Research Article

Gardner Syndrome: Complications/Manifestations in the Oral Cavity and Their Relationship with Oral Health

Antoine Gazelle and Inês Lopes Cardoso*

Health Sciences Faculty, University Fernando Pessoa, Porto, Portugal

A B S T R A C T

Gardner syndrome (GS) is a genetic disease, with autosomal dominant transmission, being a phenotypic variant of familial adenomatous polyposis (FAP). FAP is manifested by the development of numerous adenomas in the rectum during adolescence, and in most cases, if not identified and treated at an early stage, lead to colorectal cancer. This syndrome has several phenotypic characteristics and among them some changes in the oral cavity. Thus, the dentist has a preponderant role in the detection of lesions that may be present in the oral cavity in order to make possible an early diagnosis of the disease. Some manifestations of GS are observed at the dental level. Around 30 to 75% of GS patients present dental anomalies including dental agenesis, including teeth, delays in teeth eruption, dentigerous cysts, odontomas, supernumerary teeth, root fusion and hypercementosis. It is possible to see a significant difference in the presence of dental problems between patients with GS and the general population. In order to reduce morbidity and mortality, several types of surgery are used to eliminate the risk of colorectal cancer, preserving neighbouring anatomical functions.

Introduction

Gardner syndrome (GS) is a genetic disease, with autosomal dominant transmission, being a phenotypic variant of familial adenomatous polyposis (FAP). FAP is manifested by the development of numerous rectal adenomas during adolescence which, in most cases and if not identified and treated at an early stage, can lead to colorectal cancer. FAP has an incidence of 1/8,300 at birth and affects equally both sexes. In 2009, the prevalence of FAP was estimated at 1/11,300-37,600. FAP represents less than 1% of colorectal cancers [1]. The prevalence of cancer in patients with symptomatic FAP ranges from 47 to 67%. Studies show that, although diagnosed, 59% of patients die of colorectal cancer due to extensive metastasis [2]. In 1951, Gardner reported the association between surface tumors and colon polyps that are prone to malignant degeneration. In 1952, Gardner and Plenk described the dominant heritage pattern of multiple osteomas associated with colonic polyposis. In the same year Gardner and Richards reported the association between colonic polyposis and osteomas with multiple cutaneous and subcutaneous tumors. This was how Gardner's Syndrome was

discovered [3]. This syndrome has several phenotypic characteristics and among them are several changes in the oral cavity. Thus, the dentist plays a key role in detecting lesions that may be present in the oral cavity, helping in the early diagnosis of the disease [4].

Materials and Methods

A literature search was performed using the scientific databases PubMed, Science Direct, B-on and Elsevier. Used keywords were Gardner syndrome; Familial adenomatous polyposis; Osteoma; Genetic disease; Supernumerary teeth. Scientific articles from 1992 to 2018 were selected.

I Clinical Manifestations

i Gastrointestinal Tract and Adjacent Structures

The most important clinical manifestation of GS is the appearance of hundreds of adenomas (polyps) of different sizes in the colon that start

Correspondence to: Inês Lopes Cardoso, Faculdade de Ciências da Saúde, Universidade Fernando Pessoa, Rua Carlos da Maia, 296, 4200-150 Porto, Portugal; Tel: 351 225071300; E-mail: mic@ufp.edu.pt

to develop around 16 years of age [5]. However, the colon is not the only part of the gastrointestinal system to be affected. In fact, 90% of patients with FAP develop polyps in the stomach fundus, but these polyps rarely cause cancer. In 90% of cases, polyps also appear in the duodenum and periampular region, with a 5% probability of malignancy. Pancreatitis can be a consequence of an adenoma in this region. Finally, intestinal adenomas may be involved but have low risk of being malignant [1].

ii Endocrine System

Many studies have shown an association between GS and endocrine disorders with the appearance of thyroid nodules, craniopharyngioma and thyroid cancer [6]. The risk of thyroid cancer for GS patients is 100 times higher than for the general population. The most common neoplasm is papillary thyroid carcinoma and affects 17 times more women than men. The average age of onset of this cancer is 23.6 [5, 7].

