Odontomas and Supernumerary Teeth: Is There a Common Origin?

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Abstract

The aim of the present work is to analyze all scientific evidence to verify whether similarities supporting a unified explanation for odontomas and supernumerary teeth exist. A literature search was first conducted for epidemiologic studies indexed by PubMed, to verify their worldwide incidence. The analysis of the literature data shows some interesting similarities between odontomas and supernumerary teeth concerning their topographic distribution and pathologic manifestations. There is also some indication of common genetic and immuno-histochemical factors. Although from a nosological point of view, odontomas and supernumeraries are classified as distinct entities, they seem to be the expression of the same pathologic process, either malformative or hamartomatous.

Key words: Supernumerary teeth, Odontomas, Odontogenic tumors, Tooth retention.

Introduction

Odontomas (ODs) are currently still classified by the World Health Organization among the benign mixed odontogenic tumors as lesions in which all odontogenic tissues (enamel, cement and dentin) are involved in varying proportions and different degrees of development, although they are really considered as hamartomas or malformations.

They are typically divided into compound and complex ODs although mixed forms have been described. Compound ODs (CpODs) are formed by many little tooth-like structures often strictly adapted to each other and held together by a more or less complete connective capsule. CpODs are easily recognizable; they are usually small but large lesions contain up to 100 denticles. Complex ODs (CxODs) are formed by a single amorphous mass of mature odontogenic tissues without any structural organization, with tissues arranged in a more or less disorderly pattern. The degree of morpho-differentiation varies from lesion to lesion. In some cases the calcified matrix is predominant, in others there are islands of pulp tissue in association with cords and buds.

 Supernumerary teeth or supernumeraries (SPNs) are teeth present in addition to the normal tooth set, both in the permanent and the primary dentitions. They may be single or multiple, unilateral or bilateral, erupted or un-erupted and may occur in the upper or/and the lower jaws. They are morphologically classified as supplemental if their crown resembles that of normal teeth, conoid if it is conical, tuberculate if the occlusal crown surface presents several cusps, infundiboliform or invaginated if the crown presents a deep central groove starting from the occlusal surface, and odontome-like or mis-shaped if they cannot be included in any other morphological type. SPNs represent a common occurrence in the oral cavity and can lead to aesthetic and functional alterations.

Etiology

Odontomas

The exact etiology of ODs is poorly known. They may arise from tooth germs or teeth still in the growth
process induced by local trauma, infection, inheritance, and genetic mutations.

Supernumerary teeth

The etio-pathogenesis of SPNs is still controversial although several theories have been proposed over time. (5, 6) One theory suggests that the SPN is the result of a dichotomy of the tooth bud. The “hyperactivity theory”, which is well-supported by the literature, suggests that SPNs develop as a result of local hyperactivity of the dental lamina. Heredity may play a role in the occurrence of this anomaly since SPNs are more common in relatives of affected children than in the general population. (7) An abnormal reaction to local traumatic episodes and environmental factors are also to be considered as possible etiological factors.

A common origin for ODs and SPNs could be hypothesized on the basis of the following two considerations. Firstly, although ODs are nowadays classified as tumours, they usually stop increasing in volume when they are completely mineralized and this clinical behaviour is different from all other tumours of the body, while it is typical of non-tumoral lesions such as dysplastic, hamartomatous and malformative conditions, among which SPNs. Secondly, it is common to find single SPNs that are usually defined as odontoma-like teeth because of their irregular morphology.

The aim of the present review is to analyze all scientific evidence to verify if there are similarities that can support a common explanation for ODs and SPNs.

Materials and Methods

A literature search was conducted for epidemiologic studies involving ODs and SPNs that are indexed by PubMed from 1967 to 2012 to verify their worldwide incidence. The article selection was initially performed according to geographic and temporal distribution criteria. Afterwards, from the references of the selected articles, some other relevant articles were chosen. Thus, in total 42 articles were selected for ODs from 1976 to 2011 (8-49) and 19 for SPNs from 1967 to 2012 (50-68) taking into account age and gender of patients, morphologic type, topography and clinical relevance of both pathologies.

Results

Epidemiology

Odontomas

Four thousand and one ODs were evaluated (Table 1). The incidence of ODs was reported ranging from 0.24% (14, 20) to 1.21%, (12, 45) The overall incidence of the present aggregated sample was 0.64% (2774 cases) among 431,545 histological maxillo-facial samples (Table 2) and 30.4% among all the diagnosed odontogenic tumours (2731/8984 cases; Table 3).

Since not all the reviewed papers reported all epidemiological features on ODs, each feature was evaluated in a different numerical sample.

CxODs were slightly more frequent than CpODs (1:0.96; Table 1). OD male/female (M/F) ratio was variously reported in the literature, for example from Egypt with a 0.37:1 ratio (11) to Japan with a 1:0.65 ratio. (22) However, if data from different authors are pooled, M/F ratio gets close to 1:1 (50.70%/49.30%; Table 1, Figure 1) and this was true for CpODs as well as for CxODs. Overall, there is no evidence of sex-biased incidence for ODs.

| Authors                          | Total n. of ODs for gender/age | CxODs - CpODs ratio | CxODs:CpODs ratio | Total male (CxODs) | Total female (CpODs) | M/F ratio (CxODs) | M/F ratio (CpODs) | CxOD average age (range) | CpOD average age (range) |
|---------------------------------|-------------------------------|--------------------|------------------|-------------------|---------------------|-------------------|-------------------|--------------------------|--------------------------|
| SolukTekkesin et al. 2011, Turkey (8) | 160/160                      | 99/57 (4 mixed)    | 1.05:1           | 80                | 80                  | 1.1               |                  |                          |                          |
| Osterne et al. 2011, Brazil (9)  | 36/36                         | 12                 | 1.06:1           | 18                | 26                  | 0.7:1             |                  |                          |                          |
| Saghravanian et al. 2010, Iran (10) | 44/44                        | 27/17              | 1.06:1           | 8                 | 22                  | 0.37:1 (0.41)     | (0.34:1)          | 38±25.17                 | 15.29±7.72               |
| Tawfik and Zyada 2010, Egypt (11) | 11/11                         | 4/7                | 0.57:1           | 3                 | 10                  | 0.52:1 (1.1)      | (0.36:1)          | 10.85                    | 23.55                    |
| El-Gehani et al. 2009, Libya (12) | 29/29                         | 10/19              | 0.52:1           | 10                | 19                  | 0.52:1 (1.1)      | (0.36:1)          | 10.85                    | 23.55                    |
| da Silva et al. 2009, Portugal (13) | 48/48                        | 14/34              | 0.41:1           | 26                | 22                  | 1.085             |                  | 29.35±16.1               | 22.7±13.67               |
| Luo and Li 2009, China (14)      | 80/80                         | 47/33              | 1.07             | 42                | 38                  | 1.09 (1.06)       | (0.65:1)          | 24.62±16.54              | 16.48±8.16               |

