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Clinical and quantitative analysis of patients with crowned dens syndrome

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ABSTRACT

Background: Crowned dens syndrome (CDS) is a radioclinical entity defined by calcium deposition on the transverse ligament of atlas (TLA). In this study, the novel semi-quantitative diagnostic criteria for CDS to evaluate the degree of calcification on TLA by cervical CT are proposed.
Method: From January 2010 to September 2014, 35 patients who were diagnosed with CDS by cervical CT were adopted as subjects in this study. Based on novel criteria, calcium deposition on TLA was classified into "Stage" and "Grade", to make a score, which was evaluated semi-quantitatively. The correlation between calcification score and CRP level or pain score, and the effects of treatments, such as NSAIDs and corticosteroids, were statistically analyzed.
Results: The total calcification score from added "Stage" and "Grade" scores demonstrated a significantly strong and linear correlation with CRP level ($R^2 = 0.823$, $^{**}p < 0.01$). In the multiple comparison test for the treatment effects, significant improvement of the CRP level and pain score were demonstrated after corticosteroid therapy ($^{**}p < 0.01$) compared with NSAIDs. In the conditional logistic regression analysis, the rapid end of corticosteroid therapy was an independent risk factor for relapse of cervico-occipital pain [OR = 50.761, $^{*}p = 0.0419$].
Conclusion: The degree of calcification on TLA evaluated by the novel semi-quantitative criteria significantly correlated with CRP level. In the treatment of CDS, it is recommended that a low dosage (15–30 mg) of corticosteroids be used as first-line drugs rather than conventional NSAID therapy. Additionally, it is also recommended to gradually decrease the dosage of corticosteroids.

1. Background

Crowned dens syndrome (CDS) is a radioclinical entity defined by the association of microcrystalline deposition on the transverse ligament of atlas (TLA) around the odontoid process and periodic acute cervico-occipital pain with fever, neck stiffness, and biological inflammatory syndrome [1–11]. The microcrystalline deposition, most often calcium pyrophosphate dehydrate (CPPD) crystals and/or hydroxyapatite (HA) crystals, can remain asymptomatic or be responsible for chronic cervical pain or spinal cord compression [2–5]. In general, CPPD crystal deposition disease is clinically associated with acute episodic mono- or oligo-arthritis, termed "pseudogout", involving a large joint (including the knees, wrists, and ankles) or chronic arthropathy manifesting as mild joint pain, and stiffness of knees, wrists, metacarpophalangeal joints, elbows, and shoulders [2–7].

Table 1
Category and notation of radiographical calcification stage and grade of CDS.

Category	Subcategory	Contents	Score
Calcification stage	Localization (area)	Non (normal)	0
		Anterior	1
		Right	1
		Left	1
		Posterior	1
	Distribution (form)	Non (normal)	0
		Tuberous form	1
		Segmental form	2
		Ringed form	3
Calcification stage score = Area score + Distribution score			0–7
Calcification grade (0–4)	Grade 0	CT value 0–100	0
	Grade 1	CT value 100–250	1
	Grade 2	CT value 250–500	2
	Grade 3	CT value 500–750	3
	Grade 4	CT value 750–1000	4
Total calcification score = Stage score + Grade score			0–11

CT; computed tomography, CT value: −1000 = air, 0 = water, +1000 = bone.
The calcification stage score reflects the localization (area) and distribution (form) of calcium deposition around the odontoid process. The calcification grade score reflects the degree of calcium deposition based on the CT value measured by CT image processing software.

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CDS is defined as a combination of acute feverish cervical pain and calcification around the odontoid process [1–11]. The entity of CDS was primarily described and presented by Bouvet et al. in 1985 [1]. At present, computed tomography (CT) scanning focusing on cervical vertebrae C-1 and C-2 is the gold standard of CDS diagnosis [6–11]. A CT scan makes it possible to identify the anatomical substratum of CDS [6–11]. The typical tiny half-ringed crown-like form of calcification behind the dens is regarded as the most important and definitive feature of CDS [1–11]. The CPPD and/or HA microcrystalline depositions in periarticular structures, such as the TLA, around the top and sides of the odontoid process are considered to be responsible for the various clinical manifestations of CDS [1–11]. However, the correlation between the degree of the calcification on the TLA and clinical manifestations, in particular the degree of cervical pain and the inflammatory markers, such as C-reactive protein (CRP) level, is not sufficiently understood because of the lack of systematic and/or statistical study of CDS.

In general, the inflammatory symptoms of CDS are markedly improved by treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) or colchicine [1–6]. In most of the previously reported cases, NSAIDs enabled complete recovery within a few days along with normalization of inflammatory markers [1–6]. However, several reports have described cases of CDS that did not recover with NSAIDs, but were prominently improved with corticosteroid therapy [7–11]. At present, the clinical guidelines for CDS treatment are not clear as there has been no statistical comparison and/or analysis for the effects of treatment between NSAIDs and corticosteroids.

