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Original article

Occipito-atlanto-axial Hypermobility : Clinical Features and Dynamic Analysis of Cranial Settling and Posterior Gliding of Occipital Condyle.
Part 1 : Findings in Patients with Hereditary Disorders of Connective Tissue and Ehlers-Danlos Syndrome

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Abstract

Object : To investigate hereditary disorders of connective tissue (HDCT) and Ehlers-Danlos syndromes (EDS) that can present with lower brain stem symptoms attributable to occipito-atlanto-axial hypermobility and cranial settling, and relationship to Chiari malformation type I (CMI).

Methods : The diagnostic criteria for EDS and related HDCT were prospectively met by 155 patients. Osseous structures comprising the craniocervical junction were investigated morphometrically using reconstructed 2D-CT and plain x-ray images in 135 patients with HDCT・EDS and the results were compared to those in patients with normal controls (n=55).

Results : There were 124 cases (80%) in HDCT・EDS of CMI. The diagnostic features of HDCT・EDS with CMI had a greater incidence of lower brain stem symptoms and signs. The measured distances of the basion-dens interval (BDI), basion-atlas interval (BAI), atlas-dens interval (ADI), dens-atlas interval (DAI), clivus-atlas angle (CAA), clivus-axis angle (CXA), and atlas-axis angle (AXA) were the same in the supine and upright positions in normal controls. There was reduction of the BDI (3.3 mm), enlargement of the BAI (2.8 mm), and reduction of the CXA (10.8°), CAA (5.8°, $p<0.001$), and AXA (12.3°) upon assumption of the upright position. These changes were reducible by cervical traction.

Conclusions : Morphometric evidence of cranial settling, posterior gliding of the occipital condyles in the HDCT・EDS cohort suggests hypermobility of the atlanto-occipital and atlanto-axial joints. This hypermobility induces more prominent brain stem symptoms in patients associated with CMI. The patients with CMI have greater hypermobility of occipito-atlanto-axial joints.

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Key words

craniocervical instability, cranial settling, connective tissue disorders, Ehlers-Danlos syndrome, chiari malformation

Introduction

Hereditary disorders of connective tissue (HDCT) include a continuum of conditions caused by defects of extracellular matrix elements such as collagens, elastin or fibrillin[1,2]. The Ehlers-Danlos syndromes (EDS) constitute a distinct category within the HDCT group and are responsible for a wide variety of systemic manifestations including joint hypermobility, recurrent joint dislocations, skin laxity and fragility, poor wound healing, widened atrophic scars, and tendon and muscle rupture and kyphoscoliosis[3-6]. Despite a recently revised nosology

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for EDS[4], significant number of patients cannot be classified precisely. Some of these patients have an overlapping disorder with features of both EDS and Marfan syndrome. Marfan syndrome is distinguished by cardiovascular defects including mitral valve prolapse (MVP), aortic aneurysms that tend to rupture, skeletal abnormalities such as arachnodactyly and long limbs (dolicostenomelia), pectus deformity, dural ectasia, and ectopia lentis[7]. We have known that most patients of HDCT・EDS have characteristic symptoms and signs of the brain stem and upper cervical spinal cord. We reported a subset of patients with Chiari malformation which have been described the underdevelopment of the occipital bone and para-axial mesodermal insufficiency[8,9], in which varying degrees of craniocervical instability appeared[10].

We report the clinical feature of patients with HDCT・EDS, and a subset of patients with HDCT・EDS in which varying degrees of craniocervical instability appeared to be related to underlying occipito-atlanto-axial joints hypermobility. Furthermore we supporse that some patients with severe brain stem symptoms and signs have CMI.

Methods

1 Study population

The subjects of this study were 155 patients with HDCT・EDS who were evaluated consecutively between January 2004 and December 2007 in the Chiari Institute, North Shore University Hospital (**Table 1**). There were 123 females and 32 males who ranged in age from 15-56 years (mean age=31.1 years±8.4 SD) and in following up periods from 6-55 months (mean months=28.3 months± 11.9 SD) (**Table 1**).

