to influence and affect cardiovascular output, a part of ANS.[11] But what about patients who are relatively asymptomatic? Not all patients present with overt clinical features to portend bedside autonomic clinical features. Most CVJ anomalies present with subtle clinical symptoms and signs ranging from neck pain, neck movement restriction, short neck, low hair line, stiffness or weakness of limbs, C2 neuralgia, torticollis, transient attacks of paresthesia/weakness/confusion/vertigo aggravated by neck movements.[4,12] The frequency of myelopathy in anomaly-related AAD varies from 40% to 100%.[13] Autonomic testing can not only provide the extent of ANS involvement but also signify prognosis of the patient; as worser the ANS dysfunction more chances of intraoperative and post-operative prolonged cardiovascular lability. In this respect, we conclusively found pan-subclinical autonomic dysfunction of both sympathetic and parasympathetic tone in all our patients with relative asymptomatic profile. Although degree
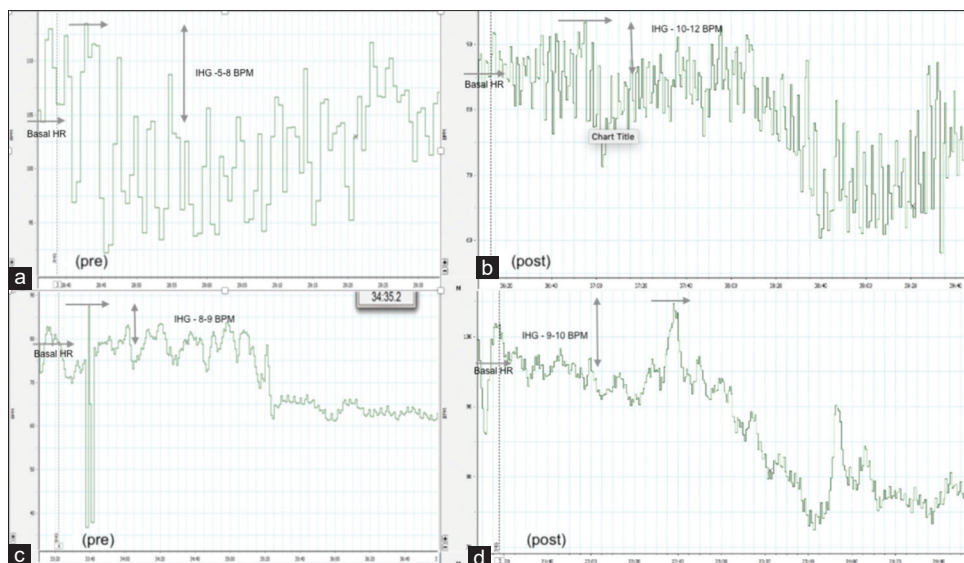
Figure 5: (a) Basal sympathetic drive is high. Rise in BPM after IHG in 1st min rises by 5 to 8 beats - significant sympathetic impairment, (b) follow-up shows a still high basal sympathetic drive of around 80 with rise in BPM after IHG of 10–12 beats in 1st min suggesting some improvement, (c) another patient with grossly affected IHG test and mild improvement in follow-up period (d). BPM - Betas per minute; IHG - Isometric Handgrip Test
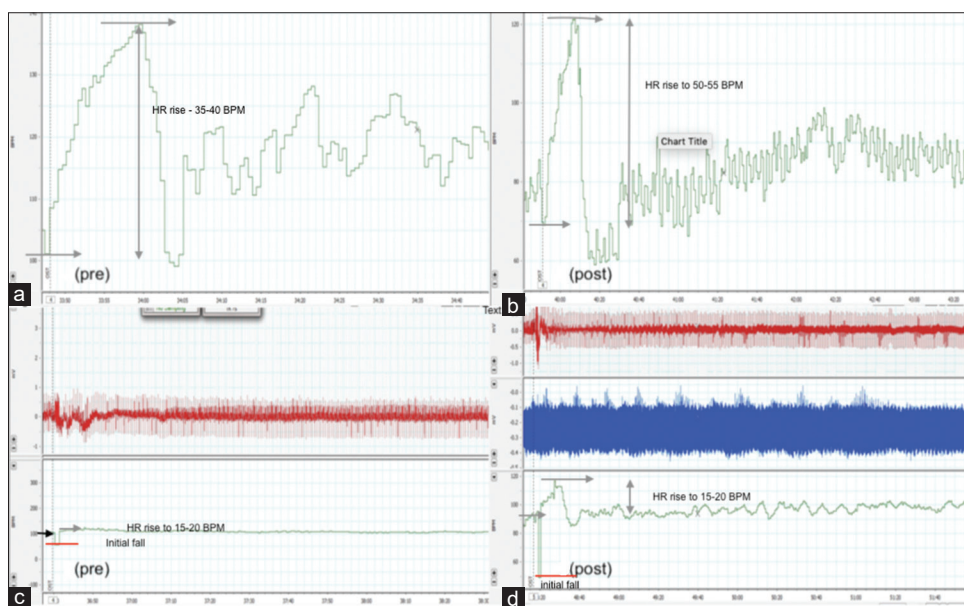

