

Incidence, Age and Gender of Subjects With the Calcium Pyrophosphate Deposition Around the Dens, and Clinical Characteristics of Patients With Crowned Dens Syndrome

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Abstract

Background: The purpose of this study was to determine the incidence, age distribution and gender of subjects with the calcifications around the dens, and to reveal the clinical, biochemical and radiological characteristics for crowned dens syndrome (CDS).

Methods: We retrospectively picked up the subjects with the calcification around the dens among patients who had undergone head and neck computed tomography (CT) between October 1, 2011 and March 31, 2012, and investigated age and gender of selected subjects. We also studied age, gender, clinical symptoms, body temperature, C-reactive protein (CRP) levels, treatment and clinical course in patients who were diagnosed as having CDS.

Results: We detected 1,056 subjects who had undergone head and neck CT, and excluded subjects who had undergone repeated CT, and also excluded patients whose CT did not show odontoid process. Three hundred sixty-five subjects were eligible for the analysis. In all subjects, age in subjects with the calcifications around the dens was significantly higher than subjects without the calcifications around the dens. In subjects who were over 65 years old, age in subjects with the calcifications around the dens was also significantly higher than subjects without the calcifications around the dens. Twenty-one (5.8%) of 365 subjects showed the calcifications around the dens. We found the calcifications around the dens in 9.6% of subjects who were over 65 years old. In the analysis of characteristics of CDS patients, we found that all patients presented neck pain, restricted neck rotation, fever, elevated CRP levels, the calcification around the dens detected by CT, and the prompt response to steroid and/or non-steroidal anti-inflammatory drugs.

Conclusion: To our knowledge, our study is the first to show the

frequency of the calcification around the dens in the elderly people, and also a significant association between the calcification around the dens and aging. Clinical, biochemical and radiological characteristics for CDS obtained from our study help many physicians make the diagnosis of CDS.

Keywords: Computed tomography; C-reactive protein; Crowned dens syndrome; Magnetic resonance imaging; Neck pain

Introduction

Crowned dens syndrome (CDS) is a very rare form of calcium pyrophosphate depositions and often presents with neck pain, neck stiffness and fever [1]. Clinical symptoms are due to pseudogout of the atlantoaxial junction induced by calcifications around the dens [1]. The computed tomography (CT) is the gold standard in identifying CDS, as it is able to depict the shape and site of calcification, and CT shows radiopaque densities surrounding the top and sides of the odontoid process in a crown-like distribution [1-4]. Characteristic CT findings have been reported [5-8]. The diagnosis of CDS may be based on clinical symptoms such as neck pain, neck stiffness and fever, and the calcifications surrounding the top and sides of the odontoid process which are detected by CT, and increased levels of inflammatory markers such as erythrocyte sedimentation rate and C-reactive protein (CRP) [1, 6, 9, 10].

We experienced the first patient diagnosed having CDS by clinical symptoms and the calcifications around the dens detected by CT in April 2012. The association between CDS and the calcifications around the dens remains largely unknown.

Therefore, first, we retrospectively picked up patients who showed the calcification around the dens by CT, and studied age and gender in patients with and without the calcification around the dens in the study I.

Only 52 reports about "CDS" written in English were found by Pubmed search, and most of such reports were case report. Clinical, biochemical and radiological characteristics also remain obscure. Second, we studied age, sex, symptoms, changes in CRP, treatment and clinical course in patients diagnosed as having CDS in the study II.

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Figure 1. The calcifications around the dens by computed tomography in three patients diagnosed as having crowned dens syndrome. The axial cervical CT shows semicircular calcification (arrow-heads) at the posterolateral side of the dens. (a), (b) and (c) are CT of cases 2, 3 and 4 in Table 2.

Methods

Study participants

This study was approved by the Institutional Ethics Committee in National Center for Global Health and Medicine (NCGM-G-002053-00), and was also performed in accordance with the Declaration of Helsinki. We retrospectively picked up the subjects with the calcification around the dens among patients who had undergone head and neck CT between October 1, 2011 and March 31, 2012 in the study I. We also studied clinical, biochemical and radiological data of patients diagnosed as having CDS by medical chart, in the study II.

Data collection and statistical analysis

We collected data about age and gender in the study I, and obtained data including age, sex, body temperature, CRP, CT findings, treatment and clinical course in the study II.

Comparisons of age and sex between patients with and

without the calcifications around the dens by CT were performed by Mann-Whitney U test and Chi-square test, respectively. $P < 0.05$ was considered to be statistically significant.

