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RESEARCH

The occurrence of keratocystic odontogenic tumours in nevoid basal cell carcinoma syndrome

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Objectives: This retrospective study reviews the occurrence of keratocystic odontogenic tumours (KOTs) in nevoid basal cell carcinoma syndrome (NBCCS) patients seen in the Oral and Maxillofacial Radiology Special Procedures Clinic in the Faculty of Dentistry at the University of Toronto.
Methods: This study examines the number and radiographic features of KOTs identified in 11 NBCCS patients who presented with 43 KOTs between January 1989 and 30 June 2007 on plain film radiographs and CT.
Results: Regression analysis revealed a statistically significant ($P < 0.01$) relationship between the age at first KOT occurrence and the total number of lifetime KOTs ($r = -0.78$). Of the KOTs identified, 25 developed in the mandible and 18 developed in the maxillae. The majority of these were associated with a change in either the size or shape of the follicular space, and both plain film radiography and CT were equally effective at demonstrating these changes. CT was, however, more effective at demonstrating endosteal scalloping of cortical bone than plain film radiography ($P < 0.001$) while the opposite was true for showing tooth displacement ($P < 0.01$). For patients imaged with both plain radiography and CT (29 KOTs), 5 KOTs were detectable only by CT.
Conclusions: Our results suggest that there should be early and frequent monitoring of NBCCS patients for the development of KOTs in youth and adolescence, and that CT imaging should play an important role in these investigations.
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Introduction

Nevoid basal cell carcinoma syndrome (NBCCS) is an autosomal dominant anomaly associated with a mutation of the human homologue of the *Drosophila* patched (PTCH) gene.[1] The syndrome is characterized by multiple basal cell carcinomas, palmar and/or plantar pitting, bifid ribs, dystrophic calcification of the falx cerebri and multiple keratocystic odontogenic tumours (KOT) (formerly known as the odontogenic keratocyst or OKC) of the jaws.[2]

To date, there have been four large-scale clinical/epidemiological studies involving NBCCS patients,[3–6] and many case reports of single individuals or small family cohorts. In the large-scale studies, data were accrued by either personal or telephone interviews and relied on patient self-reports. The prevalence of the syndrome has been reported to range from 1 case per 164 000[6] to 1 case per 55 600 population,[3] and KOTs occur in 66–92% of these patients.[3,5] The tumours in NBCCS patients may develop as early as the first decade of life and show a peak incidence in the second and third decades.[3–6] They are also more commonly found in the mandible than in the maxillae[3–6] and, while some may be asymptomatic, a jaw asymmetry may develop or there may be tooth displacement, mobility, or failure of eruption of an adjacent developing permanent tooth or teeth.

Although benign, KOTs grow aggressively by extending into adjacent areas of bone, and in some instances may either produce endosteal scalloping of

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the overlying cortex or fenestrate the cortex. Because of their relatively high rates of recurrence, variously reported at between 5% and 62%,[7] KOTs are often treated aggressively by surgery and closely monitored post-operatively. However, in spite of the aggressive nature of KOTs, only two of the clinical/epidemiological studies made recommendations regarding the diagnosis of KOTs in NBCCS patients. Evans et al,[3] for example, recommended that annual dental screening should be started at 8 years of age and "this will usually entail an orthopantomogram of the jaw". Kimonis et al,[4] who carried out the only study to develop a probability curve of the risk of developing jaw cysts at different ages, recommended that "regular early dental surveillance with annual panorex films is recommended as soon as the child can comply with the examination procedure".

This paper is a retrospective study of KOTs arising in NBCCS patients seen in the Special Procedures Clinic in Oral and Maxillofacial Radiology at the Faculty of Dentistry at the University of Toronto between 1989 and 30 June 2007.

Materials and methods

NBCCS patients were identified from the Special Procedures database (Filemaker Pro; Database Software Solutions, Santa Clara, CA) in the Discipline of Oral and Maxillofacial Radiology, Faculty of Dentistry, University of Toronto. The study was approved by the Institutional Review Board of the University of Toronto.

Clinical/epidemiological data were extracted from patient diagnostic images, written clinical records and radiographic reports. These data included patient age of first KOT, total number of KOTs and the incidence of KOTs in the maxillae and mandible. The following radiographic features of KOTs were also examined: the effects of the KOT on the position(s) of the teeth and adjacent normal anatomical structures. The latter included the expansile effects on the bone and scalloping of the endosteal surface of the bone cortex. The presence of root resorption and the effect of KOT on the follicular spaces of developing teeth were evaluated, too.

The radiographic features of the KOTs were evaluated by three certified specialists in oral and maxillofacial radiology (EWNL, SEP, MJP). These evaluations were performed independently, and a feature was determined to be present when two of the three oral and maxillofacial radiologists identified it as such. When both plain film and CT images were available, the images were evaluated separately, 1 week apart.

