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Clinical and Radiological features of Central Giant Cell Granuloma of jaws - A systematic review and meta- analysis.

Dental Science

KEYWORDS: Diagnosis; Giant Cells; Granuloma, Giant Cell; Maxilla; Mandible; Root Resorption

Dr. Mubeen Khan	Professor & Head (M.D.S), Department Of Oral Medicine & Radiology, Govt. Dental College & Research Institute, [Affiliated to Rajiv Gandhi University of Health Sciences (RGUHS)], Bangalore – 560002.
Dr. Kondajji Ramchandra Vijayalakshmi	Associate Professor (M.D.S), Department Of Oral Medicine & Radiology, Govt. Dental College & Research Institute, [Affiliated to Rajiv Gandhi University of Health Sciences (RGUHS)], Bangalore – 560002
Dr. Taranpreet Kaur	Post Graduate Student, Department Of Oral Medicine & Radiology, Govt. Dental College & Research Institute, [Affiliated to Rajiv Gandhi University of Health Sciences (RGUHS)], Bangalore - 560002. (Corresponding author)

ABSTRACT

Background: The central giant cell granuloma (CGCG) of the jaws is a relatively uncommon pathologic lesion, accounting for less than 7% of all benign jaw lesions.

Objectives: This systematic review and meta – analysis is intended to assess the clinical and radiological features of CGCG of jaws, based on data provided in the literature.

Methods:

Data sources: The databases searched for the systematic review include PUBMED, MEDLINE, COCHRANE LIBRARY and LILACS.

Study eligibility criteria: Original research articles in which clinical and radiological features of CGCG of jaws have been assessed are included in the systematic review.

Results: In the pooled proportions of population with CGCG of jaws, displacement of adjacent structures occurred in 37%, well – defined borders in 60%, expansion in 65%, multilocular lesions in 45%, pain in 12%, perforation of tissues in 38%, root resorption in 17% and the lesions recurred in 20%.

Limitations: Selection of only observational studies and published articles might have led to selection and publication bias respectively in the study.

Conclusion: CGCG of jaws present with diverse clinical and radiographic features. A number of original research studies based on standardized protocols and with a significant population are required for improvement in diagnosis and management of this lesion.

I**mplication of key findings:** Based on the present data, it implies that knowledge about varied clinical and radiographic features of CGCG is extremely important to arrive at an accurate diagnosis. However, differentiation between aggressive and non- aggressive CGCGs should be considered to improve treatment planning and prognosis.

INTRODUCTION

Rationale:

The central giant cell granuloma of jaws is a rare benign lesion with an unknown aetiology accounting for 7% of tumours in mandible and maxilla.[1, 2] World Health Organization (WHO) has defined it as an intraosseous lesion consisting of cellular fibrous tissue containing multiple foci of haemorrhage, aggregations of multinucleated giant cells and occasionally trabeculae of woven bone.[3] The origin of CGCG is unknown; however genetic abnormalities have been implicated.[4]

In 1953, Jaffe described the lesion as "giant-cell reparative granuloma" to distinguish it from giant cell tumor of long bones. Because most of the lesions were found to be destructive rather than reparative, the word 'reparative' was omitted from the term.[1, 5]

The etiopathogenesis of CGCG is complex and controversial. Various pathologists identify the lesion as a neoplasm or a reactive process. Some consider the giant cell tumor and central giant cell granuloma as a continuum of the same disease process. Deregulation of the cell cycle may also contribute to pathogenesis of CGCG.[6]

Choung R et al. (1986) confirmed the importance of clinical behaviour of giant cell lesions in determining treatment and predicting prognosis.[7] Based on clinical and radiographic features, he and Ficarra et al. classified CGCGs into two types.[8] The first type is non-aggressive; grows slowly, does not show root resorption or cortical perforation, and often shows new bone formation; the other is the aggressive type that grows quickly, causes pain, cortical perforation, and root resorption.[5]

The biologic behaviour of CGCGs is variable and ranges from a slowly growing asymptomatic swelling to an aggressive process associated with pain, paraesthesia, cortical bone destruction, root resorption, displacement of teeth, and facial asymmetry.[6, 9] Recurrence rates ranging from 11% to 49% have been reported in the literature.[10]