Table 1. Complex (Cx) and Compound (Cp) Odontomas (ODs) by patient gender and age at diagnosis.
| Study                          | Inclusion Criteria | Number of Participants | Type | Duration | Outcome Measures |
|-------------------------------|--------------------|------------------------|------|----------|------------------|
| Avelar et al. 2008, Brazil(15) | 54/54              | 17 / 37                | 0.46:1 | 27 / (4-84) | 25.8 |
| Jing et al. 2007, China(16)   | 78 / 78            | 58 / 20                | 1.034 | 0.95:1   | 18.8±11.5 |
| Pippi 2006, Italy(17)         | 27 / 28            | 13 / 15                | 0.87:1 | 1.06:1   | 20.5 |
| Buchner et al. 2006, USA(18)  | 762                |                       |       | 18.4     | (1-90) |
| Olgar et al. 2006, Turkey(19) | 109                | 67 / 42                | 1.063 | 1.085:0.91 | (1.056) |
| Ladeinde et al. 2005, Nigeria(20) | 8 / 8            | 4 / 4                  | 1.1   | 22.3±11.2| (10-45) |
| Adebayo et al. 2005, Nigeria(21) | 7                  | 4 / 3                  | 1.075 |          |       |
| Tomizawa et al. 2005, Japan(22) | 39                | 7 / 30                 | 0.23:1 | 15 / 1.065 | |
| Fernandes et al. 2005, Brazil(23) | 85 / 85          | 52 / 33                | 1.063 | 10.8:1   | 22.2±14.7 |
| Tamme et al. 2004, Estonia(24) | 26 / 26            | 14 / 12                | 1.086 | 25.4     | 23.7 |
| Amado-Cuesta et al. 2003, Spain(25) | 61 / 61          | 23 / 38                | 0.61:1 | 29 / 1.09 | (14-46) |
| Hisatomi et al. 2002, Japan(26) | 106 / 106         | 41 / 62                | 0.66:1 | 23 / 19.1| (6-46) |
| Ochsenius et al. 2002, Chile(27) | 162 / 162         | 92 / 71                | 1.077 | 17±10.7  |       |
| Miki et al. 1999, Japan(28)   | 47 / 47            | 22 / 25                | 0.81:1 | 20.8     | 23.5 |
| Lu et al. 1998, China(29)     | 51 / 51            | 37 / 14                | 1.038 | 23.7     | (8-48) |
| Philipsen et al. 1997, Denmark(30) | 134               | 56 / 78                | 0.72:1 | 18.9     | (1-74) |
| Mosqueda-Taylor et al. 1997, Mexico(31) | 120              | 63 / 49                | 1.07  | 18.69    | (1-74) |
| Macdonald-Jankowski 1996, China(32) | 39 / 39          | 21 / 18                | 1.086 | 24.6±12.4| (0.59) |
| Odukoya 1995, Nigeria(33)     | 12 / 12            | 74 / 128               | 0.58:1 | 20.7±11.7| (10-54) |
| Daly et al. 1994, Canada(34)  | 202                | 74 / 128               | 0.58:1 | 20.6     | (9-60) |
| Gunhan et al. 1990, Turkey(35) | 74 / 74            | 44 / 30                | 1.068 | 17.6     | (2-60) |
| Kaugars et al. 1989, USA(36)  | 351                | 170 / 181              | 0.94:1 |          |       |
| O'Grady et al.1987, Australia(37) | 118 / 118        | 76 / 36                | 1.047 | 0.84:1   | 14.8 |
| Or and Yucetas 1987, Turkey(38) | 49 / 49           | 20 / 29                | 0.69:1 | 22.9     | 23.8 |
| Pizzirani and Gemosio 1984, Italy(39) | 167              | 75 / 92                | 0.8:1 |          |       |
| Torelli et al. 1984, UK(40)   | 167                | 75 / 92                | 0.8:1 | 0.99:1   |       |
| Bodin et al. 1983, Sweden(41) | 65                 | 21 / 44                | 0.45:1 | 1.07:1   |       |
| Slootweg 1981, The Netherlands(42) | 121 / 126       | 78 / 48                | 1.06  | 10.55    | 14.8 |
| Morning 1980, Denmark(43)     | 31                 | 16 / 15                | 1.094 |          |       |
| Regezi et al. 1978, USA(44)   | 473                | 214 / 259              | 0.82:1 | 19       | (2-79) |
| Budnick 1976, USA(45)         | 135 / 149          | 76 / 73                | 1.096 | 1.07     | 14.8 |
Among the cases in which the OD type incidence was reported for each gender (852 cases), CxODs were slightly more frequent than CpODs in both genders (about 57%/54.8%, Table 1).

In a sample of 2496 cases, the age of patients at the time of OD diagnosis ranged from 1 to 90 with a mean age of 22.19 ± 3.9 years, however, CxODs were found at an earlier age (19.25±2.9) than CpODs (25.14±4.8; total number of ODs 1251; p=0.0004; IC=95%; Table 1).

Supernumerary teeth

The incidence of SPNs was 1.5% (770 cases/51130 examined patients; Table 4). The worldwide reported incidence, however, was quite different from one study to another, probably due to differences in the evaluated samples (school samples, general dentistry samples, orthodontic samples or paediatric dentistry samples) and/or in the evaluation methods used (radiological or clinical).

SPNs were more common in males than in females (67.5% versus 32.5%; Table 4) with a 1:0.48 ratio (1026/495).

The age of patients at the time of diagnosis ranged from 1 to 61, with a mean age of 14.13±5.6 years (984 cases; Table 4).

In a selected sample of 1176 cases, 1 SPN occurred in 72.6% of cases 2 SPNs in 23% and 3 or more SPNs in 4.4% (Table 5).

Table 2. Odontomas from histological samples.

| Authors | Sample | n (%) |
|---------|--------|--------|
| SolukTekkesin et al. 2011, Turkey | 40099 | 160 (0.39) |
| Osterne et al. 2011, Brazil | 6231 | 36 (0.58) |
| Saghravanian et al. 2010, Iran | 8766 | 44 (0.50) |
| El-Ghanehi et al. 2009, Libya | 2390 | 29 (1.21) |
| Luo and Li 2009, China | 33354 | 80 (0.24) |
| Buchner et al. 2006, USA | 91178 | 826 (0.90) |
| Ladeinde et al. 2005, Nigeria | 2890 | 6 (0.24) |
| Luo and Li 2009, China | 2390 | 29 (1.21) |
| Tawfik and Zyada 2010, Egypt | 185 | 27.07 |
| Regezi et al. 1997, Mexico | 16079 | 121 (0.75) |
| Adebayo et al. 2005, Nigeria | 202 (51.53) |
| Ochsenius et al. 2002, Chile | 100 | 7 (0.70) |
| Santos et al. 2001, Brazil | 5289 | 64 (1.21) |
| Mosqueda-Taylor et al. 1997, Mexico | 53624 | 351 (0.65) |
| Saghravanian et al. 2011, Brazil | 109 | 28 (52.8) |
| Osterne et al. 2011, Brazil | 202 (51.53) |
| Daley et al. 1994, Canada | 121 (0.75) |
| Kaugars et al. 1989, USA | 85 (2.2) |
| Happonen et al. 1982, Finland | 78 (7.4) |
| Regezi et al. 1978, USA | 104 | 7 (0.70) |