iii Ocular System

About 80% of FAP patients have congenital hypertrophy of the retinal pigment epithelium (HCEPR), but this is not a specific symptom of this disease. Almost all patients with this feature have no symptoms [1, 6]. Examination of the fundus reveals multiple egg-shaped hyperpigmented retinal lesions, surrounded by a depigmented halo, in both eyes [8]. However, when multiple bilateral lesions occur, it may be a sensitive phenotypic marker of FAP. Few adenocarcinomas have been described in these lesions [1].

iv Skin

There are also phenotypic manifestations of GS at the skin level. The presence of squamous cysts is considered the most common skin lesion and can appear on the face, scalp and less frequently at the body extremeties. Studies show that 50 to 65% of these patients have multiple cysts that are asymptomatic but may cause inflammation, itching and may even rupture [9, 10]. Other lesions such as hepatocellular carcinoma, fibromas, lipomas, leiomyomas, neurofibromatomas and pigmented skin lesions have also been reported, but have no tendency to malignancy [6]. Finally, patients with FAP may develop soft tissue tumors usually called desmoid tumors that appear in the mesentery, abdominal wall or scar areas. They are considered benign but the consequent pressure on the gastrointestinal or urinary tracts, as well as on the nervous or vascular systems can be fatal. The incidence of desmoid tumors in patients with FAP is approximately 8% in men and 13% in women [1, 11].

v Oral Cavity

Some manifestations of GS are observed at the oral cavity level. Between 30 and 75% of GS patients have dental anomalies [9] including dental agenesis, enclosed teeth, delays in tooth eruption, dentigerous cysts, odontomas, supernumerary teeth, root fusion and hypercementosis [5, 10]. As can be seen in (Table 1) the frequency of some types of dental changes is significantly higher in GS patients when compared with the general population.

Supernumerary teeth can be single (isolated) or multiple. The single or double cases are usually located in the anterior region of the maxilla and the multiples are mainly found in the premolar region of the mandible. Eruption delay of a normal tooth may also be an early sign of a supernumerary tooth and thus favor the development of enclosed teeth [13]. The odontoma is a benign odontogenic tumor of the jaws with epithelium-conective tissue origin that is composed, in varied proportions, by the tissues involved in odontogenesis. It has no typical dental morphology, which allows to be distinguished from a supernumerary tooth [14]. There are two types of odontomas that can be distinguished clinically, radiologically and histologically: the complex odontoma in which dental hard tissues are presented as a diffuse mass without any sign of organization; and the composite odontoma, consisting of structures similar to multiple teeth, but separated from each other by connective tissue [13].

Table 1: Incidence of dental changes in patients with GS and in the general population [12].

	Supernumerary teeth	**Enclosed teeth**	**Odontomas**
GS patients	11-27%	4-38%	9,4-83,3%
General population	0-4%	0-4%	0-4%

Some studies also report that 68-82% of GS patients have osteomas, consisting of a benign lesion of well-differentiated mature bone tissue with predominantly laminar structure [15-17]. The presence of multiple lesions is usually common in GS patients, being the most common site the mandible. However, osteomas may also develop in the maxilla and skull [15, 18]. Central or lobulated osteomas can be seen in the mandible and, while central osteomas appear near the root of the teeth, lobules appear in the cortex and are more common in the mandibular angle [19]. Although usually asymptomatic and with very slow evolution, this lesion can reach significant proportions, causing distortion of the face, chewing disorders and limitation of mouth opening. In some cases, compression of adjacent organs may occur, which may cause swallowing and breathing disorders [18]. The pathogenesis of osteomas remains unknown [16].

II Genetic Characteristics of GS

As noted above, GS is a genetic disorder with autosomal dominant transmission. Therefore, most individuals with this syndrome have a family history of this condition. However, up to 30% of patients may have a new dominant mutation (*de novo* mutation) and be the first affected member of the family [2]. Genetic changes that lead to the development of this condition involve the *APC* gene (adenomatous polyposis coli) [20].

i The *APC* Gene

The *APC* gene was isolated in 1991. It is a tumour suppressor gene with *locus* 5(q21-q22). This gene is 300 kb long and consists of 15 exons of different sizes. By alternative splicing, part of exon 9 (nucleotides 934-

1236) may be removed along with the exon's flanking introns, giving rise to a shorter mRNA. The coding region of the largest transcript comprises 8,535 nucleotides [21]. APC protein can be divided into three regions:

- The N-terminal portion (900 amino acids) is proline free and consists of eleven repeats of a helicoidal structures composed of a characteristic 7 amino acid sequence. The presence of this helical structure suggests a possible homodimerization and/or dimerization with other polypeptide chains. In fact, it was demonstrated that this region is responsible for protein homodimerization [22, 23].
- The central region has 7 repeats of a 20 amino acids motif. It was found that the protein immunoprecipitated APC leads to the co-purification of other proteins that have been identified as α-catenin and β-catenin. It is this central region of the APC protein that is responsible for this interaction [23].
- The C-terminal end is involved in the association with tubulin, inducing the assembly of these filaments *in vitro*. This terminal contains a region rich in basic amino acids [24, 25].