In this study, the authors proposed novel semi-quantitative diagnostic criteria in order to evaluate the degree of calcification on the TLA in CDS based on CT scan findings at the C1-C2 joint. Through the use of these novel semi-quantitative criteria, the correlation between the degree of calcification and the clinical manifestations of CDS was statistically analyzed. Moreover, in order to clarify the most appropriate

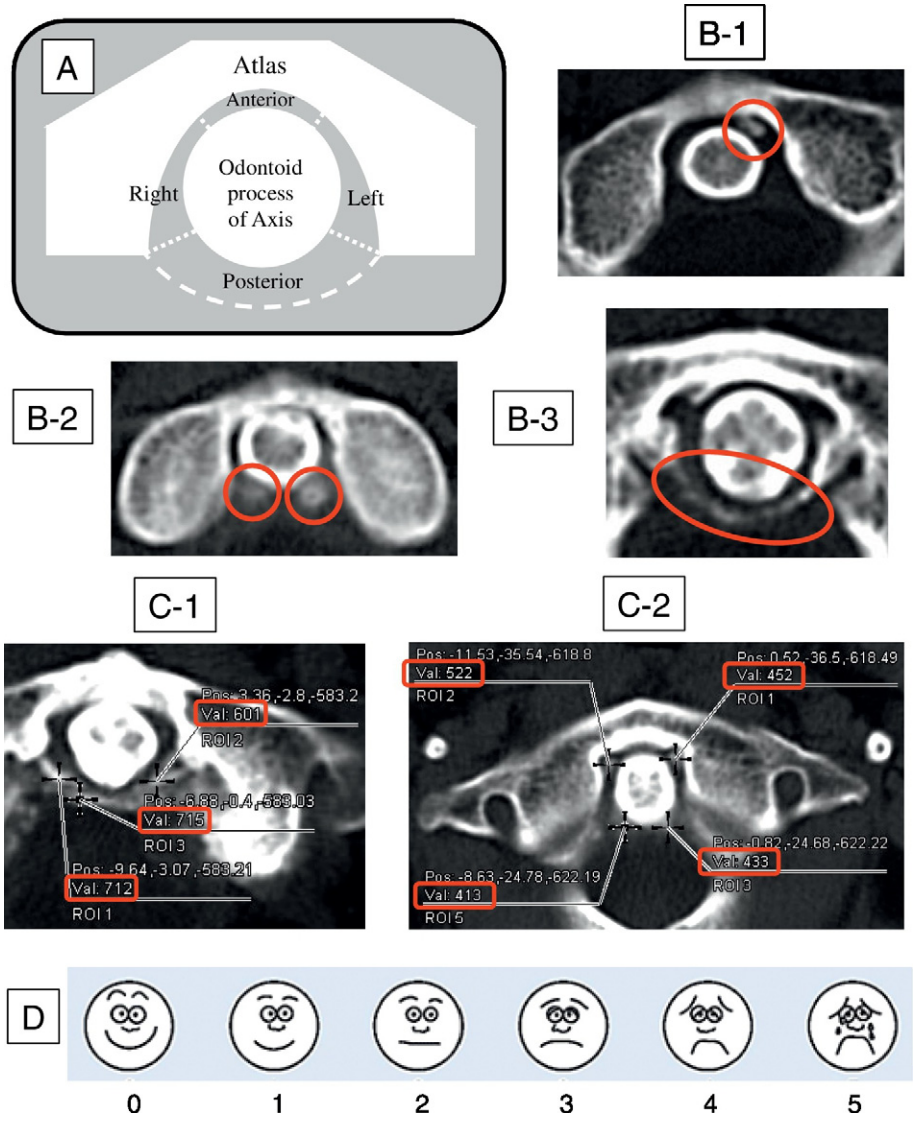


Fig. 1. The calcification "Stage" and "Grade" in the novel semi-quantitative diagnostic criteria for CDS based on CT scan findings focusing on the C1-C2 joint. (A) The schema of the divided four areas around the odontoid process. (B) Concrete example of evaluating the calcification "Stage". The calcification "Stage" score (0–7) is given as the sum of "area" and "form" scores. B-1: Case 1. Anterior area (score 1), Tuberous form (score 1), Stage score = 2. B-2: Case 23. Posterior area (score 1), Segmental form (score 2), Stage score = 3. B-3: Case 29. Posterior area (score 1), Ringed form (score 3), Stage score = 4. (C) Concrete example of evaluating the calcification "Grade". The calcification "Grade" reflects the degree of calcium deposition based on CT value measured by CT image processing software "zioTerm 2009" (Ziosoft, Inc., Tokyo, Japan). The average CT value, which was measured at more than three points where calcification was clearly demonstrated, was used. The average CT value of 0–100, 101–250, 251–500, 501–750, or 751–1000 was evaluated as the calcification "Grade" and scored as 0, 1, 2, 3, and 4, respectively. C-1: Case 3. CT value = 676 ± 65, Grade score = 3. C-2: Case 26. CT value = 469 ± 47; Grade score = 2. (D) The schema of the Face Rating Scale (FRS). The FRS shows a series of faces ranging from a happy face at 0 "No pain" to a crying face at 5 "Worst pain".

treatment approach for CDS, the treatment effects of NSAIDs and corticosteroids were examined in detail.

2. Materials and methods

2.1. Patients

Among the patients with severe cervico-occipital pain as the chief complaint who visited Nagaoka-**N**ishi **H**ospital, Hino **M**unicipal **H**ospital, and Seiwa **C**linic from January 2010 to September 2014, 35 patients were adopted as the subjects in this study. These 35 patients had periodic acute cervico-occipital pain, fever, neck stiffness, and inflammatory symptoms, and were diagnosed with CDS based on calcium deposition around the odontoid process detected by CT scanning at the C1-C2 joint. This study was approved by the Ethics Committees of all institutions, and all patients agreed to participate in this study.