Table 3. Complex (Cx) and Compound (Cp) Odontomas (ODs) among Odontogenic Tumors (OTs). Data according to the 1992 WHO Classification.

| Authors | OTs | ODs n. (%) | Cx - CpODs |
|---------|-----|------------|------------|
| Osterne et al. 2011, Brazil | 133 | 36 | 27.07 |
| Saghravanian et al. 2010, Iran | 165 | 44 (26.7) | 27.07 |
| Tawfik and Zyada 2010, Egypt | 66 | 11 (16.7) | 4.7 |
| El-Ghanehi et al. 2009, Libya | 96 | 29 (30.2) | 27.07 |
| da Silva et al. 2009, Portugal | 65 | 48 (73.9) | 4.7 |
| Luo and Li 2009, China | 802 | 80 (9.98) | 4.7 |
| Avelar et al. 2008, Brazil | 171 | 54 (31.6) | 4.7 |
| Jing et al. 2007, China | 1054 | 78 (7.4) | 4.7 |
| Pippi 2006, Italy | 53 | 28 (52.8) | 4.7 |
| Buchner et al. 2006, USA | 1088 | 826 (75.9) | 4.7 |
| Olgac et al. 2006, Turkey | 527 | 109 (20.7) | 4.7 |
| Ladeinde et al. 2005, Nigeria | 319 | 8 (2.5) | 4.7 |
| Adebayo et al. 2005, Nigeria | 318 | 7 (2.2) | 4.7 |
| Fernandes et al. 2005, Brazil | 340 | 85 (25) | 4.7 |
| Tawfik and Zyada 2010, Egypt | 75 | 26 (34.6) | 4.7 |
| Ogunnsula 2003, Jamaica | 80 | 10 (12.5) | 4.7 |
| Ochsenius et al. 2002, Chile | 362 | 162 (44.7) | 4.7 |
| Santos et al. 2001, Brazil | 127 | 64 (50.7) | 4.7 |
| Adebayo et al. 2005, Nigeria | 759 | 51 (6.7) | 4.7 |
| Mosqueda-Taylor et al. 1997, Mexico | 349 | 121 (34.6) | 4.7 |
| Olgac et al. 2006, Turkey | 289 | 12 (4.5) | 4.7 |
| Daley et al. 1994, Canada | 392 | 202 (51.53) | 4.7 |
| Günhan et al. 1990, Turkey | 409 | 74 (18.1) | 4.7 |
| Wu et al. 1985, China | 68 | 5 (7.35) | 4.7 |
| Happonen et al. 1982, Finland | 171 | 88 (50.5) | 4.7 |
| Regezi et al. 1978, USA | 706 | 473 (67) | 4.7 |

→ data according to the 2005 WHO classification (CheratocisticOdontogenic Tumors are comprised).
compared to the others (supplementary 19.6%, tuberculate 17.8%, mis-shaped/odontoma-like 5.2% and infundibuliform 0.7%; Table 9).

When observing their status within the alveolar process, the great majority of SPNs (85%; 1082/1273 cases) was impacted, and only a minority (15%; 191/1273 cases) was erupted (Table 6).

**Pathological and clinical features**

The most common OD-related pathologies were permanent tooth retention and eruptive delay (46, 46%), followed by bone swelling (11.39%), cysts (11, 12%) and infection/pain (3, 77%; Table 10).

As for SPNs, tooth retention/eruption delay accounted for 45, 29%, diastemas/dislocations/malpositions for 7, 1%, and cysts for 5, 7% (Table 11).

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**Figure 1.** Odontomas and Supernumerary teeth by gender.

**Figure 2.** Odontomas and Supernumerary teeth by location.

**Table 4.** Supernumerary teeth (SPNs) by gender, age and prevalence.

| Authors                          | Sample | Patient n. with SPNs (M-F) | Total n. of SPNs (M-F) | Mean age (years) | Sample age range (years) |
|----------------------------------|--------|-----------------------------|------------------------|------------------|--------------------------|
| NazargiMahabob et al. 2012, India(53) | 2316   | 21 (14-7)                   | 27                     | 24.6             |                          |
| Sharma and Sigh 2012, India(51)  | 21824  | 300 (224-76)                | 385                    |                  |                          |
| Fardi et al. 2011, Greece(75)    | 1239   | 23 (14-9)                   | 17.2±10.8              |                  |                          |
| Pippi 2011, Italy(93)            | 118    | 118 (73-45)                 | 191                    | 5-61             |                          |
| Vahid-Dastjerdi et al. 2011, Iran(56) | 1751   | 13 (6-7)                    | 14                     | 12.5             | 9-27                     |
| Schumuckli et al. 2010, Swiss(30) | 3004   | 69 (55-34)                  | 44                     | 8.6±0.23         |                          |
| Esenlik et al. 2009, Turkey(50)  | 2599   | 283 (157-51)                | 84                     | 7.3±2.7          | 2.1-15.2                 |
| Anthonappa et al. 2008, China(57) |        |                             |                        |                  |                          |

http://www.medsci.org
Table 5. Supernumerary teeth (SPNs) by patients (Pts) and degree of eruption.

| Authors                          | n. SPNs - Pts | Pts with 1 SPN | Pts with 2SPNs | Pts with 3 or more SPNs | Erupted SPNs | Un-erupted SPNs |
|----------------------------------|---------------|----------------|----------------|-------------------------|-------------|-----------------|
| Sharma and Sigh 2012, India(51)  | 385 - 300     | 237            | 60             | 3                       | 135         | 250             |
| Vahid-Dashtjerdi et al. 2011, Iran(52) | 14 - 13    | 12             | 1              | 0                       |             |                 |
| Pippi 2011, Italy(53)            | 191 - 118     | 70             | 38             | 10                      | 28          | 163             |
| Esselink et al. 2009, Turkey(54) | 84 - 69       | 54             | 15             | 0                       | 22          | 62              |
| Anthonappa et al. 2008, China(57) | 283 - 208    | 128            | 80             | 48                      | 235         |                 |
| de Oliveira Gomes 2008, Brazil(39) | 460 - 305    | 192            | 94             | 19                      | 107         | 333             |
| Lecofberrocal et al. 2007, Spain(59) | 24 - 21     | 15             | 1              | 0                       | 1           | 23              |
| Harris and Clark 2009, USA(40)   | 44 - 39       | 25             | 10             | 4                       | 20          | 127             |
| Fernández-Montenegro et al. 2006, Spain(61) | 147 - 102    | 79             | 15             | 8                       | 20          | 127             |
| Gabris et al. 2006, Hungary(62)  | 40 - 34       | 28             | 6              | 0                       |             |                 |
| Rajab and Hamdam 2002, Jordan(63) | 189 - 152    | 117            | 28             | 7                       | 50          | 139             |
| Salem 1989, Saudi Arabia(65)     | 12 - 12       | 12             | 0              | 0                       |             |                 |
| Davis 1987, China(67)            | 42 - 30       | 3              | 3              | 4                       |             |                 |
| Luten 1967, USA(68)              | 36 - 32       | 28             | 4              | 0                       | 14          | 22              |