Central giant cell granuloma usually occurs in patients under the age of 30 years, more often in females, and more commonly in mandible. In most series, the lesion has been reported as being confined to the tooth-bearing areas of the jaws.[11] However, it can also affect extragnathic bones, mainly in the craniofacial region, and small bones such as those of the hands and feet.[6]

Radiological findings of CGCG are diverse, ranging from small unilocular lesions to large multilocular lesions causing displacement of teeth and tooth germs, root resorption, and cortical perforation.[12]

These lesions must be differentiated from other jaw lesions such as odontogenic cysts and tumours, fibro- osseous lesions, vascular malformations and malignancies.[3]

Objectives:

This systematic review and meta- analysis is intended to address the clinical and radiological features of central giant cell granuloma of the jaws, with an objective to differentiate various other jaw lesions having similar clinical and radiographic features, which can contribute to early diagnosis and management of the lesion.

METHODS

Eligibility criteria:

1) Only original research articles on central giant cell granuloma of jaws were included in the review.
2) Studies in which both clinical and radiological features of central giant cell granuloma have been assessed were included.
3) The included articles were retrospective studies; wherein the cases of central giant cell granuloma have been procured from the previous records.

Review design:

The present systematic review was carried out by three investigators. The electronic and manual search for the review was performed by 3rd investigator. Screening of the identified titles / abstracts was carried out by first and second investigator according to set inclusion and exclusion criteria. Full text articles of the selected abstracts were retrieved by third investigator. The full text articles were assessed for eligibility by 1st and 2nd investigator and any conflicts were resolved by discussion.

Information sources:

The databases searched for relevant articles include PUBMED, MEDLINE, COCHRANE LIBRARY and LILACS.

Search:

The key words used were 'clinical features', 'central giant cell granuloma' and 'radiologic findings'. These were combined using Boolean term "AND". Time filters were used to restrict the articles to those published from 1966 to 2013. A total of 447 titles / abstracts were obtained through the electronic search, out of which 24 records were removed because of repetition. A manual literature search was done by going through the references of all the reviewed full – text articles and a single full text article was retrieved. The titles / abstracts were screened according to set inclusion and exclusion criteria. Screening yielded a total of 31 titles / abstracts. Study authors of the abstracts were contacted when the required data could not be determined from the publications. Due to non – availability of the full text articles of 10 abstracts, these were excluded and 21 full text articles were retrieved and assessed for eligibility. Finally, 14 articles were included in the systematic review and the reasons for exclusion of the remaining 7 articles are explained in Table 1.

Data collection process : Full-text articles assessed for eligibility (n = 21)

Figure 1: Flow Diagram

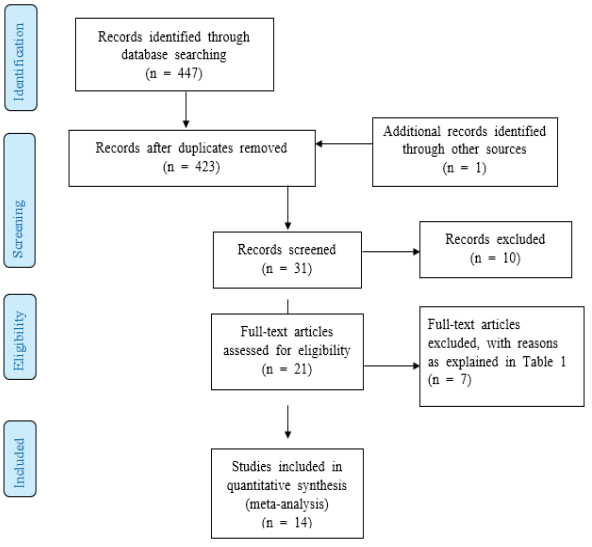

Table 1. List of excluded studies (with reasons)

S.No.	Author	Title of the study	Reason for exclusion
1.	Ficarra et al., 1987	Central giant cell lesions of the mandible and maxilla: A clinicopathologic and cytometric study.	Radiologic features not discussed
2.	Sidhu et al., 1995	Central giant cell granuloma of jaws- review of 19 cases.	Various clinical and radiographic parameters not assessed
3.	Heithersay et al., 2002	Central giant cell granuloma	Review article
4.	Aragao et al., 2006	Clinic and histopathological study of central giant cell lesions and giant cell tumours	Radiologic features not discussed
5.	Noleto et al., 2007	Radiological and epidemiological aspects of central giant cell granuloma	Other giant cell lesions also included
6.	Gomes et al., 2007	Giant cell lesion: a retrospective study of 58 cases	Radiologic features not discussed
7.	Reddy et al., 2012	Incidence of central giant cell granuloma of the jaws with clinical and histological confirmation: an archival study in Northern India.	Radiologic features not discussed