Statistical analysis of the epidemiological data was performed using Microsoft Excel (Microsoft Office; Microsoft Corporation, Redmond, WA). A χ^2 test with one degree of freedom was used to determine statistical differences between plain film and CT image characteristics of KOTs.[8] For all tests, statistical relationships were determined to be significant when $P < 0.05$.

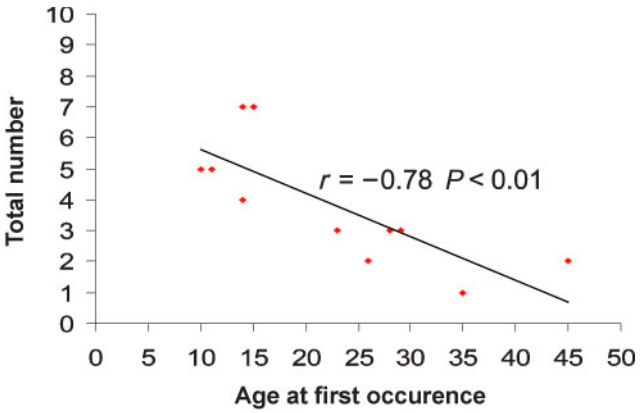

Figure 1 Regression analysis depicting total number of lifetime keratocystic odontogenic tumours (KOTs) with age of first KOT occurrence

Results

A total of 43 KOTs were identified in 11 patients, 5 males and 6 females. The patients ranged in age from 10–45 years, were evaluated between one and six times between 1989 and 2007 and were followed up clinically and radiographically between one and five times over the same time period. In total, 18 KOTs were found in the maxillae and 25 were identified in the mandible. There was an inverse relationship between the age at first KOT occurrence and the total number of KOTs detected ($r = -0.78$); this was significant to $P < 0.01$ (Figure 1).

Archived radiographic reports and images were available for all patients; however, the image sets for each patient varied depending on the date of the initial examination as well as the suspected locations of the KOTs. For example, examinations performed in the early 1990s did not include a CT study but later examinations did. Moreover, intraoral radiography, including occlusal radiography, was performed more commonly in the mandible than the maxillae. 6 of the 11 patients received intraoral images while 10 of the patients received panoramic images. All patients received some form of plain film skull imaging while 7 of the 11 patients received CT. Of the patients who underwent both plain film imaging and CT, it is of note that 5 of the total 29 KOTs identified were found only on CT and not on the plain images. In general, these KOTs were small in size (see Figure 2) and so did not attenuate the incident radiation enough to register an image. Two of these were associated with developing maxillary third molars and one was associated with a developing mandibular third molar. The remaining two were associated with erupted teeth: a mandibular first molar and a maxillary second premolar.

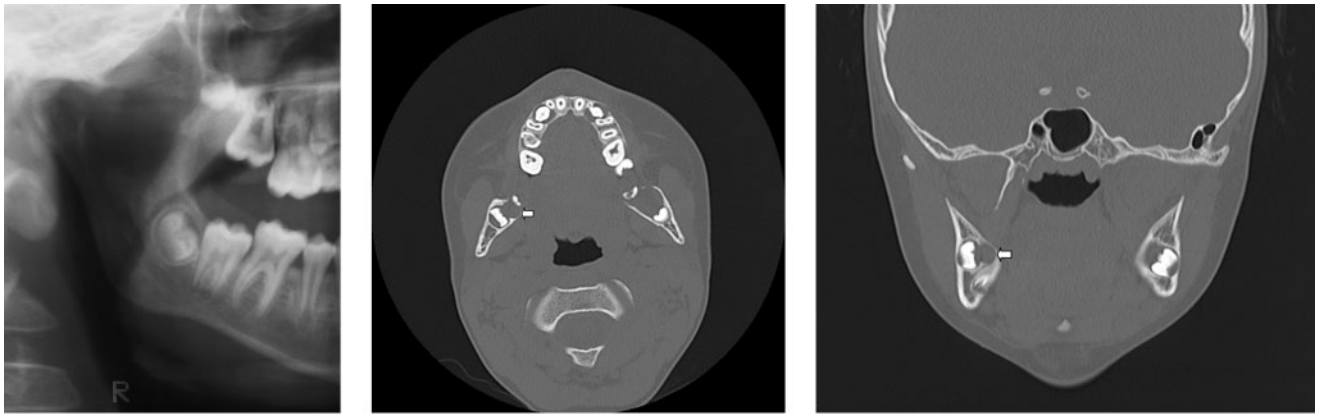

Figure 2 (a) Cropped panoramic image showing normal developing mandibular right third molar, and (b) axial and (c) coronal CT images showing small keratocystic odontogenic tumour associated with the crown of the developing third molar, unseen in (a).