Table 6. Complex (Cx) and Compound (Cp) Odontomas by location.

| Authors                          | Maxilla | Mandible | Max/Mand Ratio (Cx)/(Cp) |
|----------------------------------|---------|----------|--------------------------|
|                                  | Anterior | Posterior | NS | Anterior | Posterior | NS |                     |
|                                  | Incisive-Canine | Premolar | Molar | (Cx)/(Cp) | (Cx)/(Cp) | (Cx)/(Cp) |                     |
| Soluk-Tekkesin et al. 2011, Turkey(9) | 34 (12)(19) | 12       | 23       | 71       | 0.52:1 | (0.34:1) | (0.9:1) |
| Osterne et al. 2011, Brazil(10)    | 13      | 2        | 5        | 4        | 1.07  | (0.3:1) | (0.4:1) |
| Saghavanian et al. 2010, Iran(10)  | 9       | 14 (+1 peripheral) | 2       | 18       | 1.09  |                     |                     |
| Tawfik and Zyada 2010, Egypt(11)   | 2       | 1        | 0        | 6        | 1     | 1       | (0.33:1) | (0.4:1) |
| El-Gehani et al. 2009, Libya(12)   | 8       | 0        | 0        | 7        | 12    | 3       | (0.67:1) | (0.27:1) |
| da Silva et al. 2009, Portugal(13) | 16      | 7        | 5        | 12       | 26    | 1:0.7   | (0.62:1) | (1:0.5) |
| Luo and Li 2009, China(14)        | 30 (14)(16) | 5 | (1)(4) | (5)(7) | 24(22) | 1.074  |                     |                     |
| Avellar et al. 2008, Brazil(15)   | 31      | 23       | 23       |                     | 1.074  |                     |                     |
| Jing et al. 2007, China(16)       | 11      | 6        | 14       | 19       | 6     | 0.66:1  | (0.71:1) | (0.54:1) |
| Pippi 2006, Italy(17)             | 6       | 1        | 2        | 10       | 15(4) | 3(1)    | 0.47:1  | (0.31:0.67:1) |
| Buchner et al. 2006, USA(18)      | 161     | 57       | 109      | 109      | 43(8) | 0.58:1  | (0.34:1) | (1:0.83) |
Lodeinde et al. 2005, Nigeria(25)
Tomizawa 2005, Japan(20)
Fernandes et al. 2005, Brazil(23)
Tamme et al. 2004, Estonia(26)
Amado-Cuesta et al. 2003, Spain(27)
Hisatomi et al. 2002, Japan(28)
Ochsnerius et al. 2002, Chile(29)
Miki et al. 1999, Japan(30)
Lu et al. 1998, China(31)
Mosqueda-Taylor et al. 1997, Mexico(32)
Macdonald-Jankowski 1996, China(33)
Odukoya 1995, Nigeria(34)
Günhan et al. 1990, Turkey(35)
Kaagars et al. 1989, USA(36)
O’Grady et al. 1987, Australia(37)
Or and Yucetas 1987, Turkey(38)
Pizzirani and Gemesio 1984, Italy(39)
Toretti et al. 1984, UK(40)
Bodin et al. 1983, Sweden(41)
Slootweg 1981, The Netherlands(42)
Regezi 1978, USA(43)
Budnick 1976, USA(44)

Table 7. Supernumerary teeth by location.

| Authors | Maxilla | Mandible |
|---------|---------|----------|
|         | Incisive-Canine (Cx)(Cp) | Premolar (Cx)(Cp) | Molar (Cx)(Cp) | Anterior | Posterior | Incisive-Canine (Cx)(Cp) | Premolar (Cx)(Cp) | Molar (Cx)(Cp) |
| NazargahMalabab et al. 2012, India(45) | 12 | 0 | 2 | 0-4 | 0 | 0 | 6 | 0-3 |
| Pippi 2011, Italy(46) | 92 | 0 | 19 | 10-15 | 2 | 0 | 4 | 38-11 |
| Vahid-Dastjerdi 2011, Iran(47) | 11 | 11 | 3 | | | | | |
| Esenlik et al. 2009, Turkey(48) | 56 | 8 | 5 | 0 | 2 | 1 | 12 | 0 |
| Anthonappa et al. 2008, China(49) | 271 | 0 | 2 | 2-0 | 0 | 1 | 4 | 0-0 |
| de Oliveira Gomes et al. 2008, Brazil(50) | 399 | 12 | 7 | 2 | 4 | 6 | 30 | |
| Lecobertonco 2007, Spain(51) | 6 | 1 | 2 | 0-8 | 3 | 0 | 3 | 0-1 |
| Harris and Clark 2007, USA(52) | 15 | 0 | 9 | 0-20 | 0 | 0 | 12 | 0-8 |
| Fernández-Monteregro et al. 2006, Spain(53) | 72 | 1 | 9 | 4-24 | 2 | 3 | 26 | 4-2 |
| Gabris et al. 2006, | 28 | 0 | 2 | 0 | 3 | 0 | 0 | 0 |
| Unghery(54) 2 | 6 | | | | | | | |
| Salcido-Garcia et al. 2004, Mexico(55) | 60 | | | | | | | |
| Rajab and Handam 2002, Jordan(56) | 181 | 3 | 5 | 1-0 | 2 | 2 | 8 | 0 |
| Luten 1967, USA(57) | 33 | | | | | | | |

1: Complex and Compound Odontomas at the mandibular angle location; 2: Compound Odontomas at the retro-molar location; 3: not specified location; 4: Compound Odontomas at the mandibular angle location.

1: Incisor area; C: canine area; P: premolar area; M: DM: molar - distomolar areas.
* Maxillary + Mandibular supernumerary teeth: I=C=53; P=38; M=12.
Table 8. Supernumerary teeth by position

| Authors                        | n.  | Sagittal/Frontal plane | Axial plane |
|--------------------------------|-----|------------------------|-------------|
|                                |     | I         | T    | N-O | In | UC | O | B | E/W-A |
| Pippi 2011, Italy               | 191 |            | 131  | 19  | 41 |
| Esenlik et al. 2009, Turkey     | 84  | 6         | 0    | 58  | 14 M + 6 D |
| Anthonappa et al. 2008, China   | 283 | 135       | 38   | 93  | 17 | 224 | 6 | 51 |
| de Oliveira Gomes et al. 2008, Brazil | 460 | 80        | 3    | 363 | 141 | 388 | 22 | 50 |
| Fernández-Montenegro et al. 2006, Spain | 145 | 6        | 68   | 51  | 20 |
| Rajab and Handam 2002, Jordan   | 202 | 19        | 13   | 157 | 13 | 172 | 2 | 28 |

I: inverted; T: transverse; N-O: normal orientation; In: inclined; UC: unclassified; O: oral; B: buccal; E/W-A: erupted/well aligned; M: mesio-inclined; D: distal-inclined.