APC is a classic tumor suppressor protein that plays a central role in Wnt signaling, being involved in the regulation of β-catenin degeneration. Wnt signals influence the stability of a protein complex containing β-catenin, condutin and glycogen synthase kinase 3 (GSK3). In the absence of Wnt or in the presence of APC, β-catenin degradation occurs. On the other hand, in the presence of Wnt or in the absence of APC, as is the case with many colon cancers, β-catenin target genes, including *c-myc*, are expressed. The expression of the Myc protein leads to the expression of the polyamine ornithine decarboxylase which is a proto-oncogene [1]. APC also participates in other key cellular processes such as adhesion, migration, actin and microtubule network organization, spindle formation, chromosome segregation and apoptosis [26].

ii β-Catenin

β-Catenin is associated with the cytoplasmic end of cadherin E, an adhesion molecule (also called uvomorulin) important in morphogenesis. The E-cadherin-catenin interaction is essential for maintaining epithelial cell adhesion [27]. APC modulates the interaction between cadherins and catenins, altering the mechanisms by which intercellular interactions control cell growth and differentiation [27]. APC protein can cause epithelial cell release in the intestinal lumen, preventing the retention of proliferating cells at the level of the intestinal ridges [27].

iii Mutations in the *APC* Gene

Many mutated forms of this gene have been found in the germline of patients with familial polyposis. These changes are of various types and include point mutations, short deletions (1-14 nucleotides) or insertions (1-2 nucleotides). These changes particularly affect the 5' end of the *APC* gene. Approximately 70% of the mutations are located in the 5' portion of exon 15 (codons 713-1597) [21, 28]. The two most frequent deletions are of codons 1309 (20% of cases) and 1061 (10% of cases). These deletions lead to changes in the reading coding frame which results in the appearance of a premature stop codon and consequent synthesis of a truncated, poorly functioning or non-functional APC protein. However,

this mutated protein is able to associate with the normal protein and lead to its inactivation, thereby exerting a negative activity [23, 25]. Only mutant forms of the protein that contain the catenin binding domain are able to associate with it [23, 25]. These truncated proteins can no longer associate with cytoskeleton microtubules [23, 25]. Studies suggest a correlation between mutation location and the number of developed polyps. Thus, mutations affecting codons 1,285 to 1,465 appear to be associated with profuse polyposis (more than 5,000 polyps). On the other hand, attenuated forms of familial polyposis (number of polyps generally below 100) result from mutations in the 5' end of the *APC* gene [29]. More than 1,400 different mutations in this gene have been identified. The mutated region of the *APC* gene determines extracolonic events as well as the time period and malignant potential of adenomatous polyps [30].

Furthermore, it has been reported that mutations in the *MYH* gene and environmental factors such as diet, exercise and smoking also play an important role in the pathogenesis of GS, which classifies this syndrome as a polygenic and multifactorial disease [30].

III Diagnosis of GS

The diagnosis of this syndrome is based primarily on family history. In a second place, clinical diagnosis is performed that must be confirmed by genetic tests. Often, due to the development of psychomotor disorders or mental retardation, cytogenetic analyzes are performed at a young age. However, when there is no development of mental retardation and both parents are healthy, the disease will only be detected later in adolescence [1, 7].