Study selection:

1) Original research articles in which both clinical and radiological features of central giant cell granuloma of the jaws have been assessed were selected for the review.
2) Publications other than journal articles, such as letters, review, case reports and scientific presentations were excluded.
3) Studies in which other giant cell lesions were part of the study were excluded from the systematic review.
4) Studies in which central giant cell granuloma of bones other than maxilla and mandible was reported, were excluded from the review.

Data items:

The data obtained was analysed for the following variables: number of cases with central giant cell granuloma of the jaws, age range, mean age, gender, site of the lesion, clinical features (swelling, pain, expansion, paraesthesia, tooth displacement), radiologic features (locularity, borders and appearance of the lesion, root resorption), and recurrence of the lesion.

Synthesis of results:

The study-specific crude odds ratio of clinical and radiological features of central giant cell granuloma was calculated for each study along with their corresponding 95% confidence intervals. Odd ratios were pooled according to the random effect model by DerSimonian and Laird Method. Under the random-effect model, the assumption of common effect was relaxed, and the effect size Θi was assumed to have a normal distribution with mean Θ and variance $\tau 2$. The usual pooled estimate of random effect model (DL) estimate for $\tau 2$ was calculated.

RESULTS

Study selection: Initial search identified 447 articles, from which 31 were selected for systematic review and meta-analysis. Data was extracted from 14 studies, which met the set inclusion criteria. All the pooled proportions given are the estimates calculated by the random effects model. Random effects model was preferred due to the heterogeneity of the results.

Study characteristics:

All included studies were published between 1966 and 2013. The

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excluded studies are mentioned in Table 1 along with reasons for exclusion. The details on study characteristics of included studies are summarised in Table 2, 3 and 4.

Table 2. Details of the search under different databases for different key terms

Key terms	Databases	Total number of titles obtained	Full text articles assessed for eligibility	Full text articles excluded	Number of articles obtained through back referencing	Total number of full text articles selected for reviewing
Clinical features AND Central giant cell granuloma of jaws	PubMed	29	7	3		7
	Cochrane	1				
	Medline	99				
	Lilacs	1				
	Manual search		1	1		
Radiologic features AND Central giant cell granuloma of jaws	PubMed	14	2			2
	Cochrane	0				
	Medline	54				
	Lilacs	0				
Radiologic findings AND Central giant cell granuloma of jaws	PubMed	20	1			1
Clinical findings AND CGCG of jaws	PubMed	21				
Central giant cell granuloma	Cochrane	3			3	3
	Medline	117				
	Lilacs	57	1	2		1
Clinical features of central giant cell granuloma	Medline	99				
Radiological features of central giant cell granuloma	Medline	39				

Table 3. Characteristics of studies included in the Systematic review and Meta – analysis

Author	Cases	Age range	Cases < 30 years	Mean age	M:F	Lesions in mandible	Lesions in maxilla	Swelling	Pain	Expansion	Perforation	Displacement	Recurrence
Cohen, 1988	16	7 to 63			07:09	13	3					10	
Horner, 1989	26		14		11:15	20	6			10	10	11	
Whitaker, 1993	69	2 to 81	44	23	26/43	52	17		9		24	25	
Kaffe, 1996	80	2 to 84	48	29.8	29/51	53	27		4	62		34	
Bodner, 1996	10		10		05:05	7	3					8	
Katz, 2002	20	9 to 82	12		09:11	17	3			9	10	8	
Gungormus, 2003	27	8 to 70		31.33	06:21	15	12		3	12		9	
de Lange, 2005	83		47	30.8	36/47	60	29	3	3			15	22
Losler, 2006	26	4.8 to57.4			09:17	18	8		7		7	5	3
Farrier, 2006	9	7 to 61	7	27	06:03	6	3	8	2	8		1	0
Sun et al, 2009	22	7 to 81		31.7	08:14	16	6	18	4				4
Francisco et al, 2009	10	5 to 37		16.3	02: 08	8	2			10	3	7	1
Amirchaghmaghi, 2010	18	7 to 65	13	23.5	07:11	15	3	14	3	14	2	7	
Aghbali, 2013	23	10 to 75		37.5	08:15	7	16				18	1	