Table 9. Supernumerary teeth (SPNs) by morphology.

| Authors | n. | Cx | T | I | M-S/O-L | 1-F | C-F | P-F | M-F |
|---------|----|----|---|---|---------|-----|-----|-----|-----|
| Sharma and Sigh 2012, India      | 385 | 230 | 55 | 30* | 70 |
| Pippi 2011, Italy                | 191 | 70  | 29 | 10  | 11 | 10  | 1  | 41  |
| Vahid-Dastjerdi et al. 2011, Iran | 14 | 6   | 2  | 3   | 3 |
| Schmuckli et al. 2010, Swiss      | 44  | 31  | 2  | 10  | 1 |
| Esenlik et al. 2009, Turkey      | 84  | 42  | 2  | 40  | |
| Anthonappa et al. 2008, China    | 283 | 202 | 31 | 17  | 33 |
| de Oliveira Gomes et al. 2008, Brazil | 460 | 205 | 178 | 3 | 20* | 35 |
| Fernández-Montenegro et al. 2006, Spain | 145 | 87  | 3  | 15  | 14 |
| Rajab and Handam 2002, Jordan    | 202 | 151 | 24 | 13  | 14 |

C: conoid; T: tuberculated; I: infundibuliform; M-S/O-L: mis-shaped/odontome-like; 1-F: incisiform; C-F: caniform; P-F: premolariform; M-F: molariform. * Rudimentary/dismorphic/molariform.

Table 10. Odontomas by more frequent complications/associated pathologies.

| Authors | n. | Cx | T | I | M-S/O-L | Bone swelling | Cysts | Infection/pain |
|---------|----|----|---|---|---------|-------------|-------|----------------|
| Soluk-Tekkeşin et al. 2011, Turkey | 160 | 13 | 13 | 2 | 12 (7Cx + 5Cp) | 8 (7Cx + 1Cx) |
| da Silva et al. 2009, Portugal | 48 | 33 | 2 | 2 | 3 |
| Pippi 2006, Italy                | 28 | 15 | 7 |
| Tomizawa et al. 2005, Japan      | 39 | 19 | 1 |
| Amado-Cuesta et al. 2003, Spain  | 61 | 45 | 31 |
| Hisatomi et al. 2002, Japan      | 103 | 76 | 27 (Ct + 49Cp) |
| Miki et al. 1999, Japan          | 47 | 3  | 12 |
| Macdonald-Jankowski et al. 1996, China | 40 | 26 | 11 (Ct + 1Cx) | 6 (5Cx + 1Cx) |
| Kaugars et al. 1989, USA         | 351 | 167 | 27 | 97 |
| Or and Yucetas 1987, Turkey      | 49 | 8  | 2 | 6 (3Cx + 3Cx) |
| Bucci et al. 1983, Italy         | 75 | 34 | 22 |
| Budnick 1976, USA                | 114 | 69 | 31 |

Cx = complex; Ct = compound; Mx = mixed.

Table 11. Patients with supernumerary teeth (SPNs) by more frequent complications/associated pathologies.

| Authors                        | Patients (SPNs) | Un-eruption of permanent teeth | Cysts | Malposition/ crowding of teeth | Spacing/diastema | Malformation/root resorption of permanent teeth | Fusion with a permanent tooth | Odontoma |
|--------------------------------|-----------------|--------------------------------|-------|-------------------------------|------------------|-----------------------------------------------|-------------------------------|----------|
| Pippi 2011, Italy              | 118 (191)       | 81 (40)                        | 7 (7) | 7 (7)                         | 3 (3)            | 2 (2)                                         | 1 (1)                         | 6 (6)    |
| Esenlik et al. 2009, Turkey    | 69 (84)         | 18 (18)                        |       |                               |                  |                                               |                               |          |
| Anthonappa et al. 2008, China  | 208 (283)       | 1                             | 112 (14) |                                |                  |                                               |                               |          |
| de Oliveira Gomes et al. 2008, Brazil | 305 (460)     | 155                           | 227 (22) | 64 (18)                          |                  |                                               |                               |          |
| Lecointre et al. 2007, Spain   | 21 (24)         | 4 (4)                          | 9 (9)  | 3 (3)                          |                  |                                               |                               |          |
| Fernández-Montenegro et al. 2006, Spain | 102 (145)     | 45 (45)                        | (2)   | (6)                           |                  |                                               |                               |          |
Discussion

Epidemiology and clinical signs

From a nosological point of view, ODs and SPNs are still classified as distinct entities, although from an etio-pathogenetic and, even more, from a clinical point of view, they seem to be the expression of the same pathologic process, malformative or hamartomatic. Actually, the analysis of the literature data shows some similarities between ODs and SPNs concerning topographic distribution and pathologic manifestations.

Although the overall SPNs incidence was almost 2.5 times more than ODs, most reports on SPNs concerned selected samples in which the incidence was certainly higher than in the general population. On the other hand, the real incidence of ODs is probably higher since reported data come from histological reviews so it is possible that some CpODs, likely due to their morphological similarities with SPNs, have not been included in the reports because they were not evaluated histologically. Moreover, it is likely that some CxODs were not subjected to surgical excision since they did not determine clinical problems, especially those in the posterior area of the mandible, which are also the most frequent. Finally, the total number of ODs could be higher if all ameloblastic fibro-odontomas were considered as developing ODs, especially those in young people, which will be discussed later.

Topographic distribution in dental arches does not seem to be totally similar for the two conditions, but shows common features. They all are commonly located in upper jaw, although SPNs more often than ODs; SPN are more frequently found in the incisive, premolar and disto-molar regions, while ODs are more uniformly distributed among the different areas with only a slightly higher incidence in the incisive-canine area, which is more evident in the upper jaw. Therefore, SPNs mainly involve the areas corresponding to the extremities of the primitive as well as the secondary dental laminae and above all the mesial extremity of the primitive dental lamina, that is, the pre-maxillary area, particularly in the incisive region.

ODs and SPNs are usually asymptomatic although often associated with the same pathologic manifestations that are mainly related either to the lack of space for the regular eruption of normal permanent teeth or to their inflammatory or cystic complications with the involvement of neighboring anatomical structures (maxillary sinuses, vascular-nervous bundles, nasal cavities).

Eruption disturbances of permanent teeth are therefore the most frequent and important pathologic complications of both ODs and SPNs, especially tooth retention, reported from 6.38% to 48.73% for ODs and from 4.76% to 50,82% for SPNs. In particular, among pre-maxillary SPNs, tuberculates and supplementary (incisor-like) are more frequently associated with tooth impaction than condylar. As for ODs, tooth impaction is more frequently associated with the compound ones than with the complex ones.