2 Assessments

All patients underwent a physical examination, a complete neurological examination, cervical MRI, and measurement of articular mobility. Additional information was provided in some patients by whole neuraxis MRI, computed tomography (CT) of the head with 2D and 3D reconstruction, CINE-MRI, standup MRI, flexion and extension x-rays of the cervical spine, CT of the spine. The clinical disability of each patient was measured using the Karnofsky performance scale (KPS) of 0 to 100[11].

Table 1 Characteristics of patients

Variable	HDCT. EDS
No. cases	155
Age (years old)	31.1±8.4
range (years old)	15-56
Sex	
male	32
female	123
Follow up periods (months)	28.3±11.9
range (months)	6-55

HDCT: hereditary disorders of connective tissue, EDS: Ehlers-Danlos syndrome.

1. Hereditary disorders of connective tissue and Ehlers-danlos syndrome (HDCT・EDS)

Joint hypermobility was assessed using the Beighton score (BS)[3]. The scoring was derived as follows:

1) passive dorsiflexion of the little fingers of each hand beyond 90 degrees (one point for each hand)

2) passive opposition of the thumbs to the flexor aspect of the forearm (one point for each hand)

3) hyperextension of the elbows beyond 10 degrees (one point for each elbow)

4) hyperextension of the knees beyond 10 degrees (one point for each knee) and

5) forward flexion of the trunk with the knees fully extended so that the palms of the hands rest flat on the floor (one point).

A score of five or more points was defined as a positive test for joint hypermobility in post-pubertal persons. Tissue fragility was defined as the presence of one or more the following findings:

1) easy bruisability

2) history of poor wound healing

3) dystrophic scars having a thin and atrophic (papyraceous) appearance. Features of Marfanoid habitus such as tall stature and long limbs, arachnodactyly, asthenic appearance with low body fat, long thin face with malar hypoplasia, downslanting palpebral fissures, pectus deformity, and scoliosis were noted on clinical examination. The diagnosis of EDS and other HDCT was established on the basis of the BS, clinical examination, family history, and supplementary tests including echocardiography, MRI or CT angiography of the chest, abdomen and pelvis, bone densitometry, and skin biopsy for analysis of collagens. 155 patients were met to the criteria.

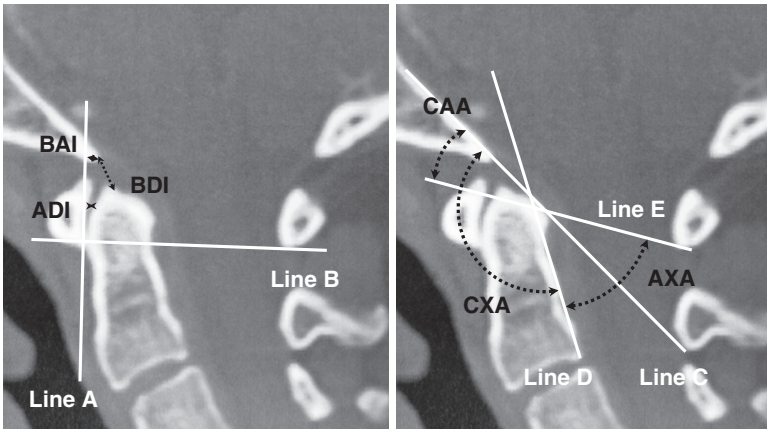

Fig. 1
Measurement intervals (left) and angles (right) for assessing osseous structures at the craniocervical junction on midsagittal reconstructed 2D-CT images of normal control.
Line A : plane of posterior surface of anterior arch of atlas, Line B : line drawn between the lowest point of the anterior arch of the atlas and the lowest point of the posterior arch of the atlas, Line C : plane of the surface of the clivus, Line D : plane of posterior surface of dens, Line E : line drawn between top of anterior arch of atlas and lowest point of posterior arch of atlas, BDI : interval between basion and top of dens, BAI : interval between basion and anterior arch of atlas (Line A), AXA : angle between atlas (Line E) and axis (Line D), CAA : angle between clivus (Line C) and atlas (Line E), CXA : angle between clivus (Line C) and axis (Line D).