Results

Study I

Figure 1 shows the calcifications around the dens by CT in three patients diagnosed as having CDS. The axial cervical CT shows semicircular calcification (arrow-heads) at the posterolateral side of the dens.

The strategy to pick up subjects and results was shown in Figure 2. We detected 1,056 subjects who had undergone head and neck CT, and excluded subjects who had undergone repeated CT, and also excluded patients whose CT did not show odontoid process. Three hundred sixty-five subjects were eligible for the analysis in the study I. In all subjects, age in subjects with the calcifications around the dens was significantly higher than subjects without the calcifications around the dens

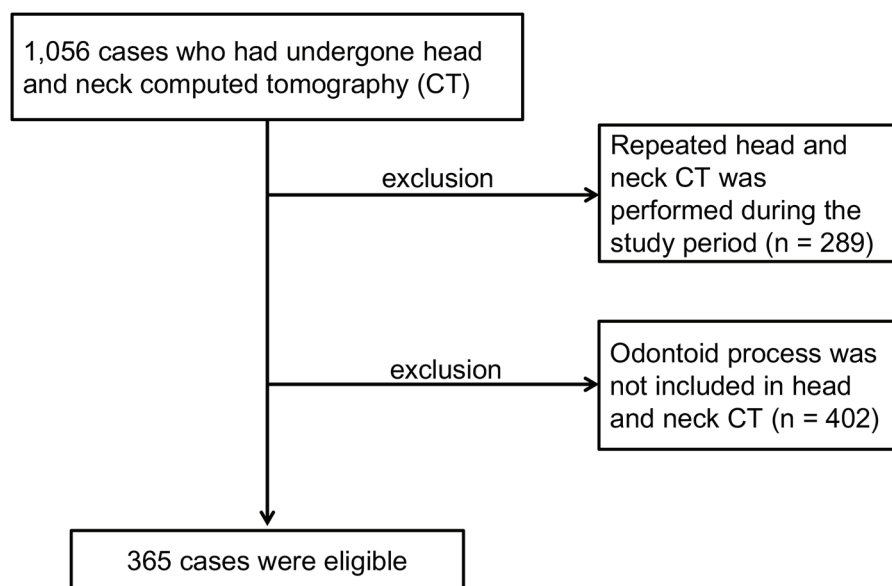


Figure 2. The strategy to pick up subjects and results.

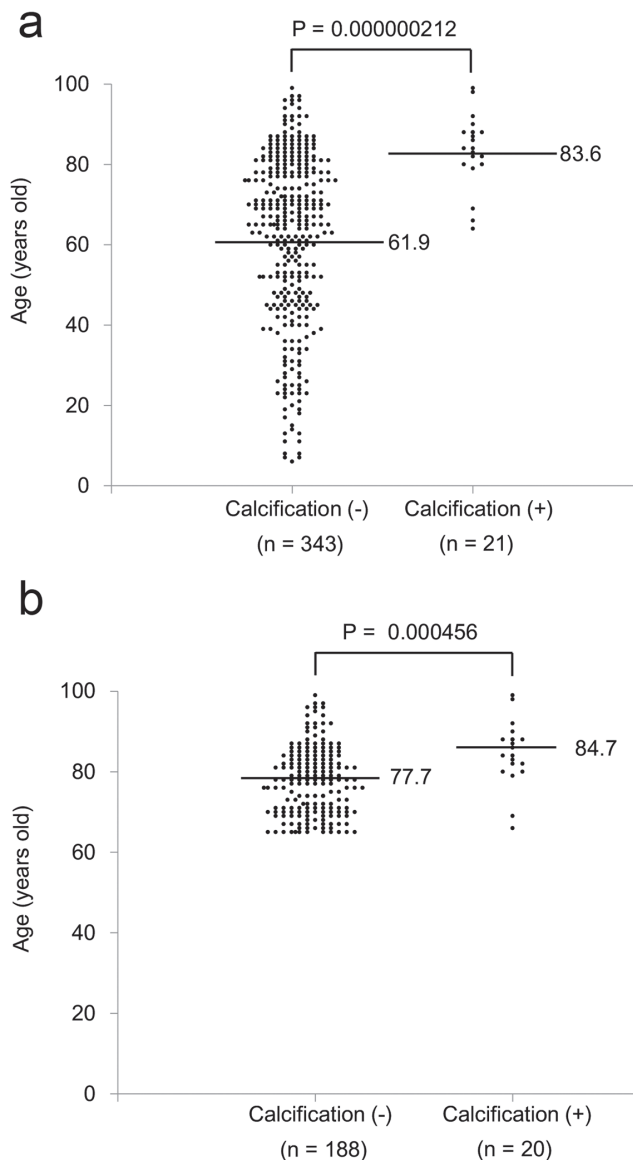


Figure 3. Age distribution and mean age in subjects with and without the calcification around the dens in all subjects (a) and subjects who were over 65 years old (b). Values on the side of horizontal bars indicate mean age.