Finally, although eruption is frequent as far as SPNs are concerned, due to their normal root structure and morphology, it can occur anyway, although rarely, in compound as well as complex ODs.

From an analysis of the epidemiological data reported by the international literature, many elements support the assumption that SPNs and ODs have the same origin and may constitute aspects of the same phenomenon: high frequency of occurrence almost in the same jaw areas; same type of pathologic sequelae; greater frequency at a young age, although earlier for SPNs than for ODs; to be formed by all completely differentiated dental tissues.

The only real difference as far as epidemiology is concerned is the different incidence in relation to gender since SPNs appear more common in males than in females, whereas ODs appear to be almost equal in both genders. This different incidence may be due to the fact that, after childhood, men tend to have fewer checkups than women, with a consequent missed diagnosis, also due to the lack of symptoms, as confirmed by the Italian ISTAT statistical database which in 2005 reported a higher percentage of women (41.2%) than men (38.1%) undergoing dental care over 18 years of age, especially in the 18-24 age range (F=49.1%; M=39.6%), in which ODs, specifically CxODs, are usually diagnosed. Moreover, a male predilection has been found for ODs in children (M:F=1.5:1; M:F=1.2:1) in children and adolescents (M:F=1.2:1), and particularly in the primary dentition (M:F=1.6:1), although an inverse ratio has also been reported in Nigerian children and adolescents (M:F=1.2).

Pathogenesis

It is nowadays accepted that CpODs and SPNs derive from the proliferation of clusters of epithelial cells arising from a localized dental lamina hyperactivity related to genetic or teratogenic stimuli. Control factors and stimuli deriving from mesenchymal tissue located around dental lamina or/and papillae seem to condition these cells to develop toward atrophy or towards more or less organized dental structures. The origin of these inductive stimuli is not completely known although they are certainly time and site re-
The Field Theory, proposed by Butler in 1939\(^{(77)}\), was an attempt to account for the common features of teeth within a morphological class postulating that the most mesially-positioned tooth in each class is usually the most phenotypically stable. According to the Field Theory, the mesenchymal influence on epithelial cells of each morphologic tooth class reduces from the incisor to the molar area. If on the one hand this can explain the higher incidence of agenesis as well as the smaller dimensions of the distal element of each morphologic tooth class, on the other hand it can justify the extreme rarity of supplementary upper canines, in comparison with the relative higher incidence of ODs in the same site (Tables 6, 7). This different incidence of events in the upper canine area can be put in relation to the poor influence that incisor and premolar morphogenetic fields exert to condition the morpho-structural evolution of epithelial cells in excess located in that transitional area.

On the other hand, the different period in which the clusters of epithelia cells start to proliferate can explain the different degrees of root structural maturation and the mineralization defects rather frequently present on the enamel surface of SPNs and ODs. Actually, the complete or almost complete root mineralization of the conoids\(^{(79)}\) may be related to their early occurrence which on the one hand does not allow the conoid crown to develop completely, influenced by the mesenchymal inductive mechanisms of the incisor morphogenetic field and, on the other hand, allows their root to reach a high degree of development\(^{(79)}\).

In the same manner, the incomplete root mineralization of the tuberculates may be related to their later occurrence\(^{(78)}\) which is contemporary or more often following that of permanent incisors. On the other hand, tuberculate morphology is probably due to the poor influence exerted by incisor morphogenetic field which has already exhausted its inductive potentiality.\(^{(79)}\)

As for the supplementary teeth, they develop at the same site and start to mineralize at the same time or just shortly before normal permanent homologous teeth\(^{(80)}\), so that they feel the same inductive stimuli as far as quality and intensity are concerned. For this reason, supplementary teeth crown morphology is often exactly like that of normal permanent incisors and they develop at the same site where normal teeth should erupt, interfering with their eruption. It is also possible that each supplementary tooth develops from a duplication of a single tooth bud due to environmental stimuli, although this seems unlikely in the case of the contemporary occurrence of two or three supplementary teeth in the same area, incisive and especially premolar, also considering that in those cases all teeth, normal and supernumeraries, have normal dimensions.

Finally, it is important to observe that CpODs are associated to tooth retention more than the complex ones (111/59; Table 10) and that CpODs are found at an earlier age than the CxODs (Table 1).\(^{(79)}\) If it is considered that CpODs more frequently involve the pre-maxilla and that they are diagnosed at an earlier age, it can be supposed that their development occurs earlier,\(^{(41)}\) as early as the pre-eruptive phase of dentition or at the beginning of the pre-functional eruptive phase. This can justify the considerable interference of CpODs with tooth eruption as well as their greater morphologic differentiation.

On the other hand, CxODs are diagnosed later than CpODs, are slightly more frequent in the lateral-posterior areas (Table 6), where the differentiation of dental tissues ends later, and less frequently cause tooth retention (Table 10). Therefore, it is possible that they develop later and that may represent a morphologically less differentiated expression of the same hyper-productive process which, in its best developed expression, is constituted by completely structured and morphologically normal dental elements, that is the supplementary teeth.\(^{(79)}\) Actually, the clinical behaviour of ODs is different from that of all benign tumours since they stop increasing at a certain point, they do not infiltrate but only squeeze and displace the neighbouring structures and tissues, and finally, they do not recur or move towards a malignant transformation.

A similar hypothesis on CpOD origin was proposed by Philipsen and co-workers\(^{(4)}\) who suggested considering this lesion as a real malformation probably due to a localized hyperactivity of the dental lamina similarly to supernumerary teeth. On the other hand, these authors\(^{(4)}\) suggested that the CxOD belongs to a so-called hamartomatous line of development of the mixed odontogenic tumours, which they also defined as a developing complex odontoma line, including some ameloblastic fibromas, that is those occurring before the completion of the odontogenesis (about 20 years of age), and the ameloblastic fibro-odontoma. The proper neoplastic line of odontogenic tumours includes only the ameloblastic fibroma and the related ameloblastic fibrodentinoma. However, not all cases of ameloblastic fibro-odontoma should be considered hamartomatous since some cases have shown neoplastic behaviour, also malignant, although it is difficult to distinguish between a developing odontoma and a true neoplastic ameloblastic fibro-odontoma.\(^{(81)}\) Actually, differences exist in loca-
tion and age distribution at the time of diagnosis between complex and compound ODs, the first ones being more frequent in the lateral posterior areas of the jaws and diagnosed at a slightly earlier age than the second ones. However, transitional or mixed cases of ODs in which both types of ODs coexist, have sometimes been found to show that a real different categorization of the two types of OD cannot be justified, although it seems to be correct to separately record each kind of OD for epidemiological purposes, as Philipsen and co-workers suggested. Furthermore, a different pattern of matrix protein expression, particularly as far as amelotin and amelogenin are concerned, has been found by immuno-histochemical analysis, to distinguish complex odontomas from all other odontogenic tumours, including ameloblastic fibroma. Since these proteins are immuno-detected in different phases of amelogenesis, their simultaneous expression has been explained by the presence of ameloblasts in various stages of differentiation which is typical of the normal odontogenic process. The pattern of protein distribution (linear between the enamel matrix and ameloblasts) was similar to that described in the normal rat tooth germ to further suggest a common origin for ODs and SPNs. Similar data were already found by Crivelini et al. in 2003 using different antibodies for cytokeratin polypeptides and vimentin. These authors found differences with ameloblastic fibromas, whose immuno-phenotype resembled that of dental lamina, to CpODs, whose immuno-histochemical findings resembled those of the enamel organ of the dental germ. The authors suggested that in ODs, pre-ameloblasts and ameloblasts did not reach complete differentiation so that some enamel matrix remained unable to undergo complete mineralization. This could explain a various degree of morpho-differentiation in ODs.