Table 4. Characteristics of studies included in the Systematic review and Meta – analysis

Author	Cases	Lesions in mandible	Lesions in maxilla	Multilocular lesions	Unilocular lesions	Well defined borders	Root resorption
Cohen, 1988	16	13	3	8	8	9	3
Horner, 1989	26	20	6	4	22	18	3
Whitaker, 1993	69	52	17	42	27	13	13
Kaffe, 1996	80	53	27	41	35	45	10
Bodner, 1996	10	7	3	5	5	6	2
Katz, 2002	20	17	3	9	11	13	6
Gungormus, 2003	27	15	12	15	12	24	0
de Lange, 2005	83	60	29	14	75		11
Losler, 2006	26	18	8	11	15	15	6
Farrier, 2006	9	6	3	7	2	6	0
Sun et al, 2009	22	16	6	7	15	14	
Francisco et al, 2009	10	8	2	4	6		4
Amirchaghmaghi, 2010	18	15	3	14	4		2
Aghbali, 2013	23	7	16	0	23	16	2

Table 5. Overall association of clinical and radiological features with CGCG

Clinical/ Radiological features	% of pooled proportion of patients with this feature
Displacement of adjacent structures	37 (95% CI = 0.27 – 0.48)
Expansion	65 (95% CI = 0.46 – 0.80)
Lesions in mandible	70 (95% CI = 0.63 – 0.76)
Lesions in maxilla	31 (95% CI = 0.24 – 0.38)
Unilocular lesions	57 (95% CI = 0.44 – 0.70)
Multilocular lesions	45 (95% CI = 0.34 – 0.57)
Pain	12 (95% CI = 0.08 – 0.20)
Perforation	38 (95% CI = 0.24 – 0.55)
Root resorption	17 (95% CI = 0.13 – 0.21)
Swelling	58 (95% CI = 0.11 – 0.94)
Well defined borders	60 (95% CI = 0.48 – 0.72)
Recurrence of lesion	20 (95% CI = 0.12 – 0.31)

Synthesis of results:

In the pooled proportion of central giant cell granuloma patients, displacement of adjacent structures occurred in 37% (95% CI = 0.27 – 0.48), well – defined borders were seen in 60% (95% CI = 0.48 – 0.72), expansion was present in 65% (95% CI = 0.46 – 0.80), multilocular lesions in 45% (95% CI = 0.34 – 0.57), pain in 12% (95% CI = 0.08 – 0.20), perforation of tissues in 38%

(95% CI = 0.24 – 0.55), resorption of roots occurred in 17% (95% CI = 0.13- 0.21) and the lesions recurred in 20% (95% CI = 0.12 – 0.31).

Figure 2 represents a forest plot for displacement of adjacent structures by Central giant cell granuloma of jaws; where the actual average effect is 0.37 (95% CI= 0.27-0.48). The analysis of heterogeneity for the 13 observational studies gave an I-squared value of 69.1% with a p value of 0.0001.

The forest plot (Figure 3) for borders of CGCG gave an I-squared value of 77.6% for well-defined borders of the lesion. Based on the random effect model, the actual average effect is 0.60 (95% CI= 0.48-0.72), with a p value of < 0.0001.

Figure 4 is the forest plot for expansion caused by CGCG of jaws; where I-squared value is 77.2%, which indicates that the heterogeneity of the study is more. The actual average effect is 0.65 (95% CI= 0.46- 0.80), with a p value of 0.0002. The actual average effect for swelling caused by CGCG is 0.58 (95% CI= 0.11- 0.94) with a p value of <0.0001 (Figure 5).

Figure 6 represents the forest plot for number of lesions in mandible as reported in all the 14 observational studies. The actual average effect is 0.70 (95% CI= 0.63 - 0.76) and the analysis of heterogeneity for these studies gave an I-squared value of 44.6% with a p value of 0.0364. In relation to the lesions in maxilla (Figure 7), the overall effect is 0.31 (95% CI = 0.24- 0.38) with an I-squared value of 44.8% (p= 0.0356).

The actual average effect for multilocularity (Figure 8) in CGCG of jaws as reported in 13 studies is 0.45 (95% CI = 0.34- 0.57), with an I-squared value of 76.6% and a p value of <0.0001.