Figure 6: (a) Preoperative patient with significant orthostatic hypotension-increase in HR of 35–40 beats/min. HR >130bpm signifying parasympathetic baroreceptor failure (excessive HR rise) as per "VASIS" classification, (b) improvement in OST during follow-up with HR <120bpm, (c) another patient with "mixed" type I picture suggesting sympathovagal imbalance. An initial phase of blunted/reverse response and bradycardia followed by resurgence (in 1st 20 sec) to a higher baseline, d) follow-up period - minimal improvement. HR - Heart rate

of autonomic dysfunction was not used as criteria for surgery, it did help us prioritize patients requiring early surgery. As noted, we did not find any correlation between Nurick's grade and degree of compression with ANS dysfunction. Also in postoperative period again, there was nil significant association between ANS recovery and Nurick's grade or degree of compression. Thus, prioritizing patients for surgery based only on Nurick's grade and degree of compression may hamper overall outcomes. Furthermore, Barthel's index which signifies overall quality of life and highlights more

subtle clinical dysfunction was significantly associated with not only degree of compression but also ANS recovery in follow-up period. This outlines that Barthel's index provides a better picture of subclinical dysfunction in day-to-day life. Furthermore, it has better correlation with ANS dysfunction. This challenges the present prognostic and staging criteria. A better approach would be to evaluate the extent of subclinical ANS dysfunction, clinical grade, and degree of compression and then prioritize patients for surgery. We also found that clinical gain commensurates into equivalent

ANS improvement at follow-up helping predict outcomes in preoperative period. Thus, knowing AFT prior can affect the time of intervention and final outcomes.

In the searched English literature of PubMed, Scopus, Google Scholar, and Crossref database, we could not find any studies regarding subclinical AFT dysfunction in CVJ anomalies. Hence, we compared our study with AFT in compressive myelopathy by Srihari *et al.*[14] Table 5 shows a comparative data analysis of AFT in compressive cervical myelopathy and our study. Our mean age group is 32 years which is quite younger than in study by Srihari et al group. Most patients in our study had a better Nurick's grade of 1.8 than other study of 2.8 signifying that clinically our patients were less symptomatic. The follow-up improvement in our group in terms of Nurick's grade is better and significant than the other study signifying a better clinical outcome in patients with

better Nurick's grade at presentation. Sphincter disturbances in our series were almost half than Srihari *et al*. series which signify a more subtle subclinical presentation in our series. Also due to longer follow-up, we have an added advantage of documenting the trend in improvement of clinical versus autonomic functions which indeed show an improving trend in sympathetic functions. Srihari *et al*.'s study, however, showed a worser sympathetic tone in preoperative and significant improvement in 30:15 ratios signifying early return of parasympathetic functions. As opposed to theirs, our study showed exactly opposite results. Maximum improvement was noted in OST Max/Min ratio, IHG followed by DBD (a) suggesting better sympathetic improvement though not reaching significance [Figure 7]. All conventional AFT values remained significantly lower than control values even in the follow-up period.