The majority of KOTs were associated with dental follicles of unerupted teeth. The ability of the imaging modalities to depict changes to the appearances of the follicles was almost equal: 58% on plain images and 41% on CT for asymmetric enlargements; 6% on plain film images and 14% on CT for symmetric enlargements. No statistically significant differences were found between the two modalities. Interestingly, the majority of KOTs were associated with asymmetrically enlarged follicles (58%); that is, a transition or inflection point was found between the outer cortical contour of the follicle and the KOT, indicating that the whole tooth follicle was not involved as seen in dentigerous cysts (Figure 3). Fewer than half of all KOTs arose centrally in the bone and were not related to unerupted teeth.

Figure 3 Cropped panoramic image highlighting an inflection point in the distal aspect of the follicle surrounding the mandibular right third molar

Both plain film and CT images of the patients demonstrated displacements of normal anatomical structures, expansion of bone and loss of cortical integrity; however, there were no statistically significant differences in the abilities of the two modalities to show this. CT was more effective (59% *vs* 16%) at demonstrating endosteal scalloping of the cortex, and this was significant to $P < 0.001$.

With regard to the teeth, plain film radiography was more effective (81% *vs* 50%) at demonstrating tooth displacement; this was significant to $P < 0.01$. Tooth resorption was not observed in any of the cases.

These findings are summarized in Table 1.

Discussion:

The prevalence of nevoid basal cell carcinoma syndrome (NBCCS) has been reported to range between 1 case per 164 000[6] and 1 case per 55 600[3] population, and keratocystic odontogenic tumours occur in 66–92% of these patients.[3,7] Although mutations of the human homologue of the *Drosophila* patched gene (PTCH), located on the long arm of chromosome 9, has been identified as the molecular lesion responsible for the disease,[1] patient diagnosis continues to rely on the identification of a combination of major (the presence of basal cell carcinomas, odontogenic keratocysts of the jaw, palmar or plantar pits, calcification of the falx cerebri, rib anomalies or a first degree relative who has

Table 1 Summary of radiographic features of keratocystic odontogenic tumours in nevoid basal cell carcinoma syndrome patients

		Plain images	*CT*	P
Tooth follicle relationships	Arising centrally within bone	11/31 (35%)	10/22 (45%)	NS
	Causing asymmetrical follicle enlargement	18/31 (58%)	9/22 (41%)	NS
	Causing symmetrical follicle enlargement	2/31 (6%)	3/22 (14%)	NS
Effects on bone	Displacement of anatomical structure(s)	11/31 (35%)	11/22 (50%)	NS
	Producing expansion of bone	11/31 (35%)	11/22 (50%)	NS
	Causing loss of cortical integrity	15/31 (48%)	15/22 (68%)	NS
	Causing endosteal scalloping	5/31 (16%)	13/22 (59%)	<0.001
Effects on teeth	Tooth displacement	25/31 (81%)	11/22 (50%)	<0.01
	Tooth resorption	0/31 (0%)	0/22 (0%)	NS

NS, not significant

already been diagnosed with the syndrome) and minor phenotypic anomalies (macrocephaly, congenital craniofacial malformations, skeletal abnormalities of the scapula, sternum or fingers, bridging of the sella turcica, ovarian fibroma or medulloblastoma).[9] The diagnosis is based on the identification of two major criteria, or one major and two minor criteria.

All of the four large-scale clinical/epidemiological studies examining NBCCS stigmata have relied almost exclusively on either personal or telephone interviews and on patient self-reports.[3–6] And while KOTs were discussed as one stigma of patients in these studies, the jaw lesions were not the central focus. Furthermore, only two of the studies made recommendations regarding diagnosis and monitoring of the jaws in NBCCS patients. Specifically, Evans et al[3] recommended that annual dental screening should be started at 8 years of age and ''this will usually entail an orthopantomogram of the jaw''. Kimonis et al[4] developed a probability curve of the risk of developing KOTs and estimated that 75% of patients developed KOTs by the age of 20 years. After that age, the probability of KOT development appeared to reach a steady state until the final data point at 55 years. Kimonis et al recommended that ''regular early dental surveillance with annual panorex films is recommended as soon as the child can comply with the examination procedure''. Our results support somewhat the theoretical KOT probability model of Kimonis et al.[4] Likewise, we found an inverse relationship between the age at first KOT occurrence in our patient population and total number of KOTs identified. In other words, the younger the patient was when the first KOT was identified, the greater the likelihood that the patient would develop more KOTs during his or her lifetime. Patients who developed their first KOT at an older age were less likely to develop more.