2. Invasive cranial traction (ICT)

Patients with a clinical suspicion of craniocervical instability underwent a trial of invasive cervical traction (ICT). Cranial tongs were applied in the operating room under propofol sedation and local anesthesia. After the patient had awakened fully, ICT was performed with the patient sitting in 80° Fowler's position. The CCJ was distracted under fluoroscopic guidance using graduated weights, and a checklist of symptoms and neurological findings obtained immediately prior to testing were assessed as loading proceeded. Once an optimal level of relief had been achieved, permanent fluoroscopic images were obtained to compare morphometric measurements of osseous structures at the craniocervical junction (CCJ) in the supine, upright (sitting), and distracted positions.

3. Morphometric analysis of the craniocervical junction

Using reconstructed 2D-CT sagittal images and plain x-rays, osseous components of the CCJ were measured in 135 patients with HDCT・EDS/PTC and 55 age and sex-matched normal controls. Morphometric measurements in the two cohorts were compared in the supine, upright (sitting), and extracted positions.

Occipito-atlantal motion was measured using the method described by Wiesel and Rothman[12] with some modification ; occipito-axial motion was measured using the method described by Harris et al.[13,14] with some modification ; and atlanto-axial motion was measured using the method described by Rahimi, Ranawat et al.[15,16] with some modification. We established a means for assessing occipito-atlanto-axial motion by combining these methods with new measurements developed by us (**Fig. 1**). On saggital wiews, we measured the interval between the basion and top of dens (BDI), the interval between the basion and the posterior surface of the anterior arch plane of atlas (BAI), the interval between the posterior surface of the anterior arch of atlas and the dens (ADI), and the interval between the top of the dens and a line drawn between the lowest point of the anterior arch of atlas and the lowest point of the posterior arch of atlas (DAI). The following lines were established to assess osseous relationships. We calculated the angle between the atlas and axis (angle between line D and lineE) (AXA), the angle between the clivus and atlas (angle between line C and line E) (CAA), and angle between the clivus and axis (angle between line C and line D) (CXA).

3 Statistical analysis

Statistical analyses of clinical data were performed with SPSS for Windows (version 15.0 ; SPSS, Inc., Chicago, IL). Mean values are presented with their standard deviations. The incidence of associated abnormalities was analyzed using the chi-square test. Demographic differences between patients and normal controls were tested with nonparametric Mann-Whitney *U*-test. Comparisons of data with patients in the supine, sitting, and traction positions were tested with rANOVA. The distribution of the data was analyzed using the *F*-test. Significance was indicated by a two-tailed p value of less than 0.01.

Results

1 Clinical presentation of patients

Variations in the clinical presentation of HDCT・EDS with or without CMI are given in **Table 2**. Clinical symptoms and signs were very similar among HDCT・EDS patients. Compared to patients without CMI, those with the combined disorder experienced a greater incidence of lower brain stem symptoms including dysesthesia or numbness, sleep apnea and palpitations ($p<0.01$). Compared to patients without CMI, diagnostic distinctions in patients with CMI included an increased incidence of motor weakness and sensory disturbance of the extremities ($p<0.01$). Within the same comparison, radiographic distinctions in patients with CMI included an increased incidence of cervical disc disease, cervical spine subluxation and scoliosis ($p<0.01$). The KPS of the HDCT・EDS with CMI cohort (mean=67.5±3.9 SD) was lower than that of the HDCT・EDS without CMI cohort (mean=77.8±8.4 SD in HDCT・EDS) ($p<0.01$).