Another interesting immuno-histochemical difference between ODs and ameloblastomas was more recently found by Kiyoshima et al. as to thymosin β4 (Tβ4), a member of the actin-binding polypeptide family, which has been shown to carry out different functions in several tissues and cell types, including carcinomas. Actually, Tβ4 immuno-reactivity was significantly higher in ameloblastomas than in both types of ODs. In the latter, all calcified materials associated with epithelial cells and the dentin matrix were negative for Tβ4, while only pre-secretory ameloblasts at the epithelium-enamel interface as well as few cells of the odontoblastic layer, located in the pulpal tissue faced with predentin matrix, showed positive staining for Tβ4. Since the high Tβ4 expression in ameloblastomas was always similar in samples taken from the same patient at different times and tended to be higher in the peripheral polarized cells than in the central cells of the same nest, Tβ4 expression seemed to be related with tumour progression through its anti-apoptotic activity. Moreover, it is peculiar that ameloblastic fibro-odontomas showed a Tβ4 pattern of distribution similar to ameloblastomas as to epithelial nests or strands while similar to ODs as to dental hard tissues, suggesting that both lines of development, neoplastic and hamartomatous, may occur in this lesion.

Similar observations have already been made histologically in CpODs’ undemineralized sections by Piattelli and Trisi who suggested that the altered enamel appearance they observed could be due to qualitative, quantitative and temporary modifications in enamel organ function with differences in mineralization and maturation of ameloblasts. Moreover, two different types of dysplastic calcifying cells, which could represent two different stages of dysplastic epithelial ameloblastic cells, derived from the stellate reticulum or from the intermediate layer of the enamel organ, were detectable in the un-mineralized material producing two different types of tissue other than normal dental mineralized tissue.

As far as enamelysin is concerned, differences were also reported by Takata et al. who found a strongly positive pattern within the immature enamel of the tooth germ during the late bell stages as well as in the enamel matrix with inductive hard tissue formation typically present in ODs and ameloblastic fibro-odontomas.

On the other hand, a similar distribution of amelogenins, keratins, collagen types III and IV, vimentin, fibronectin, osteonectin and osteocalcin has been shown in children, in comparisons between normal human teeth and selected areas of mixed odontogenic tumours, which are ameloblastic fibromas, ameloblastic fibro-odontomas and complex odontomas, supporting the concept that these pathologies represent stages of evolution of a single pathologic process whose phenotype is characterized by well-differentiated odontogenic cells, such as in normal teeth. The different expression of enamel-associated genes can therefore represent different stages of tumour differentiation, also within the same histological type, in relation to different cell maturation degrees and tumour morpho-differentiation, as already suggested by Dodds et al.

A genetic component in SPN aetiology has already been suggested by the report of many family cases, also in two monozygotic twins whose mother had already been treated for SPNs during childhood, by Brooks’ observation that the prevalence of SPNs in the population sample of first-degree relatives was greater than in the child population of his
study, and by the frequent occurrence of SPNs in several hereditary syndromes (108-134) (Table 12). SPNs have also been found in association with localized gingivitis/parodontitis/aggressive periodontitis either in several sporadic case reports (135, 136) or in Noonan syndrome, (121) a heterogeneous genetic condition in which not only the Ras/MAPK (rat sarcoma/mitogen-activated protein kinase), which is a product of the PTPN11 (protein Tyrosine phosphatase non-receptor type 11) gene, has been shown to be mutated but also many other genes and certainly others which still have to be identified. This further suggests an association between multiple genetic and non-genetic factors in aetiology of the two pathologic conditions.

Table 12: Main hereditary syndromes in which supernumerary teeth were found.

| Syndromes                              | Authors                                      |
|----------------------------------------|----------------------------------------------|
| Apert Syndrome                         | VadiatiSaberi&Shakoorpour 2011(94)            |
| Autosomal-dominant Ankyloglossia        | Acevedo et al. 2012(93)                      |
| Cleft Lip-Alveolus-Palate              | Lai et al. 2009, (89) Wu et al. 2011(95)      |
| Cherubism                              | Schindel et al. 1974(94)                     |
| Cleidocranial Dysplasia                | Ida et al. 1981, (89) Jensen and Kreiberg 1990(97), Kreiberg et al. 1999(99) Cooper et al. 2001(98) |
| Down Syndrome                         | Chow and O’Donnell 1997(100)                 |
| Ehlers-Danlos Syndrome                 | Majaron and Facchetti 1992, (101) Melamed et al. 1994, (102) Ferreira OJr et al. 2008, (103) Premalatha et al. 2010(104) |
| Ekman-Westborg-Julin Syndrome          | Yoda et al. 1998(105)                        |
| Ellis-van Creveld Syndrome             | Brindley et al. 1975, (106) Prabhu et al. 1978, (107) Hattab et al. 1998, (108) Cahuana et al. 2003(109) |
| Familial Adenomatous Polyposis, including Gardner’s Syndrome | Fader et al. 1962, (110) McFarland et al. 1968, (111) Wolf et al. 1986, (112) Wijn et al. 2007(113) |
| Fabry-Anderson Disease                 | Regattieri and Parker 1973(114)              |
| IncontinentiaPigmenti                  | Himelhock et al. 1987(115)                   |
| Kabuki Make-Up Syndrome                | Rocha et al. 2008(116)                       |
| Larsen’s Syndrome                      | Perçin et al. 2002(117)                      |
| Marfan Syndrome                       | Khonsari et al. 2010(118)                    |
| Nance-Horan Syndrome                   | Walpole et al. 1990, (119) Hibbert 2005(120) |
| Noonan Syndrome                        | Tourreno and Park 2011(121)                  |
| Otodental Dysplasia                    | Chen et al. 1998, (122) Van Doorne et al. 1998(123) |
| Pyknody sostosis                       | Ramaiial et al. 2011(124)                    |
| Robinow Syndrome                       | Mazzeu et al. 2007(125)                      |
| Rubinstein Taybi Syndrome              | Stalib et al. 2006(126)                      |
| SOX2 Anophthalmia Syndrome             | Numakura et al. 2011(127)                    |
| Sotos Syndrome                        | Bale et al. 1985, (128) Raith and Laragnoit 2009(129) |
| Ttricho-rhino- phalangeal Syndrome     | Kantaputra et al. 2008(130)                  |
| Zimmerman-Laband Syndrome             | Chadwick et al 1994, (131) Holzhausen et al. 2003(132) |
| Others                                 | Silengo et al. 1993, (133) Nieminen et al. 2011(134) |

The rarity of ODs in humans does not allow performing epidemiologic studies to verify such a genetic/etiological supposition. However, in the last 30 years selected transgenic mice, in which SPNs (137) and odontogenic tumours (138, 139) frequently develop, have been used to investigate the complex odontogenic process that yields to the formation of both pathologies as well as of normal teeth. In the light of these studies, a genetic regulation seems therefore important in developing not only SPNs but also ODs, although differences exist in the expression of different genes.