The forest plot (Figure 9) for pooled proportion for pain in CGCG has an actual average effect of 0.12 (95% CI= 0.08- 0.20). The analysis of heterogeneity for 8 studies gave an I-squared value of 54.2%. (p= 0.0326). Similarly, the forest plot (Figure 10) for root resorption has an actual average value of 0.17 (95% CI= 0.13- 0.21), with a p value of 0.3922.

Figure 11 represents a forest plot for perforation of tissues in central giant cell granuloma of jaws. Here the actual average effect is 0.38 (0.24 - 0.55) with an I-squared value of 69.7% (p= 0.003). This indicates that the variability of the study is high.

Recurrence of CGCG of jaws (Figure 12) has been reported by 5 observational studies. The analysis of heterogeneity for these studies gave an I-squared value of 14.7% with a p value of 0.3184.

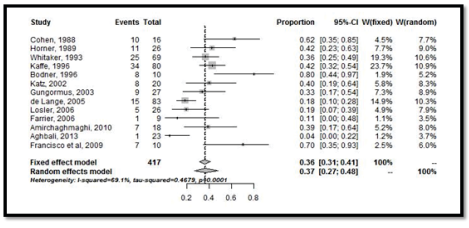

Fig 2. Forest plot: Pooled proportion of CGCG with displacement of adjacent structures