Table 5: Comparison between 2 studies of autonomic functions, 1st one for cervical compressive myelopathy and 2nd one for cranio-vertebral junction anomalies

Studies	Mean age	Sample size	Nurick's grade (mean)		Valsalva ratio		Isometric hand grip (mm hg)		Deep breathing difference (beats/min)		30:15 ratio		Spincter disturbances Pre (%)	Mean follow up in months Post
			Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post		
Srihari *et al*.	44.5	29	2.8	2.7	1.3	1.27	10	12	14	13	1.19*	1.11*	51.7	3.9
Current study	32	40 preoperative, 22 - pre- and post-operative	1.8	1.1	1.32*	1.33*	7.5*	10.4**	21.1*	22.7*	1.17*	1.25*	22.5	17.4

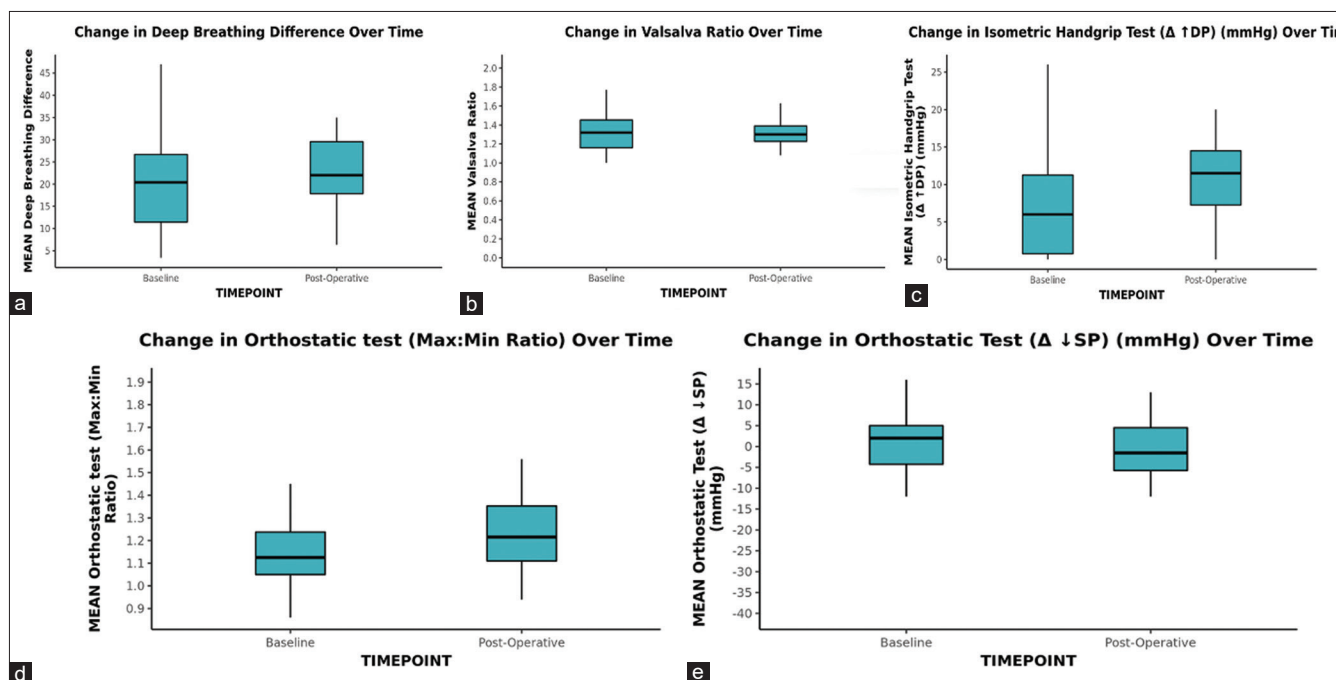*Significant at $P < 0.05$

Figure 7: The Box-and-Whisker plots depict the distribution of conventional AFT over different time points. In each box, the middle horizontal line represents the median, the upper and lower bounds of the box represent the 75th and the 25th centile, respectively, and the upper and lower extent of the whiskers represent the Tukey limits at each of the timepoints, respectively

Such gross difference of ANS involvement at two different levels of cervical spine is quite intriguing. This adds to our ever increasing complex understanding of CVJ which never fails to surprise. Does the neurovascular unit[15] and its reparative process differ in complexity or the anatomic orientation of parvocellular neurons is varied or the dorsolateral periventricular tracts of respiratory rhythm behave differently or the myelination of type "b" and "c" autonomic neurons has a role to play in this variation is far from understood. Also due to longer follow-up, we have an added advantage of documenting the trend in improvement of clinical versus autonomic functions which indeed show an improving trend in sympathetic functions.