(Fig. 3a). In subjects who were over 65 years old, age in subjects with the calcifications around the dens was also significantly higher than subjects without the calcifications around the dens (Fig. 3b).

Age, gender and frequency of the calcifications around the dens in all eligible subjects, and frequency of calcifications around the dens in subjects who were over 65 years old, and gender in subjects with calcifications around the dens are shown in Table 1. Approximately 6% of 365 subjects showed the calcifications around the dens. We found the calcifications around the dens in about 10% of subjects who were over 65 years old.

Table 1. Age, Gender and Frequency of Calcifications Around the Dens in All Eligible Subjects, and Frequency of Calcifications Around the Dens in Subjects Who Were Over 65 Years Old, and Gender in Subjects With Calcifications Around the Dens

All eligible subjects (n = 365)	
Range of age (years)	6 - 99
Male/female (n)	169/196
Calcification around the dens	
Absence, n (%)	343 (94.2%)
Presence, n (%)	21 (5.8%)
Subjects who were over 65 years old (n = 208)	
Calcification around the dens	
Absence, n (%)	188 (90.4%)
Presence, n (%)	20 (9.6%)
Subjects with calcification around the dense (n = 21)	
Male/female (n)	6/15

The positive rate of the calcifications around the dens in females (7.7%) tended to be higher than those in males (3.6%) (P = 0.093).

Study II

Age, gender, clinical symptoms, body temperature, changes in CRP levels, treatment and clinical course in patients diagnosed as having CDS are shown in Table 2. All patients presented neck pain, restricted neck rotation, fever and elevated CRP levels. Symptoms and CRP in cases 1 - 9 were promptly ameliorated by steroid and/or non-steroidal anti-inflammatory drugs (NSAIDs).

However, symptoms and CRP were deteriorated by NSAID in case 10, and blood culture showed the growth of *Staphylococcus aureus*. The CT in case 10 showed the calcification around the dens as well as cases 1 - 9 (Fig. 4). However, magnetic resonance imaging (MRI) revealed pyogenic spondylodiscitis in C5 and C6 vertebrae and the C5-C6 disc (Fig. 5).

Discussion

In the study I, we studied the association between age and the calcifications around the dens, and found that age in subjects with the calcifications around the dens was significantly higher than subjects without the calcifications. The mean age of patients with the calcification around the dens was 83.6 years old. Further, we found that approximately 10% of subjects who were over 65 years old showed the calcifications around the dens. Further, the mean age of subjects diagnosed having CDS was 83.1 years old, and the range of age was 69 - 92 years old. Present study indicated a significant association of the calcifications around the dens and CDS with old age.

Table 2. Age, Sex, Symptoms, Body Temperature, Changes in CRP Levels, Treatment and Clinical Course in Patients Diagnosed as Having Crowded Dens Syndrome

Cases	Age/sex	Symptoms	BT (°C)	Changes in CRP levels (mg/dL)	Treatment	Clinical course
1	85/F	Neck pain, restricted neck rotation	37.9	0.57 → 1.57 (day 3) → 0.22 (day 7)	Celecoxib 400 mg/day	Symptoms and fever were promptly ameliorated on day 2
2	79/F	Neck pain, restricted neck rotation, polyarthralgia	38.0	23.91 → 10.01 (day 2) → 1.25 (day 7)	Celecoxib 400 mg/day, PSL 10 mg/day	Symptoms were ameliorated on day 2, and fever was gone on day 5
3	69/M	Neck pain, restricted neck rotation	37.6	4.63 → 0.91 (day 4) → 0.35 (day 6)	PSL 15 mg/day	Symptoms and fever were promptly ameliorated on day 2
4	92/F	Neck pain, restricted neck rotation	37.5	9.72 → 3.85 (day 2) → 0.36 (day 6)	Celecoxib 400 mg/day	Symptoms were gradually ameliorated, and fever was gone on day 3
5	85/F	Neck pain, restricted neck rotation	38.4	14.33 → 5.88 (day 5) → 4.21 (day 7)	No medication	Symptoms were promptly ameliorated on day 1, and fever was gone on day 2
6	87/F	Neck pain, restricted neck rotation	38.1	5.99 → 1.38 (day 4) → 0.37 (day 7)	Celecoxib 400 mg/day	Symptoms were promptly ameliorated on day 1, and fever was gone on day 2
7	85/M	Neck pain, restricted neck rotation	37.5	11.14 → 6.45 (day 4) → 6.05 (day 9)	Sulindac 200 mg/day → loxoprofen 180 mg/day (from day 4)	Symptoms were promptly ameliorated on day 2, and fever was gone on day 3
8	84/M	Neck pain, restricted neck rotation	37.4	14.06 → 8.36 (day 2) → 1.10 (day 7)	Celecoxib 400 mg/day	Symptoms were promptly ameliorated on day 1, and fever was gone on day 2
9	82/M	Neck pain, restricted neck rotation, polyarthralgia	39.2	12.45 → 7.42 (day 2) → 0.52 (day 4)	PSL 30 mg	Symptoms were promptly ameliorated on day 1, and fever was gone on day 2
10	79/F	Neck pain, restricted neck rotation	38.3	14.30 → 16.41 (day 1)	Celecoxib 400 mg/day	Any amelioration in symptoms and fever were not observed on day 2