2.2. The novel semi-quantitative diagnostic criteria for CDS

The novel semi-quantitative diagnostic criteria that the authors proposed in this study are shown in Table 1. Based on the CT scan findings at the C1-C2 joint, the calcium deposition on the TLA around the odontoid process was classified into "Stage" and "Grade". "Stage" and "Grade" were added to make a score, and evaluated semi-quantitatively. In this study, all of the CT scans were performed under the bone condition (Window Wide 2000, Window Level 200).

The calcification "Stage" reflects the localization (area) and distribution (form) of calcium deposition around the odontoid process. The region around the odontoid process was divided into 4 areas; anterior, posterior, right, and left (Fig. 1A), and assigned a score of 1 for each area (Table 1). Additionally, the distribution (form) of calcium deposition was classified into 3 types; tuberous, segmental, and ringed form, and assigned a score of 1, 2, and 3 respectively (Table 1, Fig. 1B1–3). The calcification "Stage" score (0–7) is given as the sum of "area" and "form" scores. On the other hand, the calcification "Grade" reflects the degree of calcium deposition on the basis of CT value measured by CT image processing software "zioTerm 2009" (Ziosoft, Inc., Tokyo, Japan). In general, the CT values were −1000, 0, +1000 exhibit air, water, and bone respectively. In this study, the average CT value, which was measured at more than three points where calcification was clearly demonstrated, was used. The average CT value of 0–100, 101–250, 251–500, 501–750, or 751–1000 was evaluated as the calcification "Grade", and scored as 0, 1, 2, 3, and 4, respectively (Table 1, Fig. 1C1–2). The total calcification score (0 − 11) is the sum of the "Stage" and "Grade" scores.

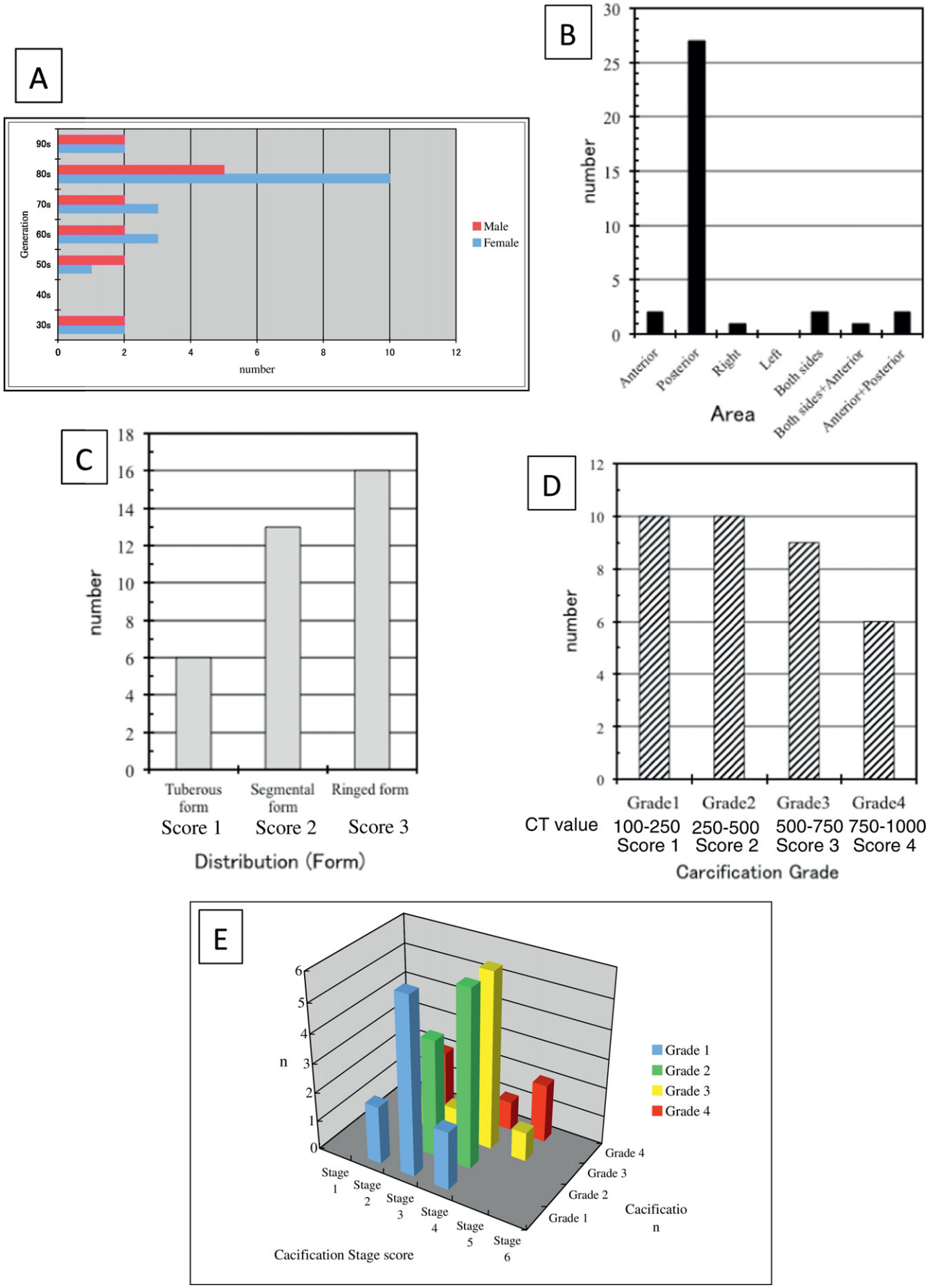
2.3. Evaluation of pain

In order to appropriately evaluate the cervico-occipital pain of patients, the Face Rating Scale (FRS) was adopted in this study. The FRS is one of the most frequently used international pain scales developed by Donna Wong and Connie Baker. This scale shows a series of faces ranging from a happy face at 0 "No pain" to a crying face at 5 "worst

Table 2A
Clinical features of the 35 patients with CDS on initial diagnosis.