CONCLUSION

What causes lesser involvement and better improvement in sympathetic tone can be explained by an alerted subclinical respiratory dysfunction which may alter or modulate the dynamics of respiratory effect on parasympathetic tone which remains affected even in postoperative follow-up period. We speculate that dysfunction of both respiratory and autonomic dysfunction is compromised in CVJ anomalies. However, it remains subclinical either due to compensation because of its chronic course or its inherent resistance in view of anatomical arrangement of fibers which are more medial than other major motor and sensory fibers. This theory is also supported by Toyoda *et al.*[16] Longer follow-ups may show complete recovery of sympathovagal balance. It is known that ANS controls heart rate variability and positional blood pressure.[9,10] Hence, subclinical autonomic involvement could be a predecessor to more clinical and life-threatening presentation.

Ethics approval
Taken from the institutional ethics committee for conduction of this study.

Availability of data and material– present– there is complete data transparency.

Patients' consent was duly taken to perform the tests and for surgery. For publishing this article none of patient's identity is disclosed. Hence no consent was required for preparing this manuscript.

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Conflicts of interest
There are no conflicts of interest.

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PROFORMA FOR DATA COLLECTION

Name/Neuro No :

Age: UHID :

Sex: Occupation :

Address :(Contact phone no:

Email Id:

Presenting Symptoms :(Duration :) ....

A.Neck pain	1. Yes 2. No
B.Neck Tilt	1. Yes 2. No
C.Movement restriction	1. Yes 2. No
D.Difficulty in walking	1. Yes 2. No
E.Stiffness of Limbs	1.None 2. Lower limbs 3. One side Limbs 4. All 4 limbs
F.Weakness of Limbs	1.None 2. Lower limbs 3. One side Limbs 4. All 4 limbs 5. Upper limbs Only
G.Transitory Attacks	1. Yes 2. No
	1a Paresthesia 1b Weakness
	1c Flexing neck forward 1d Others
H.Progressive weakness	1. Yes 2. No
I.Sphincter Disturbances	1. Yes 2. No
J.Sensory Symptoms	1. Yes 2. No
K.Comorbidities	1. Yes 2. No

Findings :

A.Health 1. Yes 2. No	
B.Short Neck	1. Yes 2. No
C.Low Hairline	1. Yes 2. No
D.Neck movement restriction 1. Yes 2. No	
E.Respiratory Reserve	1.Good 2.Affected yet Adequate 3. Poor
F.Spinal Deformity	1 Kyphosis 2.Scoliosis 3. None
G.Cranial nerves	1. Yes 2. No
H.Papilledema	1. Yes 2. No
I.Lower cranial nerves	1. Yes 2. No
J.Nystagmus	1. Yes 2. No

L.Posterior column Involvement   1. Yes   2. No

M.Ataxia   1. Yes   2. No

N.Paresis   1.Upper limbs 2. One side limbs 3. All limbs and trunk 4. No involvement

O.Hand Muscle Involvement   1. Yes   2. No

P.Increased Tone   1 Absent 2. Lower Limbs 3. One side Limbs 4. All Limbs

Q.DTR 's Increased   1 Absent 2 Lower Limbs 3. One side Limbs 4. All Limbs

R.Plantars   1.Upgoing 2. Downgoing 3. Not elicitable

S.C2 sensory impairment/neuralgia   1. Yes   2. No

Nurick Grade/Social Functioning Before treatment

0 sign or symptom of root involvement, but no evidence of cord disease

1 sign of cord disease but no difficulty walking

2 slight difficulty walking not preventing full-time employment

3 difficulty walking preventing full-time employment or ability to do all housework, but not so severe as to require someone's help to walk

4 able to walk with someone's help or with the aid of frame

5 chairbound or bedridden

THE BARTHEL INDEX
Activity Score
FEEDING
0 = unable
5 = needs help cutting, spreading butter, etc., or requires modified diet
10 = independent _____

BATHING
0 = dependent
5 = independent (or in shower) _____

GROOMING
0 = needs to help with personal care
5 = independent face/hair/teeth/shaving (implements provided) _____

DRESSING
0 = dependent
5 = needs help but can do about half unaided
10 = independent (including buttons, zips, laces, etc.) _____

BOWELS
0 = incontinent (or needs to be given enemas)
5 = occasional accident
10 = continent _____

BLADDER
0 = incontinent, or catheterized and unable to manage alone
5 = occasional accident
10 = continent _____