i Clinical Diagnosis

The first visible symptoms are osteomas and dental anomalies. The dental doctor may be the first health professional to suspect of the presence of this syndrome, by the use of palpation methods and panoramic radiography. Osteomas precede the formation of intestinal polyps, so they may be good markers for the disease [31, 32]. As discussed earlier, HCEPR is reported in 80% of GS patients and appears shortly after birth and may also represent the first sign of syndrome detection [6]. Osteomas can be detected by observing a bulge under the skin at the face level, however radiography remains the best detection method. Radiologically, osteomas present as a dense, well-circumscribed, sometimes lobulated, uniformly radiopaque mass, often overlapping the underlying bone. Standard radiography (panoramic or retro-alveolar radiography) remains the first-line examination and should be complemented by three-dimensional imaging (computed tomography or cone beam), which is the reference image in the diagnosis of osteoma. Bone scintigraphy is especially useful for early diagnosis and as a guide for more accurate complementary examinations. Magnetic resonance imaging (MRI) is most suitable in cases where the medullary bone is affected or to guide the diagnosis when other imaging techniques are not conclusive. The differential diagnosis concerns exostosis, osteoid osteoma, odontoma and osteoblastoma [18, 33]. Regarding dental changes, the presence of an included supernumerary tooth in the oral cavity may be one of the signs and symptoms indicative of the presence of this syndrome. The most frequent dental signs are characterized by retention of one or more deciduous teeth, persistence of

the interincisal diastema, movements of neighboring teeth and articular teeth disorders [34]. Hyperdontics may be associated with other dental abnormalities such as fusion, agenesis, evagination or concrescence [35]. Oral cavity pain is the main clinical sign but there may also be dermatological signs such as angiokeratomas [36].

Supernumerary teeth are often asymptomatic and are discovered by panoramic, retro- alveolar, occlusal or cone beam radiography. Any of these techniques can determine the position, size and orientation of supernumerary teeth [37]. These supernumerary teeth can have three different locations: the conical or tubercular mesiodens that are usually in the palatal position relative to the central incisors; the molar-shaped paramolar that develops between premolars or molars, or exceptionally on the palatal or lingual side; or the distomolar that develops behind the wisdom tooth [13, 38]. When GS diagnosis is suspected, the patient is referred for gastroenterology consultation. A colonoscopy will confirm the presence or absence of intestinal polyps. These polyps may cause constipation, diarrhea, intestinal pain or rectal bleeding and may alert the physician to the disease [7].

ii Differential Diagnosis

GS can be associated and distinguished from other forms of FAP, as shown in (Table 2).

Table 2: Characteristics of different forms of FAP [5, 39].

	Classical form of FAP	**Attenuated form of FAP**	**Gardner syndrome**	**Turcot syndrome**
Gene	APC: 5q21	APC: 5q21 N-terminal mutation	APC: 5q21	APC: 5q21
Transmission	Autosomal dominant	Autosomal dominant	Autosomal dominant	Autosomal dominant
Colic manifestations	Adenomatous polyps	Adenomatous polyps, late onset, low number	Adenomatous polyps	Adenomatous polyps
Extra-colic manifestations	Absent	Absent	HCEPR, epidermoid cysts, pilomatrixoma, fibrous hyperplasia, desmoid tumour, multiple osteomas various digestive tumours and extra digestive	Brain tumour: glioblastoma, medulloblastoma. Basal cell carcinoma. Brown spots.
Evolution	Colonic adenocarcinoma	More or less favorable	Appearance of polyps: second and third decades. Cancers: third and fourth decades.	Colon cancer – Nervous system disorders.

iii Genetic Diagnosis

After clinical diagnosis, GS should be confirmed by genetic testing. Nowadays, several genetic tests are available to detect germline mutations in the *APC* gene [40]. Complete gene sequencing is the most sensitive method for the detection of these mutations (70%), but it is time consuming, intensive and expensive. Alternatively, the protein truncation test has the advantage of being less expensive despite the lower detection rate of gene mutations. Southern blot analysis can be used to detect partial or total gene deletions or other major rearrangements [1, 40].

iv Prenatal Diagnosis

Identification of the mutant *APC* gene responsible for FAP allows pre-symptomatic and even prenatal diagnosis of the disease. In fact, if a mutation is identified in a family member, prenatal testing may be performed [1]. There are two conventional tests to look for the possible presence of mutation. The first is amniocentesis which is the most common, being performed with a small needle that is inserted through the abdomen and uterus into the amniotic sac to collect approximately 30 mL of amniotic fluid. The exam is done between the 16th and 20th weeks of pregnancy. The second is called CVS (Chorionic Villous Sampling) and is performed between the 10th and 12th weeks, allowing earlier results. CVS is usually performed trans-cervically, with the insertion of a thin plastic tube into the placenta, and the suction of a small sample of chorionic villous tissue [1]. There are ethical issues associated with these prenatal diagnoses since the result might lead to the decision of pregnancy arrest. The answer to this complex problem is affected by cultural and religious factors. Studies show that only 20% of prenatally diagnosed women decide to abort when a mutation in the *APC* gene is detected [1]. During pregnancy, due to changes in multiple growth factors and endogenous hormones, women have an increased risk of development of demoid tumors and adenomas. During this period, treatments should be postponed to avoid fetal damage [1].