				Cervical CT findings								Initial routine laboratory examinations			
				Calcification stage			Calcification grade								
Case no.	Year	Sex	Age	Area score	Form score	Stage score	CT value (average ± SD)	Grade score	Total score	Body temp.	Pain scale (FRS)	WBC	CRP	CK	UA
1	2010	M	39	A: 1	T: 1	2	615 ± 113	3	5	36.8	5	10,800	10.2	54	5.6
2		M	86	P: 1	R: 3	4	978 ± 175	4	8	38	5	13,300	21.4	82	4.7
3	2011	M	90	P: 1	R: 3	4	676 ± 65	3	7	38	5	9600	18.2	98	5.7
4		M	64	P: 1	R: 3	4	416 ± 111	2	6	37.2	5	9100	13.7	78	4.8
5		F	75	P: 1	R: 3	4	341 ± 75	2	6	38.4	5	10,000	10.8	164	3.5
6		M	83	A, Rt, Lt: 3	S: 2	5	721 ± 49	3	8	36.8	5	9600	15.4	139	5.2
7		M	85	P: 1	S: 2	3	279 ± 159	2	5	37.4	4	9700	9.8	n.d.	n.d.
8		F	84	P: 1	R: 3	4	173 ± 49	1	5	37.3	4	7200	8.04	n.d.	n.d.
9		M	84	P: 1	T: 1	2	202 ± 26	1	3	36.8	5	5400	1.8	48	4.3
10	2012	M	91	P: 1	R: 3	4	200 ± 30	1	5	36.9	4	8700	8.35	n.d.	n.d.
11		F	88	P: 1	S: 2	3	155 ± 10	1	4	36.7	4	7200	4.18	38	6.1
12		M	56	P: 1	T: 1	2	839 ± 64	4	6	37.5	4	8800	10.4	64	2.5
13		M	71	Rt: 1	T: 1	2	203 ± 21	1	3	36.8	5	5700	2.5	n.d.	n.d.
14		F	81	P: 1	R: 3	4	654 ± 123	3	7	37.7	5	13,800	20.3	228	3.9
15		F	73	P: 1	S: 2	3	190 ± 16	1	4	37.1	4	6500	3.75	59	4.2
16		F	86	P: 1	S: 2	3	169 ± 50	1	4	37.5	4	10,800	7.85	146	6.2
17		F	35	P: 1	S: 2	3	138 ± 16	1	4	36.2	4	6600	2.8	72	5.3
18		F	84	P: 1	R: 3	4	306 ± 83	2	6	37.2	4	9600	14.6	n.d.	n.d.
19		M	68	P: 1	S: 2	3	375 ± 111	2	5	37.4	4	5800	7.5	47	5.4
20		F	63	P: 1	R: 3	4	271 ± 43	2	6	37.6	4	9400	15.8	34	4.8
21		M	38	P: 1	S: 2	3	158 ± 5	1	4	36.4	4	7000	3.2	n.d.	n.d.
22		F	63	Rt, Lt: 2	T: 1	3	842 ± 453	4	7	38	5	13,400	12.7	33	2.5
23		F	86	P: 1	R: 3	4	573 ± 248	3	7	36.9	5	10,100	8.63	72	5.2
24		F	89	P, A: 2	R: 3	5	864 ± 69	4	9	38.5	5	11,100	23.8	47	4.0
25		F	85	P: 1	R: 3	4	295 ± 41	2	6	37.8	4	9100	11.3	58	3.2
26	2013	M	59	Rt, Lt: 2	S: 2	4	469 ± 47	2	6	37.2	4	10,800	13.2	67	3.4
27		M	81	P: 1	R: 3	4	533 ± 74	3	7	37.4	4	10,400	17.7	47	3.7
28		F	91	P: 1	S: 2	3	217 ± 44	1	4	37.5	4	6800	6.1	n.d.	n.d.
29		F	78	P: 1	S: 2	3	410 ± 112	2	5	36.5	4	13,300	5.7	n.d.	n.d.
30		F	80	P: 1	R: 3	4	554 ± 154	3	7	37.6	5	10,400	12.5	21	2.8
31	2014	F	56	P: 1	R: 3	4	733 ± 315	3	7	36.8	5	9700	14.3	122	4.3
32		F	83	P, A: 2	R: 3	5	879 ± 302	4	9	37.2	5	8800	18.6	69	5.2
33		F	34	A: 1	T: 1	2	960 ± 242	4	6	38.1	5	11,300	12.6	204	5.8
34		M	76	P: 1	S: 2	3	715 ± 158	3	6	36.8	4	7600	8.65	165	6.2
35		F	68	P: 1	S: 2	3	471 ± 140	2	5	37.5	5	9300	9.7	88	3.9