Table 2 Diagnostic distinctions of HDCT.EDS in patients with and without Chiari malformation type Ⅰ *

Variable	HDCT.EDS	
	HDCT.EDS/CMI	HDCT.EDS
Total no.	124	31
Symptoms		
nausea	87(70)	21(68)
dysesthesia or numbness of extremities	84(68) †	7(23)
sleep apnea	37(30) †	4(13)
palpitations	77(62) †	15(48)
double vision	35(28)	2(6)
Diagnostic findings (neurological abnormalities)		
motor weakness of extremities	30(24) †	4(13)
sensory disturbance of extremities	32(26) †	4(13)
downward nystagmus	21(17)	2(6)
ataxia	20(16)	3(10)
orthostatic hypotension	20(16)	4(13)
postural orthostatic tachycardia syndrome	22(18)	2(6)
Radiologic findings		
cervical disc disease	75(60) †	10(32)
cervical spine subluxation	50(40) †	4(13)
scoliosis	61(49) †	7(23)
Karnofsky performance score	67.5±3.9 †	77.8±8.4

Numbers in parentheses denote percentages. Mean values are expressed as±standard deviations.
HDCT：hereditary disorders of connective tissue, EDS：Ehlers-Danlos syndrome, CMI：Chiari malformation type Ⅰ.
†：significant differences as compared to patients without CMI ($p<0.01$).

2 Morphometric analysis in supine, sitting, and traction positions

Morphometric measurements of the CCJ in supine position demonstrated no significant differences in the BDI, BAI, ADI, DAI, CAA, CXA and AXA in patients with HDCT・EDS and normal controls (**Table 3**). In patients with HDCT・EDS, however, assumption of an upright (sitting) position resulted in a reduction of the BDI from a mean of 7.2 mm to 3.9 mm ($p<0.001$, **Fig. 2**), posterior gliding of the occipital condyles with an increase of the BAI from a mean of 2.4 mm to 5.2 mm ($p<0.001$, **Fig. 2**) and anterior flexion of the atlanto-occipital joint, as demonstrated by a decrease of the CAA, CXA and AXA by a mean of 5.8° ($p<0.001$), 10.8° ($p<0.001$), and 12.3° ($p<0.001$), respectively (**Fig. 3**). These abnormalities were reducible by traction (**Fig. 2, Fig. 3**). Morphometric measurements in sitting position and traction demonstrated no significant differences in the ADI and DAI in patients with HDCT・EDS, and normal controls, compared to these in the supine position (**Table 3**).

In patients with CMI, assumption of the upright (sitting) position resulted in a reduction of the BDI from a mean of 7.2 mm to 3.7 mm ($p<0.001$, **Fig. 2**), posterior gliding of the occipital condyles with an increase of the BAI from a mean of 2.4 mm to 5.4 mm ($p<0.001$, **Fig. 2**) and anterior flexion of the atlanto-occipital joint, as demonstrated by a decrease of the CAA, CXA and AXA by a mean of 5.9° ($p<0.001$), 11.6° ($p<0.001$) and 12.5° ($p<0.001$), respectively (**Fig. 3**). In patients without CMI, assumption of the upright (sitting) position resulted in a reduction of the BDI from a mean of 7.2 mm to 5.1 mm ($p<0.001$, **Fig. 2**), posterior gliding of the occipital condyles with an increase of the BAI from a mean of 2.4 mm to 4.1 mm ($p<0.001$, **Fig. 2**)and anterior flexion of the atlanto-occipital joint, as demonstrated by a decrease of the CXA and AXA by a mean of 6.2° ($p<0.001$), and 11.3° ($p<0.001$), respectively (**Fig. 3**). Reductions of BDI, BAI and CXA in the upright (sitting) position are significantly larger in the patients with than without CMI.