TOILET USE
0 = dependent
5 = needs some help, but can do something alone
10 = independent (on and off, dressing, wiping) _____

TRANSFERS (BED TO CHAIR AND BACK)
0 = unable, no sitting balance
5 = major help (one or two people, physical), can sit
10 = minor help (verbal or physical)
15 = independent _____

MOBILITY (ON LEVEL SURFACES)
0 = immobile or < 50 yards
5 = wheelchair independent, including corners, > 50 yards
10 = walks with help of one person (verbal or physical) > 50 yards
15 = independent (but may use any aid; for example, stick) > 50 yards _____

STAIRS
0 = unable
5 = needs help (verbal, physical, carrying aid)
10 = independent _____
TOTAL (0-100): _____

Radiology :
X ray

CT C spine

Ct angiogram

MRI

A.AAD	1.Reducible 2. Non-reducible
B.Rotary dislocation	1. Yes 2. No
C.Basilar Invagination	1. Yes 2. No
D.C1 Assimilation	1. Yes 2. No
E.Os odontoideum	1. Yes 2. No
F.Os terminale	1. Yes 2. No
G.Absent odontoid	1. Yes 2. No
H.Lateral mass anomaly	1. Yes 2. No
I.Lower Clivus anomaly	1. Yes 2. No
J. Klippel-Feil anomaly	1. Yes 2. No
K. Others	
L. Compression	1. Anterior 2.Posterior 3.Both 4. None
M. Degree of Compression	1.Mild 2.Moderate 3.Severe 4. None (After reduction)
N. Arnold Chiari Malformation	1. Yes 2. No
O.Syringomyelia	1. Yes 2. No
P. Traction	1. Yes 2. No
Q.Clinical improvement after traction	1. Yes 2. No
R.X ray Reduction after Traction	1. Yes 2. No

Management :
1.Anterior decompression   2. Anterior and posterior decompression with fusion
3. Posterior decompression and fusion. 4. Posterior fusion

Operative complications:

A.Durotear	1. Yes 2. No
B.Cord trauma	1. Yes 2. No

Postoperative complications:
1.open wound infection
2.Closed wound infection
3.Dislocation
4.Neurological deterioration
5.Others
6. None

Immediate Results :
1.Improved 2.Status quo 3. Deteriorated 4. NA

A.Muscle Power	1.Improved 2.Status quo 3. Deteriorated
B.Sensation	1.Improved 2.Status quo 3. Deteriorated
C.Spincter Involvement	1. Improved 2.Status quo 3. Deteriorated
Spasticity	1.Improved 2.Status quo 3. Deteriorated
E.Gait	1.Improved 2.Status quo 3. Deteriorated
F.Respiration	1.Improved 2.Status quo 3. Deteriorated

Outcome :   1. Alive 2. Dead
Follow up: 1. Yes   2. No

Clinical Status at follow up :

Duration in months ....

1.Improved 2.Status quo 3. Deteriorated 4. NA

A. Muscle Power

Right upper limb	1.Improved 2.Status quo 3. Deteriorated
Right lower limb	1.Improved 2.Status quo 3. Deteriorated
Right hand Grip	1.Improved 2.Status quo 3. Deteriorated
Left upper limb	1.Improved 2.Status quo 3. Deteriorated
Left lower limb	1.Improved 2.Status quo 3. Deteriorated
Left hand Grip	1.Improved 2.Status quo 3. Deteriorated

Spasticity(Modified Ashworth scale)

Right upper limb	1.Improved 2.Status quo 3. Deteriorated
Right lower limb	1.Improved 2.Status quo 3. Deteriorated
Left upper limb	1.Improved 2.Status quo 3. Deteriorated
Left lower limb	1.Improved 2.Status quo 3. Deteriorated
B.Sensation	1.Improved 2.Status quo 3. Deteriorated
C.Spincter Involvement	1.Improved 2.Status quo 3. Deteriorated
Spasticity	1.Improved 2.Status quo 3. Deteriorated
E.Gait	1.Improved 2.Status quo 3. Deteriorated
F.Respiration	1.Improved 2.Status quo 3. Deteriorated

Expired During Follow up :   1. Yes   2. No

Nurick's Grade/Social Functioning at last follow up   ....

THE BARTHEL INDEX   ....

Appendix 1: A detailed clinical questionnaire used for collecting data