CT; computed tomography, A; anterior, P; posterior, Rt; right, Lt; left, T; tuberous, S; segmental, R; ringed, Temp; temperature, WBC; white blood cells, CRP; C-reactive protein, UA; uric acid, CPK; creatine phosphokinase, n.d.; not done.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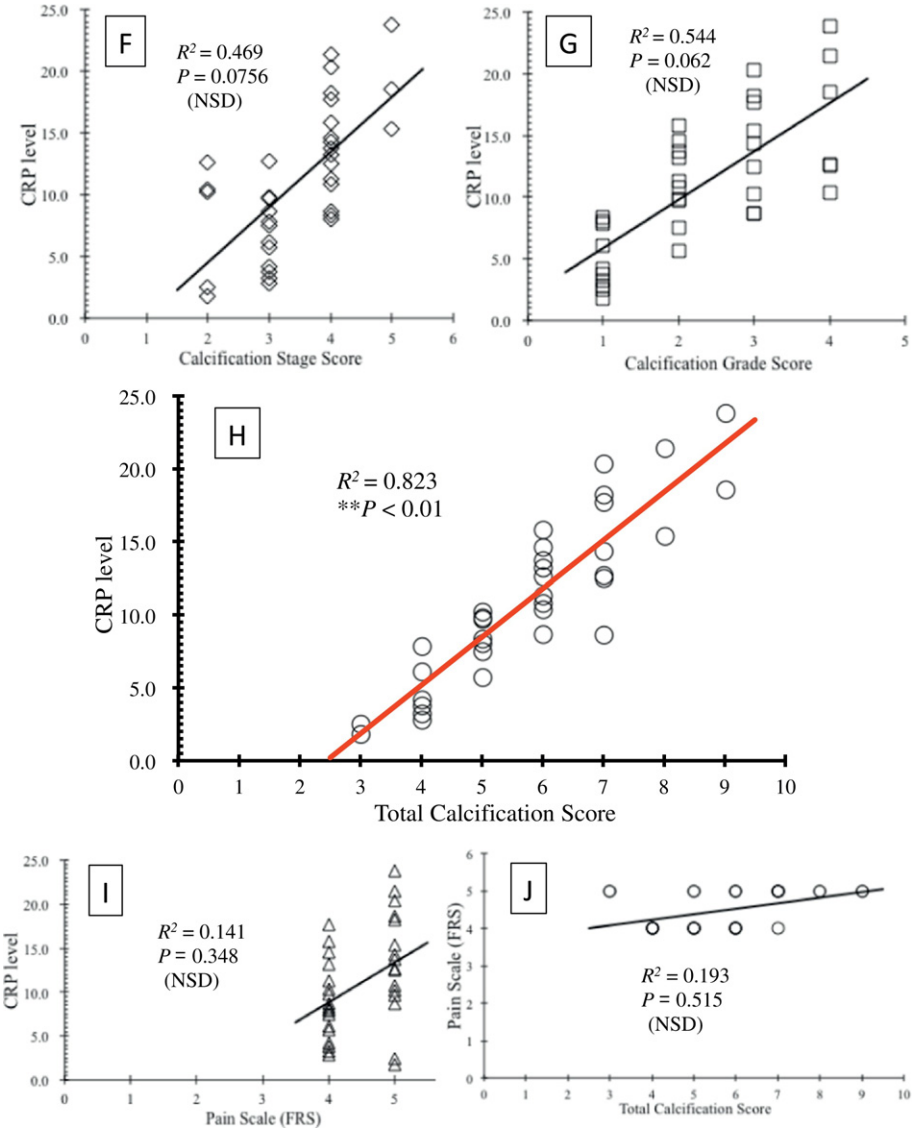

Fig. 2. The clinical features of the 35 patients with CDS. (A) Bar chart of male-to-female ratio by age series. (B) The frequency of calcium deposition in the four areas around the odontoid process. (C) The frequency of calcium deposition forms. (D) The frequency of calcium deposition degree "Grade". (E) The frequency of "Stage" and "Grade" based on our semi-quantitative diagnostic criteria. (F)–(H) Correlation between the calcium deposition on the TLA and CRP level was statistically analyzed by simple regression analysis. There was no significant correlation between the "Stage" score alone (F) or the "Grade" score alone (G) and the CRP levels. On the other hand, the total calcification score, which added the "Stage" score to the "Grade" score, demonstrated a significantly strong and linear correlation with CRP level ($R^2 = 0.823$, $^{**}p < 0.01$) (H). (I), (J) The score of the cervico-occipital pain evaluated by the FRS demonstrated no significant correlation with CRP level (I) or total calcification score (J) by simple regression analysis.

pain" (Fig. 1D). In clinical practice, the patients choose the face that best demonstrates how they are feeling. Thus, the cervico-occipital pain of patients with CDS was semi-quantitatively evaluated by the FRS in this study.

2.4. Statistical analysis

Statistical analysis was conducted using the data analysis software program SPSS 13.0 for Windows. A value of $p < 0.05$ was considered significant.

3. Results

A summary of the clinical data of the 35 patients is shown in Tables 2A and B. The male-to-female ratio was 0.75, and the mean age at the time of onset was 72.9 years old (male: 71.4 years old, female: 74.1 years old). Nineteen patients (54.3%) were more than eighty years of age (Fig. 2A). Plain CT scanning at the C1-C2 joint demonstrated that calcium deposition largely occurred in the posterior area around the odontoid process (Fig. 2B). The ringed form was the most frequent distribution of calcium deposition (Fig. 2C). On the other hand, Grade-1, which corresponds to the CT value 100–250, was most often recognized, and the degree of calcification tended to decrease with the rise of the CT value (Fig. 2D). The score of cervico-occipital pain evaluated by the FRS demonstrated high levels (score 4 or 5) in all cases (Table 2A). In the laboratory examinations, the CRP level rose in all cases, whereas the levels of uric acid and CPK were within the normal range in all cases (Table 2A).