IV Treatments

In order to reduce morbidity and mortality, various types of surgery are used to eliminate the risk of colorectal cancer while preserving

neighbouring anatomical functions. Types of surgery include total ileorectal anastomosis colectomy, ileal pouch anal anastomosis proctocolectomy, and ileostomy proctocolectomy [39]. Ileorectal anastomosis colectomy seems to be the recommended treatment for patients with GS and colon polyps [39]. Ileostomy is only used in cases of recurrent neoplasms after an ileorectomy [39]. The complete removal of desmoid tumours, which are often invasive, can be very difficult. Some studies suggest the use of drugs, such as nonsteroidal anti-inflammatory drugs (sulindac), tamoxifen or ascorbate, to temporarily reduce the number and volume of polyps [2]. Chemotherapy and radiotherapy may also be used. However, it is often difficult to control these recurrent, morbid or even fatal tumours [2]. Oral calcium has also been shown to inhibit rectal epithelial proliferation because of its ability to reduce colorectal cell turnover [39]. The treatment of osteomas consists of complete surgical excision of the lesion and the prognosis is excellent. The surgical approach may be intraoral or extraoral. For mandibular localization, if possible, intraoral rather than external access is preferred to avoid possible facial nerve injury [41, 42]. However, in some cases, the location of the lesion makes it impossible to perform intraoral surgery due to difficult access. It should be noted that some cases of spontaneous remission of osteoid osteoma were observed. Although osteoma recurrence is extremely rare, the patient should be followed for a long period of time after surgical removal of the primary lesion to control the evolution of healing [41, 42].

The treatment of supernumerary teeth will depend on its type and position and on possible complications. There is no consensus on when the best time for removal of the supernumerary teeth is [43]. However, in most cases, extraction is the treatment of choice. After extraction, orthodontic treatment may be useful to maintain sufficient clearance or to allow traction of the misplaced tooth. In some cases, when the supernumerary tooth is clinically and radiologically asymptomatic or when it is deeply embedded, therapeutic abstention and regular radiological examinations are decided on patient follow-up. When needed, treatments should be done as soon as possible to minimize complications [36].

Discussion and Conclusion

GS is distinguished from FAP by the presence of extra-colonic clinical manifestations. The genetic cause of this syndrome has been identified as the presence of mutations in the *APC* gene [30]. The protein encoded by this gene is a key molecule in the Wnt signaling pathway, which is involved in the development of teeth and bones [44]. This pathway is expressed in the human oral epithelium during the morphogenetic stages of dental development [45]. It has been shown in the oral epithelium of rat embryos that APC ablation and Wnt/β-catenin activation result in the development of supernumerary teeth [46]. Regarding bone development, the association between the APC protein, differentiation of skeletal precursors and osteogenesis was confirmed. Mutations in the *APC* gene result in high osteoblast activity and increased bone deposition associated with high levels of β-catenin. Thus, patients with FAP have significantly higher bone mineral density when compared to healthy individuals of the same age and sex [47]. Oral mucosa vascular changes have also been associated with FAP [48]. All this explains the presence of Garner Syndrome symptoms in the oral cavity. On the other hand, the heterogeneity of clinical manifestations observed in this syndrome can

be explained by other factors such as non-genetic environmental factors, not involving changes in the *APC* gene [26].

GS is characterized by the development of numerous rectal adenomas that may lead to colorectal cancer. However, manifestations in the oral cavity develop even before the appearance of adenomas. For this reason, the dentist may be the first health professional to be involved in the diagnosis of the disease. This clearly shows the dentist's power and duty in diagnosing systemic genetic diseases because of his ability to detect early oral cavity anomalies and thus refer the patient to more specialized services. Therefore, the management of genetic diseases is multidisciplinary, and the dentist can be an important link in this chain.

Conflicts of Interest

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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