Table 3　Results：morphometric measurements at cranio-cervical junction

Variable	Normal controls	HDCT・EDS total	HDCT・EDS/CMI	HDCT・EDS
No. of patients	55	135	115（85）	20（14）
Basion-the top of dens（BDI）（mm）				
supine	7.4±1.58	7.2±1.91	7.2±1.87	7.2±1.98
sitting	7.2±1.59	3.9±1.80 †‡	3.7±1.81 †‡§	5.1±1.76 †‡
traction	NA	8.8±2.72 §	8.7±2.71	9.4±2.75
Basion-anterior arch of atlas（BAI）（mm）				
supine	1.8±1.21	2.4±1.32	2.4±1.31	2.4±1.37
sitting	2.1±1.88	5.2±1.44 †‡	5.4±1.45 †‡§	4.1±1.40 †‡
traction	NA	1.5±1.14 §	1.5±1.14	1.5±1.15
Top of dens-arch of atlas（DAI）（mm）				
supine	12.3±2.17	12.5±2.73	12.7±2.70	11.4±2.81
sitting	12.5±2.00	12.8±2.54	13.0±2.53	11.7±2.57
traction	NA	11.7±2.77	11.8±2.75	11.0±2.81
Anterior arch of atlas-dens（ADI）（mm）				
supine	1.5±0.55	1.8±0.58	1.8±0.62	1.8±0.50
sitting	1.5±0.57	1.7±0.70	1.8±0.74	1.1±0.57
traction	NA	1.5±0.65	1.6±0.64	0.9±0.68
Clivus-atlas angle（CAA）（°）				
supine	37.9±7.14	38.3±5.35	38.4±5.33	37.7±5.45
sitting	36.5±7.52	32.5±5.14 †‡	32.5±5.12 †‡	33.6±5.23
traction	NA	45.5±7.27	45.4±7.26	46.1±7.32
Clivus-axial angle（CXA）（°）				
supine	147.6±6.61	147.8±6.41	147.7±6.42	148.4±6.34
sitting	147.8±6.00	137.0±6.27 †‡	136.1±6.29 †‡§	142.2±6.15 †‡
traction	NA	164.0±6.54 ‡	164.1±6.55	163.5±6.50 ‡
Atlas-axial angle（AXA）（°）				
supine	64.8±4.71	66.7±5.73	66.8±5.72	66.1±5.81
sitting	62.0±4.88	54.4±5.22 †‡	54.3±5.21 †‡	54.9±5.22 †‡
traction	NA	65.1±4.74	65.1±4.72	65.1±4.87

Numbers in parentheses denote percentages.
Mean value expressed as±standard deviatioins.
HDCT：hereditary disorders of connective tissue, EDS：Ehlers-Danlos syndrome, CMI：Chiari malformation type Ⅰ, NA：not applicable.
†：significant differences as compared to patients with normal controls（$p<0.001$）.
‡：significant differences as compared to supine position（$p<0.001$）.
§：significant differences compared to patients without CMI（$p<0.01$）.

Discussion

1 Cranial settling and posterior gliding of occipito-atlantal joint and hypermobility of the atlanto-axial joint

Currently standard measurements of CVJ position include the BDI, for evaluating the vertical relationship of the clivus and odontoid[12-14]; the CXA, for evaluating the angle between clivus and odontoid[15]. The new measurements developed by the authors for investigating motion of the occipito-atlanto-axial complex include BAI for evaluating the horizontal relationship of the clivus and anterior arch of the atlas, the AXA for evaluating the angle between atlas and axis, and the CAA, for evaluating the angle between clivus and atlas[10].