In the analysis using our semi-quantitative diagnostic criteria, the combination of Stage-3 and Grade-1, Stage-4 and Grade-2, and Stage-4 and Grade-3 were observed frequently (Fig. 2E). The correlation between calcium deposition on the TLA and CRP level was statistically analyzed. In the simple regression analysis, there was no significant correlation between the "Stage" score alone and CRP levels (Fig. 2F). Similarly, there was no significant correlation between the "Grade" score alone and CRP levels (Fig. 2G). On the other hand, the total

calcification score, which added the "Stage" score to the "Grade" score, demonstrated a significantly strong and linear correlation with CRP level ($R^2 = 0.823$, $^{**}p < 0.01$) (Fig. 2H). The score of the cervico-occipital pain evaluated by the FRS was not significantly correlated with the CRP level or total calcification score (Fig. 2I and J).

A summary of the clinical course of the 35 patients is also shown in Table 2B. For the clinical outcome, all cases were improved by the treatment. Only two cases (cases 9 and 15) improved among the 15 cases primarily treated with NSAIDs such as loxoprofen sodium hydrate and diclofenac sodium. On the other hand, all 33 patients who were primarily or secondarily treated with corticosteroids improved. The details of corticosteroid use are as follows; prednisolone at 30 mg, 20 mg, and 15 mg daily was orally administered to the 14, 11, and 7 cases, respectively, and semi-pulse was only in one case (Case 2). Additionally, the corticosteroid dosage was tapered in 17 cases. In 22 of the 33 cases, the HbA1c level was measured after corticosteroid therapy, and the HbA1c level was within the normal range in all 22 cases. Therefore, the decline of glucose tolerance by low or moderate dosage of corticosteroids was not observed in this study. In the 20 cases in which a follow-up CT was performed 3 to 6 months later, calcium deposition on the TLA remained in 19 cases. TLA calcification disappeared in only one case (Case 33). In this case (Case 33), differentiation from "Calcific retropharyngeal tendinitis" is necessary. Relapse of cervico-occipital pain occurred in 7 cases (20%).

In order to examine the treatment effects, clinical markers, such as CRP level and pain score, were statistically compared before and after treatment with NSAIDs and corticosteroids. In the multiple comparison test (Tukey-Kramer test), significant improvement of CRP level and pain score were demonstrated after corticosteroid therapy ($^{**}p < 0.01$), but there was no significant differences among the corticosteroid dosages (Fig. 3A and B). On the other hand, there was no significant difference in CRP level or pain score between before and after treatment with NSAIDs because the inflammatory symptoms and cervico-occipital pain remained, albeit with slight improvement (Fig. 3A and B).

The correlation of the six clinical parameters (predictors), such as "Age", "Total calcification score", "CRP level", "Pain score", "Remaining Calcification", and "No corticosteroid tapering", with the relapse of cervico-occipital pain was tested with the conditional logistic regression analysis. "No corticosteroid tapering" was an independent risk factor for the relapse of cervico-occipital pain [OR = 50.761, 95%CI = 1.154–2231.975, $^{*}p = 0.0419$] (Table 2C). However, the other five clinical parameters, in particular "Remaining Calcification", were not significant risk factors for the relapse of cervico-occipital pain (Table 2C).

4. Discussion

Previously, CDS was considered to be a relatively rare disease. In 2007, Goto et al. reported that CDS was diagnosed in 40 out of 2023 patients (1.9%) who visited Senboku Kumiai General Hospital over a period of 2.5 years with severe neck pain as the chief complaint [8]. In the study reported by Goto et al., the male-to-female ratio was 0.6, the mean age at the time of onset was 69 years old in males and 75 years old in females, and 26 patients (65%) were more than seventy years old [8]. Similar trends were observed in the 35 patients in this study. Infectious meningitis, polymyalgia rheumatica (PMR), giant cell arteritis (GCA), cervical spondylotic myelopathy, pyogenic spondylitis, and spinal injury are known as diseases which cause acute severe cervico-occipital pain [7–14]. As CDS is not as well documented as these

Table 2B
Clinical course of the 35 patients with CDS.