In the present study, we retrospectively examined a group of 11 patients diagnosed with NBCCS who presented with 43 KOTs between 1989 and 30 June 2007 in the Oral and Maxillofacial Radiology Special Procedures Clinic at the University of Toronto's Faculty of Dentistry. Because the time span of the study was 18 years, and because developments and access to imaging modalities changed over the years, patients received plain radiographs, CT, or a combination of the two. A small subset of these patients (six) received both plain film imaging and CT.

In 6 patients who received both plain and CT imaging, 29 KOTs were identified. Interestingly, 5 of the 29 KOTs were seen only on CT and not on plain films. In these cases, the KOTs were small and tucked behind the crowns or between the roots of teeth. The KOTs were so small that we hypothesize that the loss of attenuation in the bone created by their presence was not significant enough to be seen over the attenuation of superimposed structures. Three of these five patients had unrestored dentitions. For the other two patients who had amalgam restorations, beam hardening artefact did not confound the identification of these KOTs. In order to identify KOTs when they are small, our results suggest that there should be early and frequent monitoring of KOT development in young and adolescent NBCCS patients, and that CT should be a part of this monitoring process. Less vigilance may be required if the first KOT develops later in adulthood.

In this study, we found that 35% of KOTs identified on plain film images and 45% of KOTs identified on CT images arose centrally within the bone and were not associated with a tooth or tooth follicle at all. In the instance that a KOT were to arise within the bone but abut a dental follicle, this would be considered to be a KOT arising from within the bone if the cortex of the follicle was deemed to be intact and uninterrupted. In contrast, 64% (total) of KOTs identified on plain film images and 55% (total) of KOTs identified on CT were associated with changes to the size and/or shape of a dental follicle. In our analysis, we chose to separate out those enlarged follicles that caused a symmetrical enlargement of the follicle and those that caused an asymmetric enlargement of the follicle because we believe this distinction to be an important diagnostic sign. Compared with dentigerous cysts, in which there is usually symmetrical enlargement of the follicle from the cemento-enamel junction (CEJ) area, only 6% of KOTs on plain film radiographs and 14% of KOTs on CT demonstrated a symmetrical enlargement pattern of the follicle.

While CT was effective at demonstrating many characteristics, including scalloping of the endosteal cortical surface ($P < 0.001$), compared with plain film radiography, the opposite was the case for demonstrat-

ing tooth displacement by a KOT ($P < 0.01$). So while advanced imaging procedures may play an important role in the identification of disease in NBCCS patients, it does not, at this time, totally supersede plain radiography as an imaging tool for teeth. Also, although the survey instrument was not designed to evaluate the number and extent of loss of cortical integrity, the impression of the observers was that CT demonstrated more regions of discontinuity and their extents better than plain films. This information is useful for the surgical treatment of KOTs if the oral and maxillofacial radiologist or the surgeon were concerned about the encroachment of a large KOT into an adjacent soft tissue space.

The separation of new KOT occurrences versus recurrences is potentially problematic because at this time it is not possible to ''tag'' a KOT and then re-examine a recurrence for this tag. Therefore, our interpretation of what constitutes a new or recurrent KOT is based exclusively on the position and epicentre of a lesion and our having access to archived images. Of the 43 KOTs we identified in this study, we identified one recurrence on the basis of its position, but did not count the recurrence as a separate entity.

NBCCS patients have been cautioned to avoid excessive exposure to ultraviolet and X-radiation, as sporadic case reports have associated therapeutic doses of ionizing radiation with the development of malignancy.[10,11] At this time, these reports are few and there are no studies that look specifically at this effect. That said, some patients (or their parents) may fear repeat imaging studies, particularly when these include the relatively high effective radiation doses that are inherent to medical CT. Therefore, small field-of-view cone beam CT with its lower effective doses but equally effective three-dimensional image reconstruction paradigms may be a viable low-dose option for long-term monitoring and follow-up of children and adolescent NBCCS patients.

Conclusions

This retrospective study of 11 patients with NBCCS with 43 KOTs revealed a statistically significant negative association between age at first KOT and total lifetime KOT number. Not reported previously, our findings demonstrate that CT was able to identify small KOTs not found on plain film images in 5 of 29 KOTs found in patients who were imaged with both procedures. CT was also able to depict endosteal scalloping of a cortical border better than plain film images, but the latter was more effective for demonstrating tooth displacement. A novel finding in analysing the CT images was a coronal relationship of KOTs with unerupted teeth that is different from the involvement of the whole follicle by dentigerous cysts: the finding of the asymmetrically enlarged dental follicle. Our results suggest that there should be early and frequent monitoring of KOT development in young NBCCS patients, and that CT imaging, in particular cone beam CT imaging, should play an important role in these investigations.

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