BT: body temperature; CRP: C-reactive protein; F: female; M: male; PSL: prednisolone.

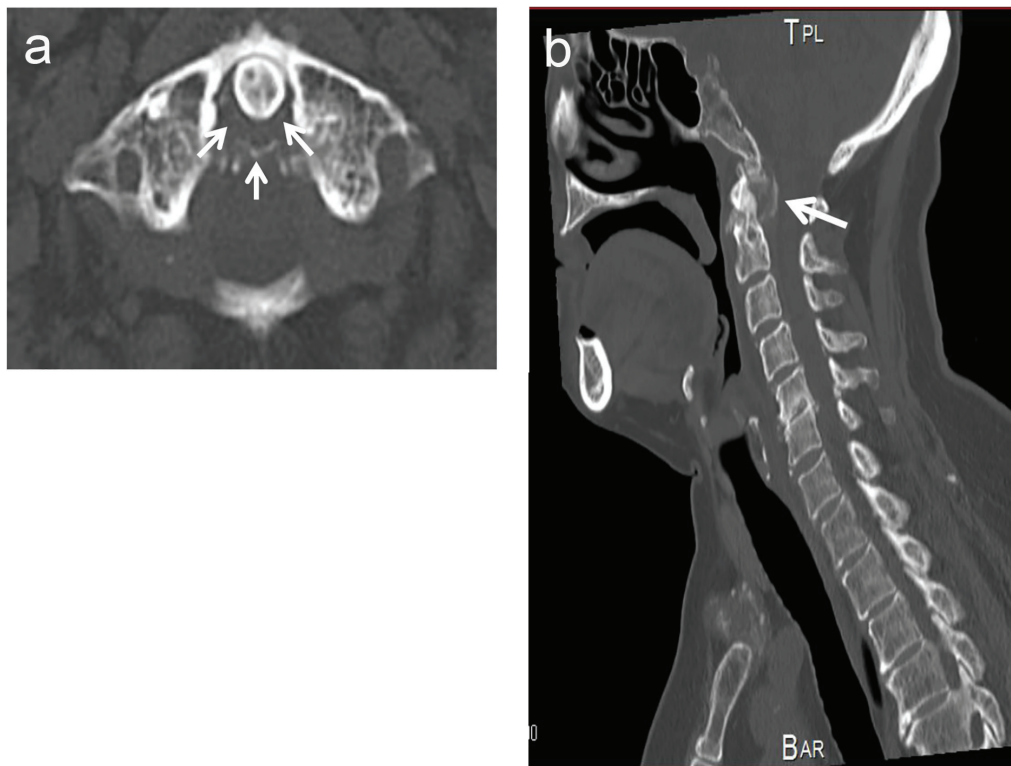


Figure 4. The axial cervical computed tomography (CT) image (a) and the sagittal CT image (b) of case 10 in Table 2. CT showed the calcification (arrow-heads) at the posterolateral side of the dens.