	Clinical course										
	Primary treatment			Secondary treatment							
Case no.	Agents	CRP	Pain scale (FRS)	Agents	CRP	Pain scale (FRS)	corticosteroid tapering	HbA1c	Follow-up CT findings	Out come	Relapse
1	NSAIDs	7.85	4	PSL 30 mg	0.33	0	+	n.d.	n.d.	Improved	−
2	NSAIDs	18.3	4	Semi Pulse	1.3	1	+	5.6	Remain	Improved	−
3	NSAIDs	11.2	5	PSL 30 mg	0.78	1	+	5.5	n.d.	Improved	−
4	NSAIDs	10.7	4	PSL 30 mg	0.85	0	−	n.d.	n.d.	Improved	n.d.
5	NSAIDs	11.56	4	PSL 20 mg	2.35	0	−	n.d.	n.d.	Improved	n.d.
6	NSAIDs	13.74	5	PSL 30 mg	1.46	1	+	5.1	n.d.	Improved	−
7	PSL 20 mg	2.26	0	−	−	−	−	n.d.	Remain	Improved	−
8	PSL 20 mg	0.35	0	−	−	−	−	4.7	Remain	Improved	+
9	NSAIDs	0.15	2	−	−	−	n.d.	n.d.	n.d.	Improved	−
10	PSL 20 mg	n.d.	n.d.	−	−	−	−	n.d.	n.d.	Improved	n.d.
11	PSL 15 mg	n.d.	n.d.	−	−	−	−	n.d.	n.d.	Improved	n.d.
12	NSAIDs	8.7	3	PSL 30 mg	2.19	0	+	5.6	n.d.	Improved	−
13	PSL 15 mg	n.d.	n.d.	−	−	−	−	n.d.	n.d.	Improved	n.d.
14	NSAIDs	16.7	4	PSL 30 mg	1.23	0	+	5.3	Remain	Improved	−
15	NSAIDs	0.02	2	−	−	−	n.d.	n.d.	n.d.	Improved	−
16	NSAIDs	7.42	3	PSL 20 mg	0.76	0	+	5.5	Remain	Improved	+
17	PSL 15 mg	0.05	0	−	−	−	−	n.d.	n.d.	Improved	−
18	PSL 30 mg	1.68	1	−	−	−	−	n.d.	n.d.	Improved	n.d.
19	PSL 20 mg	0.92	1	−	−	−	−	4.7	Remain	Improved	+
20	PSL 20 mg	0.54	0	−	−	−	−	n.d.	n.d.	Improved	n.d.
21	NSAIDs	0.12	1	−	−	−	−	n.d.	n.d.	Improved	−
22	NSAIDs	9.87	4	PSL 30 mg	3.84	1	+	5.5	Remain	Improved	−
23	NSAIDs	10.4	4	PSL 30 mg	0.83	0	+	4.8	Remain	Improved	−
24	NSAIDs	16.9	4	PSL 30 mg	1.2	0	+	5.1	Remain	Improved	−
25	PSL 20 mg	0.64	1	−	−	−	−	5.4	Remain	Improved	+
26	PSL 30 mg	1.33	0	−	−	−	−	5.1	Remain	Improved	−
27	PSL 30 mg	2.21	0	−	−	−	+	4.9	Remain	Improved	−
28	PSL 20 mg	1.17	0	−	−	−	−	5.2	Remain	Improved	+
29	PSL 30 mg	0.87	0	−	−	−	+	5.5	Remain	Improved	−
30	PSL 30 mg	1.5	1	−	−	−	+	5.3	Remain	Improved	−
31	PSL 20 mg	1.3	0	−	−	−	+	4.8	Remain	Improved	+
32	PSL 20 mg	1.74	0	−	−	−	−	5.3	Remain	Improved	+
33	PSL 15 mg	2.17	1	−	−	−	+	5.1	Disappeared	Improved	−
34	PSL 15 mg	0.58	0	−	−	−	+	5.5	Remain	Improved	−
35	PSL 15 mg	1.23	1	−	−	−	+	5.2	Remain	Improved	−

NSAIDs; non-steroidal anti-inflammatory drugs, PSL; prednisolone, Semi Pulse; methylprednisolone 500 mg/day for 3 days, n.d.; not done.

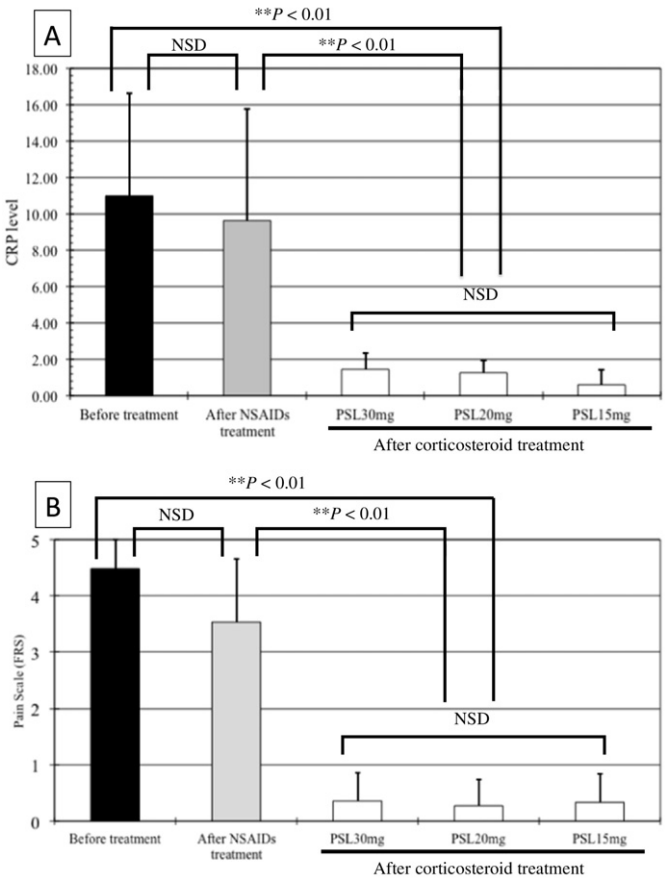

Fig. 3. The results of comparison for the effects of treatment between NSAIDs and corticosteroids. Statistically analyzed by one way ANOVA (Tukey-Kramer test). The CRP level was statistically compared before and after treatment with NSAIDs and corticosteroids. The pain score was statistically compared before and after treatment with NSAIDs and corticosteroids. In the Tukey-Kramer test, significant improvement of the CRP level and the pain score were demonstrated after corticosteroid therapy ($^{**}p < 0.01$), but there was no significant difference between before and after treatment with NSAIDs.

common diseases, it may be missed in routine clinical practice of elderly patients who exhibit cervico-occipital pain. In addition, the incidence of calcium deposition disease, such as pseudogout, including CDS, probably increases with age [1–11]. Therefore, CDS may be a relatively common cause of severe cervico-occipital pain. However, the exact prevalence of CDS in actual clinical practice is unknown.