As shown on **Table 3**, there were no significant differences in the 5 baseline measurements of patients with HDCT・EDS and normal controls in supine position. Baseline measurements of the BDI, ADI, and CXA were consistent with previously published values[12-14,15,17]. In patients with HDCT・EDS, assumption of the upright（sitting）position resulted in hypermobility of the occipito-atlanto-axial complex and cranial settling. Reduction of the BDI in the upright position（mean 3.3 mm, $p<0.001$）established the diagnosis of functional cranial settling. Hypermobility of the atlanto-occipital joint was evidenced by posterior gliding of the occipital condyles, as demonstrated by an increase of the BAI（mean 2.8 mm, $p<0.001$）and by anterior flexion of the atlanto-occipital joint, as demonstrated by a reduction of the CAA and CXA by a

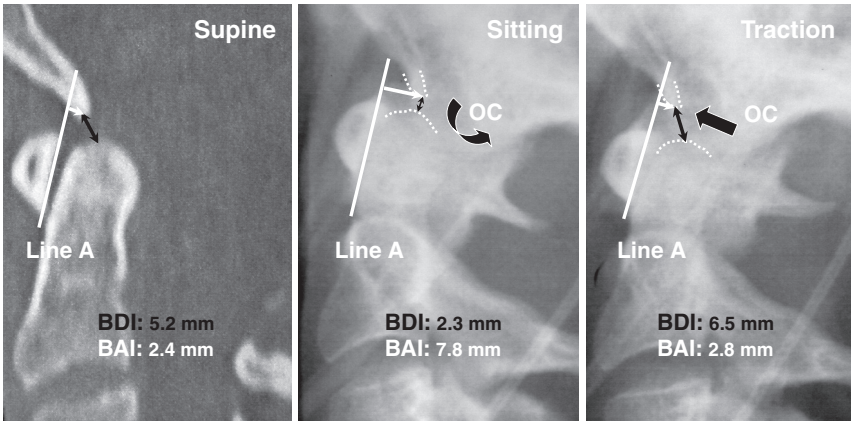

Fig. 2 Evidence of functional cranial settling and posterior gliding of occipital condyles in 25 year old female with HDCT／CMI

Midsagittal reconstructed 2D-CT image in supine position (left) shows baseline BDI of 5.2 mm and BAI of 2.4 mm on midsagittal reconstructed 2D-CT image (left). Plain X-ray images (center and right) show a decrease of the BDI (2.3 mm) and an increase of the BAI (7.8 mm) in the sitting position and an increase of the BDI (6.5 mm) and a decrease of the BAI (2.8 mm) during traction with 10 kg weight. Line A, plane of the posterior surface of the anterior arch of the atlas.
BDI：interval between basion and top of dens, BAI：interval between basion and Line A, OC：occipital condyle.

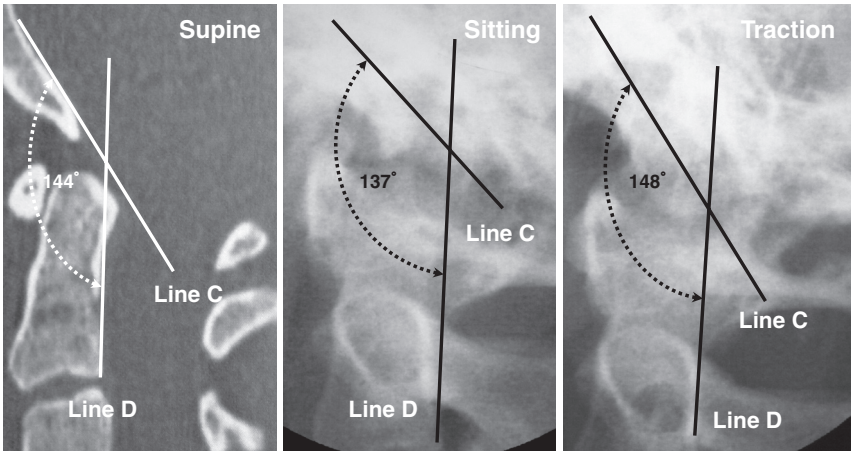

Fig. 3 Evidence of anterior flexion of occipital condyles in 41 year old female with HDCT/CMI