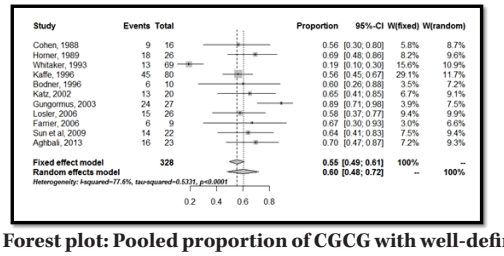

Fig 3. Forest plot: Pooled proportion of CGCG with well-defined borders

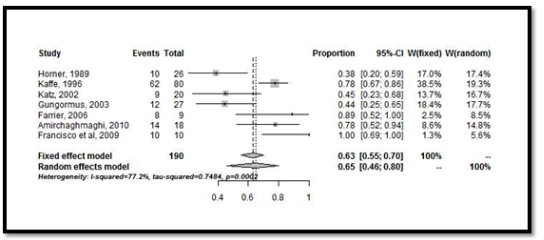

Fig 4. Forest plot: Pooled proportion of CGCG with expansion of cortical plates

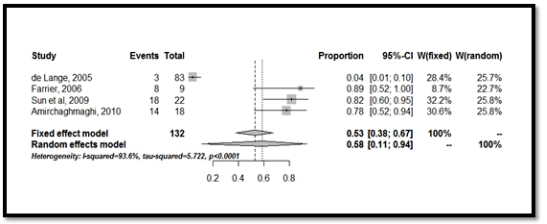

Fig 5. Forest plot: Pooled proportion of CGCG with swelling

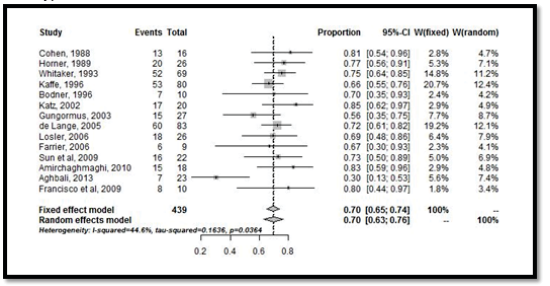

Fig 6. Forest plot: Pooled proportion of CGCG with lesions in mandible

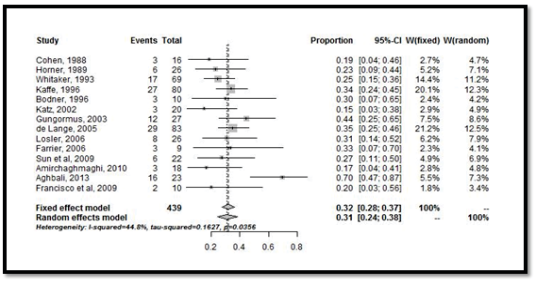

Fig 7. Forest plot: Pooled proportion of CGCG with lesions in maxilla

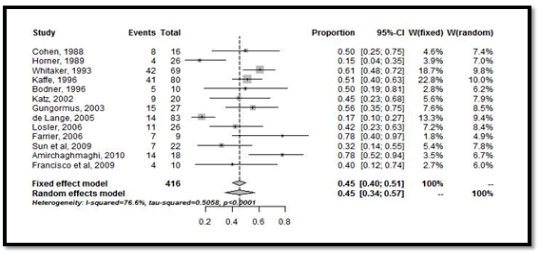

Fig 8. Forest plot: Pooled proportion of CGCG with multilocular lesions

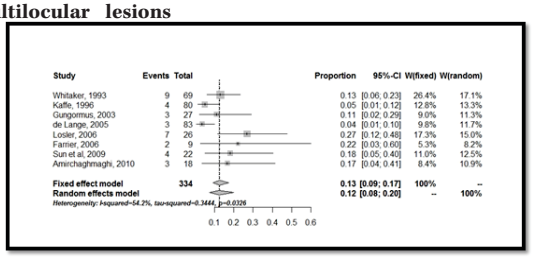

Fig 9. Forest plot: Pooled proportion of CGCG with

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pain

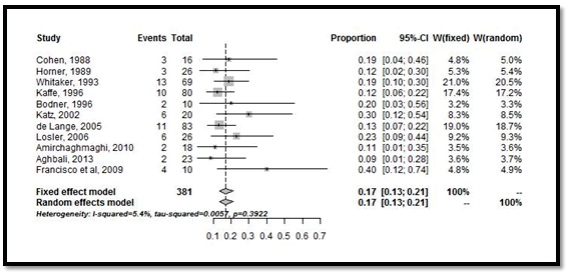

Fig 10. Forest plot: Pooled proportion of CGCG with root resorption

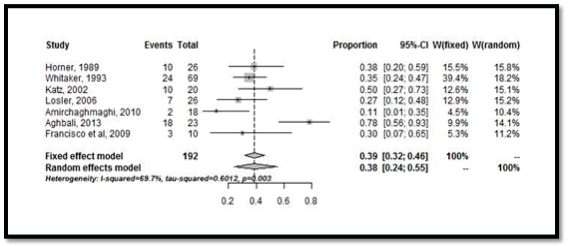

Fig 11. Forest plot: Pooled proportion of CGCG with perforation of tissues

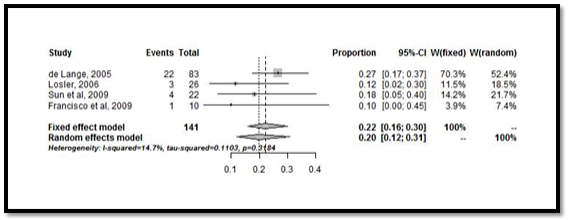

Fig 12. Forest plot: Pooled proportion of CGCG with recurrence of the lesion

Table 6. Overall association of clinical and radiological features with CGCG

Clinical / Radiological features	% of pooled proportion of patients with this feature
Displacement of adjacent structures	37 (95% CI = 0.27 – 0.48)
Expansion	65 (95% CI = 0.46 – 0.80)
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Perforation	38 (95% CI = 0.24 – 0.55)
Root resorption	17 (95% CI = 0.13 – 0.21)
Swelling	58 (95% CI = 0.11 – 0.94)
Well defined borders	60 (95% CI = 0.48 – 0.72)
Recurrence of lesion	20 (95% CI = 0.12 – 0.31)

DISCUSSION

Summary of evidence:

The central giant cell granuloma is classified as a true neoplasm and a reactive proliferative process because of its dynamic biologic characteristics and variable clinical patterns. Regardless of the specific cause, the CGCG seems to be a distinct entity from a true giant cell tumour of bone showing significant differences in terms of age, distribution, and biologic behaviour.[6] This systematic review comprising of 14 well established studies on CGCG of jaws, published in literature, revealed a myriad of radiographic features of the lesion. In most cases, the lesions exhibit a unilocular appearance (57%), with well-defined borders (60%), displace teeth and anatomic structures (37%), cause expansion of cortical bone (65%), and cortical perforation (38%). In this systematic review and meta-analysis, a slight female predilection is seen in central giant cell granuloma of jaws which is explained by the association between hormonal secretion and appearance of the lesion.[2] It has been proposed that hormonal and hemodynamic changes occurring during pregnancy act as stimulating factors, and promote the growth of the lesion but does not cause it. Witaker and Bouquot concluded that factors other than a direct influence of the ovarian hormones are responsible for the development and growth of the lesion.[1]