Western blot analysis, in situ hybridization and immuno-histochemistry have been used in addition to histology to search for a possible role of genes, proteins, growth factors, receptors, extra-cellular matrix molecules, and other factors and molecules, in aetio-pathogenesis and morpho-differentiation of odontogenic tumours and SPNs, compared to normal tooth formation.

Observations have suggested that tumour proliferation and growth are principally driven by mesenchymal tumour cells (138) and that, although enamel does not derive from dental mesenchyma, unlike all other dental structures, dental mesenchyma is able to induce non-odontogenic epithelium to form odontogenic epithelium. (140)

The existence of a specific pathway of molecule signalling seems therefore important in defining the complex mechanism that controls the acquisition of odontogenic potentialities. The under/over expression of some of these signalling factors/molecules, most of which are still unknown, may influence different development times, aggregation and morpho-differentiation of dental tissues. Actually, many signalling molecules belonging to Hedgehog, FGF, Wnt, TNF, BMP PAX, SHH families and others have been proven to be important in the normal tooth germ development and seem to be able to give rise to supernumerary teeth if inappropriately regulated. (141, 142)

It is suggestive that in Familial Adenomatous Polyposis (FAP), (143) an autosomal-dominant disorder, and specifically in Gardner’s Syndrome, a FAP variant condition, many affected patients show multiple SPNs and ODs. Specifically, SPNs and ODs have been found approximately in 11-27% and, respectively, in 9.4-83.3% of patients with FAP, although no specific codon mutation has been found to be correlated with SPNs and/or ODs. (144) Actually, FAP has been shown to result from a mutation in adenomatous polyposis coli (APC) tumour suppressor gene which is known to inhibit Wnt signalling, an important family of proteins including β-catenine and Lef-1, which have been demonstrated to be important in tooth number and development regulation. (142, 144) Moreover, multiple odontoma-like SPNs have been found in transgenic mice whose oral epithelium expressed a stabilized form of β-catenine (141) and multiple SPNs have been
Cleidocranial Dysplasia (CCD), an autosomal dominant disorder, may be involved in the related epigenetic factors, such as DNA methylation and non-genetic factors, which are environmental, such as foetal, teratogenic, nutritional, traumatic and x-ray related, or epigenetic, such as DNA methylation and histone modifications, may also be involved in the formation of SPNs as already suggested in human Cleidocranial Dysplasia (CCD). An autosomal-dominant disorder in which the defective RUNX2 related protein seems incapable of preventing excess budding of successional dental laminae due to their different pattern of expression in siblings with identical gene mutation in RUNX2 as well as to the highly variable intra-familial expressivity, as specifically concerns presence and number of SPNs, in families with 100% genetic penetrance in which the dental phenotype seems to be associated with specific mutations in the CBFA1 transcription factor, on chromosome 6p21. Actually, local abundance of odontogenic epithelium has been previously found in perilental tissues of patients with CCD by histological and immuno-histochemical studies.

Finally, copy number variation, which includes insertion, deletions and inversions of genes, has also been suggested as a possible cause of different phenotypical expression in individuals with CCD having identical gene mutation.

This pathogenetic hypothesis can also be supported by the sporadically reported simultaneous presence of ODs and SPNs in non-syndromic cases and by many cases of non-syndrome multiple (more than five) SPNs. Moreover, CxODs and supernumerary microdontic teeth have been alternatively found in Otodental Dysplasia, an autosomal dominant inherited condition whose locus has been mapped to 20q13.1 within a 12-cM critical chromosomal region and a CxOD has been found as well in association with 1 SPN in a variant of Ekman-Westborg-Julin Syndrome.

Several transcription factors, including the LIM homeo-domain (Lhx) family proteins, have been shown to play an important role in tooth development. Denaxa et al. showed that the deletion of Lhx6 and Lhx7 homeo-box transcription factors in mice resulted in the presence of SPNs in the maxillary incisor domain. Since Lhx6 and Lhx7 expression has been found to persist at later developmental stages of tooth development, it is likely that Lhx6 and Lhx7 LIM homeo-domain proteins are key factors in the complex network of relationships which regulates the acquisition of odontogenic potential by the mesenchyme, allowing developing teeth to progress from the dental lamina to the bud stage. Shibaguchi et al. have already proposed the role of another member of the Lhx family proteins, the LIM homeo-box 8 (Lhx8), in the regulation of tooth morphogenesis, while Kim et al. recently demonstrated that LHX8 plays a similar role in the morphogenesis of compound as well as complex ODs and that the Lhx8 gene and protein over-expression in ODs, unlike normal dental stem cells, is associated with a wide spectrum of tooth-like structures characterized by different stages of morpho-differentiation.

Notch signalling mediated by Jagged 2 genes (Jag2) has also been found to play a critical role in normal tooth development and its absence has shown to interfere in the complex network of epithelial-mesenchymal interactions which regulate the expression of genes involved in odontogenesis, of both ameloblastic and odontoblastic components, leading to an abnormal bud morphology with lack of enamel, due to an incorrect BMP and FGF protein regulation of cell proliferation, differentiation and apoptosis.

Wright et al. found three different types of tissue organization in the odontogenic tumours of homozygous TG.AC transgenic mice, with a different yet always positive expression of the k-Ha-ras gene and production of p21 ras oncoprotein, as well as a different tumour development times. Over-expression of the ras p21 protein was also found in human odontogenic tumours by Sandros et al., although no odontomas were included in the study sample analyzed by the authors. Furthermore ras p21 expression has been found in the epithelium components of the normal developing human teeth. Expression of ras transgene is also thought to be triggered by chemical or physical local injuries and, since the proliferation of odontogenic tumour tissues seems to start from the periodontal ligament, it may be hypothesized that any kind of trauma on teeth and tooth bearing areas can activate the ras transgene resulting in stimulation of odontogenic cell proliferation in the periodontal ligament.

In conclusion, from the present review, epidemiological, clinical, immuno-histochemical and ge-
netic data suggest a common origin for SPNs and ODs which appear to be the expression of the same odontogenic hyper-productive process with different gradients of morpho-differentiation, in relation to a time and site-related signalling pathway of molecules and factors, genetically, non-genetically and epigenetically determined and modulated. Further studies are however required to substantiate this pathogenetic hypothesis.

Competing Interests

The author has declared that no competing interest exists.

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