Midsagittal reconstructed 2D-CT image in supine position (left) shows baseline CXA of (144°). Plain X-ray images (center and right) show a decrease of the CXA (137°) in the sitting position and an increase of the CXA (145°) during traction with 10 kg weight. Line D：plane of the posterior surface of dens, Line C：superior plane of clivus.
CXA：angle between clivus (Line C) and axis (Line D).

mean of 5.8° ($p<0.001$) and 10.8° ($p<0.001$), respectively. Hypermobility of the atlanto-axial joint was evidenced by anterior flexion of the atlas over the axis, as demonstrated by a reduction of the AXA (mean 5.3°, $p<0.001$).

The term functional cranial settling has been introduced to describe a reduction of the distance between the basion and odontoid (BDI) that occurs only in the upright position and is not caused by bone and cartilage destruction. Functional cranial settling is probably due to

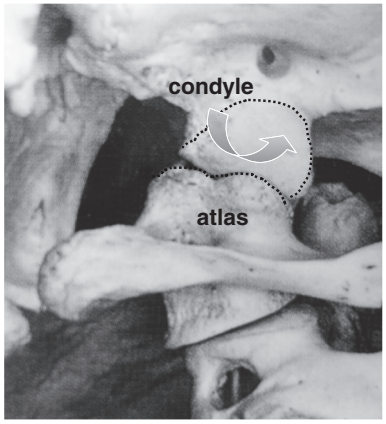

Fig. 4 Picture showing left occipito-atlantal joint from left oblique posterior view
Occipital condyle shows cranial settling, posterior gliding and anterior flexion to the atlas.

one or both of the following mechanisms：

1）laxity of ligaments supporting the atlanto-occipital joint resulting in posterior gliding of the occipital condyles and reduction of the CXA；or

2）generalized laxity of connective tissue structures at the CCJ including the cruciate ligament, the tectorial membrane, and supporting ligaments of the atlanto-axial joint, sufficient to permit upward migration of the odontoid process[18].

The observation that functional cranial settling and reduction of the BDI can be reduced by cervical traction or returning to the supine position appears to rule out significant bone and cartilage damage of the occipito-atlanto-axial complex in these groups of patients.

2 Clinical features and relationship between HDCT/EDS and Chiari malformation

We reported that the diagnostic criteria for EDS and related HDCT were met in 357 cases（12.7％）of the 2813 cases with CMI[10]. The diagnostic features of HDCT.EDS/CMI were distinguished from those of CMI by clinical stigmata of a greater incidence of lower brain stem symptoms and occipito-atlanto-axial instability[10]. Some previously evidenced conclusions have been confirmed with our results Main symptoms of the brain stem in this cohort are nausea, dysesthesia or numbness of extremities, sleep apnea, palpitations and double vision. These clinical parameters associated with CMI indicated high incidence of brain stem symptoms, and suggested that occipito-atlanto-hypermobility combined with CMI makes the symptoms and signs worse. Functional cranial settling, posterior gliding and anterior flexion of occipito-atlanto-axial joints were greater in patients with CMI than in patients without CMI. Both occipito-atlanto-axial hypermobility and CMI in HDCT・EDS affect the appearance and deterioration of brain stem symptoms[10,19,20]. Occipito-atlanto-axial hypermobility might be closely related with CMI.

Conclusions

In this report, we described a previously unrecognized association of occipito-atlanto-axial hypermobility in patients with HDCT・EDS. Evidences were presented that patients with the combined disorder exhibited varying degrees of occipito-atlanto-axial hypermobility that resulted in functional cranial settling, posterior gliding and anterior flexion of occipital condyle. Occipito-atlanto-hypermobility combined with Chiari malformation type Ⅰ made the symptoms and signs of the brain stem worse. In patients with CMI, functional settling, posterior gliding and anterior flexion of occipito-atlanto-axial joints were greater than in patients without CMI.

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