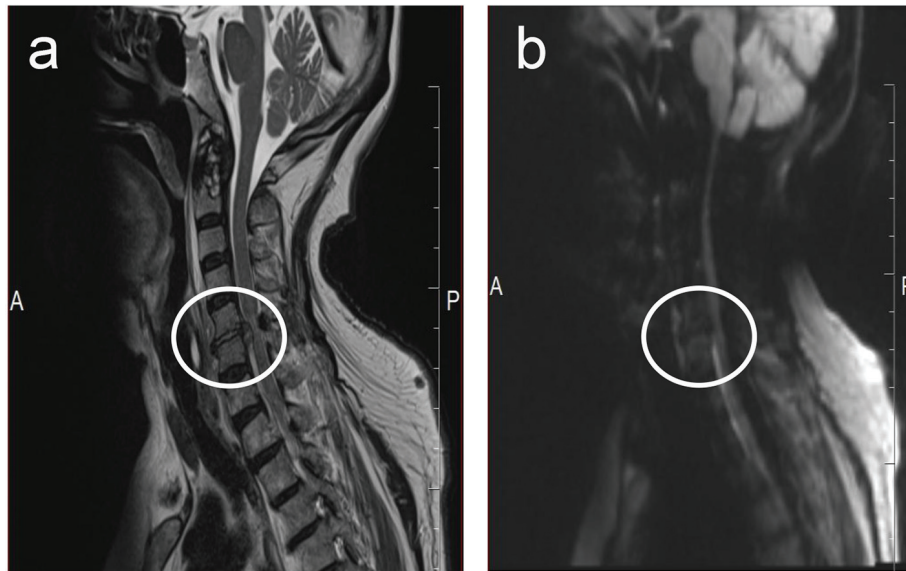


Figure 5. Magnetic resonance imaging of case 10 in Table 2. (a) and (b) are T2-weighted image and diffusion-weighted image, respectively. High-intensity area (area inside the circle) was observed in both T2-weighted image and diffusion-weighted image, suggesting the existence of pyogenic spondylodiscitis in C5 and C6 vertebrae and the C5-C6 disc.

According to our Pubmed search (reports written in English), the mean age in patients with CDS was 78.1 years old (11 males and 11 females), supporting a significant association between CDS and old age [2, 4, 5, 7, 8, 11-23].

The positive rate of the calcifications around the dens in females was about twice as high as those in males in study I, suggesting a female predominance in the calcifications around the dens. The previous study reported that the male-to-female ratio was 0.6 in 40 CDS patients [10]. Godfrin-Valnet et al reported 18 cases of CDS and they also suggested that CDS affects women over 60 years old [24]. However, nine subjects with CDS in our study II included five females and four males, which did not agree with the previous two studies [10, 24]. Further, according to case reports accumulated by our Pubmed search, 11 of 22 cases with CDS were women, challenging a female predominance in CDS [2, 4, 5, 7, 8, 10-24]. To confirm a female predominance in CDS, further studies, preferably with a greater number of CDS subjects, are needed.

Clinical, biochemical and radiological characteristics for CDS obtained from our study II are shown in Table 3. All CDS patients (cases 1 - 9) and also case 10 showed neck pain, re-

Table 3. Clinical, Biochemical and Radiological Characteristics for Crowned Dens Syndrome

1	Elderly people
2	Neck pain, restricted neck rotation and fever
3	Elevated serum CRP levels
4	The calcification around the dens detected by CT
5	The prompt response to steroid and/or NSAIDs

CRP: C-reactive protein; CT: computed tomography; NSAIDs: non-steroidal anti-inflammatory drugs.

stricted neck rotation, fever and elevated CRP levels and the calcification around the dens detected by CT (Table 2). Further, the prompt response to steroid and/or NSAIDs helped us make the diagnosis of CDS. The patient who did not show the prompt response to NSAID was finally diagnosed as having pyogenic spondylodiscitis due to *Staphylococcus aureus* by MRI and blood culture. This patient is very suggestive. First, the prompt response to steroid and/or NSAIDs is a very important tool to differentiate CDS from other diseases. Second, CT cannot detect pyogenic spondylodiscitis, which can be found by MRI. CT is the gold standard in identifying CDS, as it is able to depict the shape and site of calcification [1-4]. If we diagnosed patients as having CDS and the prompt response to steroid and/or NSAIDs was not obtained, we should perform MRI to differentiate other diseases such as infections or neurological emergencies.

We have to mention the limitation of our study. First, the study I is a cross-sectional and retrospective study which did detect the calcification around the dens but did not detect the development of CDS. Briefly, in the study I, it is unknown whether the subjects with the calcifications around the dens developed CDS or not. Second, the number of subjects in both study I and II was small.

Conclusion

To our knowledge, our study is the first to show the frequency of the calcification around the dens in the elderly people, and also a significant association between the calcification around the dens and aging. CDS has been reported to be misdiagnosed and under-recognized as a cause of acute neck pain and fever of unknown origin [25, 26]. Clinical, biochemical and radiological characteristics for CDS obtained from our study may

help many physicians make the diagnosis of CDS.

Author Contributions

RY and HY designed the research. RY, YM and SM collected data. RY and HY analyzed data, and wrote the paper. All authors read and approved the final paper.

Conflicts of Interest

The authors declare that they have no conflicts of interest concerning this article.

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