Table 2C
Independent predictors for the relapse of cervico-occipital pain by conditional logistic regression analysis.

Independent predictors		OR	95% CI	*p*-value
Age (year)		1.094	0.979–1.221	0.1118 (NSD)
Initial findings	Total calcification score	0.472	0.693–3.195	0.4399 (NSD)
	CRP level	0.989	0.644–1.517	0.9584 (NSD)
	Pain score	3.803	0.401–361.615	0.5653 (NSD)
Remaining calcification		2268.898	0.0001–7774.56	0.9962 (NSD)
No corticosteroid tapering		50.761	1.154–2231.975	*0.0419

The correlation of the six independent clinical parameters with risk for the relapse of cervico-occipital pain was tested by conditional logistic regression analysis. A backwards elimination procedure was used for multivariable analysis. For multivariate risk predictors, the adjusted OR values are given with the 95% CI values.
NSD; no significant difference.
* involves statistically significant.

Previously, Goto et al. reported that the degree of calcium deposition on the TLA around the odontoid process did not correlate with the levels of inflammatory indicators such as CRP [8]. However, the authors consider the conventional evaluation method for calcium deposition on the TLA in the CDS to have serious problems. In the conventional evaluation method, the localization (area) and distribution (form) of calcium deposition around the odontoid process were evaluated separately [8]. In addition, it is difficult to exactly measure the area of calcium deposition around the odontoid process on cervical plain CT images because it exhibits many forms and localizations. Moreover, the level of calcification, namely the quality of the calcium deposition, has not been considered at all in the conventional evaluation method [8]. Therefore, in order to accurately evaluate the degree of calcification on the TLA in CDS, novel unified criteria are necessary. In this study, the authors proposed novel semi-quantitative diagnostic criteria for CDS based on CT scan findings focusing on the C1-C2 joint. In these criteria, the calcium deposition on the TLA around the odontoid process was classified as "Stage", which reflects the localization (area) and distribution (form) of calcium deposition around the odontoid process, and "Grade" which reflects the degree of calcium deposition based on CT value. Both "Stage" and "Grade" were added to make a score, and evaluated semi-quantitatively. As a result, a significantly strong and linear correlation between the total calcification score, the added "Stage" and "Grade" scores, and the CRP level ($R^2 = 0.823$, $^{**}p < 0.01$) was demonstrated by simple regression analysis. On the other hand, there was no significant correlation between the "Stage" or "Grade" score alone and CRP level, similar to the previous report by Goto et al. [8]. These results indicate that the degree of calcium deposition on the TLA in CDS should be evaluated comprehensively by the localization (area), distribution (form), and level of calcification. To our knowledge, there is no study in which the correlation between the calcium deposition on TLA in CDS and the CRP level was statistically analyzed. Therefore, our novel semi-quantitative diagnostic criteria are clinically useful for the statistical evaluation of calcium deposition in CDS compared with other clinical indicators. Incidentally, the score of cervico-occipital pain evaluated by the FRS demonstrated high values in all 35 CDS cases, and revealed no significant correlation with the CRP level or total calcification score. These results indicate that even if the degree of calcification or inflammation is low, the cervico-occipital pain may be severe in CDS.

In this study, the use of low or moderate dosages of corticosteroids demonstrated significant improvement of CRP level and scores of cervico-occipital pain in CDS compared with NSAIDs. Conventionally, NSAIDs have been regarded as the first-line drugs for CDS [1–6]. However, several previous reports have suggested that treatment with corticosteroids was more effective for the improvement of the symptoms in CDS than treatment with NSAIDs [7–11]. To our knowledge, this study is the first report that statistically demonstrated the superiority of corticosteroid therapy in CDS. Moreover, the results of the conditional logistic regression analysis revealed that the "No corticosteroid tapering" was an independent risk factor for relapse of cervico-occipital pain in the CDS [OR = 50.761, 95% CI = 1.154–2231.975, $^{*}p = 0.0419$]. In the 20 cases in which a follow-up CT was performed 3 to 6 months later, the calcium deposition on the TLA remained in 19 cases (95%). However, "Remaining Calcification" was not a significant risk factor for the relapse of cervico-occipital pain in CDS. Based on the statistical results of this study, the authors recommend that low dosage corticosteroids should be used as the first-line drugs for the treatment of CDS. In addition, because the rapid end of corticosteroid therapy is an independent risk factor for the relapse of cervico-occipital pain in CDS, the authors also recommend that the dosage of corticosteroids be decreased gradually.

At present, CDS is regarded as a rare neurological condition, and there are only a few previous reports about it. Therefore, further research and an accumulation of cases are necessary to obtain a good

understanding of the pathological conditions of CDS. Our novel semi-quantitative diagnostic criteria may be clinically useful for the statistical evaluation of the pathological conditions in CDS.

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Authorship agreement

I declare that all authors have agreed and approved submission of this manuscript for '*Journal of the Neurological Sciences*'. I also declare that there is no conflict of interest in connection with this manuscript.

Author's contribution

1) Teruyuki Takahashi, M.D.; First and corresponding author. Study concept and design. Writing the first draft of this manuscript.
2) Masato Tamura, M.D.; Acquisition of data and statistical analysis.
3) Toshiaki Takasu, M.D.; Critical revision of the manuscript.
4) Satoshi Kamei, M.D.; Study supervision.

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