In the present review, majority of patients are younger than 30 years of age; this supports the age distribution reported by other investigators; CGCG appears most frequently in the first and second decade of life (48%), and almost 60% of the lesions are diagnosed before 30 years of age.[1] The craniofacial skeleton is actively developing in young children to include osteogenesis, exfoliation and eruption of teeth. These processes cease in adulthood and may therefore predispose to CGCG in younger individuals.[2]

The majority of the studies in the present review reported mandible as the most common site of involvement. According to Austin et al., CGCG involves the mandible more frequently than maxilla and that no predilection exists for any specific site, whereas Waldron and Shafer reported that CGCGs tend to occur in the anterior portion of both the jaws.[1] It has been reported that in mandible, the lesions are located in the tooth bearing areas previously occupied by primary dentition and may cross the midline.[13]

There is considerable variation in the clinical behaviour of CGCG. They may present with rapid onset of symptoms including pain, parasthesia, root resorption and tooth displacement, with expansion or local destruction of surrounding bone, leading to facial asymmetry; or simply discovered incidentally on routine examination as an asymptomatic lesion.[9] Only, 12% of the pooled proportion of population in our analysis presented with pain whereas swelling was observed in 58%.

Central giant cell granuloma presents with variable radiographic features ranging from incidental findings on routine radiographic examination to large destructive multilocular radiolucencies involving contiguous bony structures.[8] In this meta- analysis, 57% of the pooled proportion of patients presented with unilocular lesions, whereas multilocularity was seen in 45%. It is believed that CGCG begins as a single resorption lacuna that enlarges in conjunction with the formation of adjacent resorption lacunae. V – shaped bony ridges separate the resorption lacunae, thus create a multilocular appearance.[13]

Central giant cell granuloma may envelope the roots of adjacent teeth completely, causing them to protrude in the lesions. It may cause divergence of roots of adjacent erupted teeth, displacement of unerupted teeth or may lead to resorption of adjacent root apices.[13] In this meta- analysis, displacement of adjacent structures was seen in 37% of the pooled proportion of the population whereas root resorption was seen in 17%. According to Miles and co- authors (1991), CGCG tends to resorb the root apex in a slightly concave- cervical direction, creating a curved appearance. It may cause root resorption along multiple root planes on the same root and at two or more locations on an adjacent root. Evidence of root resorption is considered as a marker for more aggressive disease process.[13]

CGCG is reported to have a low growth index, therefore, the borders appear to be distinct and non-diffuse.[2] The present review and meta- analysis is in agreement to this as 60% of the pooled proportion of population presented with well-defined

borders.

A variable degree of expansion is observed in CGCG, which leads to thinning of cortical plates, with possible perforation to involve the surrounding soft tissues.[9] In this review and meta – analysis, expansion accounted for 65% of the pooled proportion of patients while perforation was seen in 38%. It is believed that the larger the CGCGs grow in size, the more is the probability they will cause expansion of the bones.[5] Perforation of the cortical bone, when present, is regarded as typical for aggressive growth.[6]

CGCGs are known to recur, and recurrence is a feature of aggressive type.[13] It has been reported that recurrence of CGCG is most frequent when the primary lesion perforates the cortical plate to involve the surrounding soft tissues. Treatment and complete resolution of CGCG occurs with surgical excision; however, the extent of surgery is related to the size and position of the lesion and may range from simple excision and curettage to en bloc resection and reconstruction.[9] In cases with multiple recurrences of CGCG, the Brown tumour of hyperparathyroidism should be strongly suspected.[13]

Limitations:

This meta – analysis includes only observational studies, hence may lead to selection bias. Secondly, the meta – analysis is based on published articles; which may account for publication bias.

CONCLUSION:

Implications for practice

Due to diverse clinical and radiographic presentation of central giant cell granuloma, the accurate diagnosis of the lesion lies on correct interpretation of clinical, radiographic and histopathological data. Amalgamating this information enables correct diagnosis from other lesions such as hyperparathyroidism, ameloblastoma and giant cell tumour of long bones.

Implications for research

For the improvement of diagnosis and management of CGCG, controlled studies based on standardized protocols and with a significant population may help to enhance the knowledge about this rare bone tumour.

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