

# Developmental malformations of human tongue and associated syndromes (review)

E.-N. EMMANOUIL-NIKOLOUSSI, C. KERAMEOS-FOROGLOU

*Laboratory of Histology-Embryology, Faculty of Medicine, Aristotelian University of Thessaloniki (Greece).*

## SUMMARY

The development of the tongue begins as known, in the floor of the primitive oral cavity, when the human embryo is four weeks old.

More specifically, the tongue develops from the region of the first three or four branchial arches during the period that the external face develops. Malformations of the tongue, are structural defects, present at birth and happening during embryogenesis. The most common malformations are:

1. Aglossia
2. Microglossia, which is always combined with other defects and syndromes, like Moëbius syndrome
3. Macroglossia, which is commonly associated with cretinism, Down's syndrome, Hunter's syndrome, Sanfilippo syndrome and other types of mental retardation
4. Accesory tongue
5. Long tongue
6. Cleft or Bifid tongue, condition very usual in patients with the orodigitofacial syndrome
7. Glossitis Rhombica Mediana, a developmental malformation?
8. Lingual thyroid.

Malformations are extensively analysed and discussed.

## KEY WORDS:

Developmental - Malformations - Defects - Syndromes - Tongue

## RÉSUMÉ

### MALFORMATIONS DE LA LANGUE HUMAINE ET SYNDROMES ASSOCIES (REVUE DE LA LITTERATURE)

Le développement de la langue commence au niveau du plancher de la cavité orale primitive lorsque l'embryon humain est âgé de 4 semaines.

Plus précisément, la langue se développe dans la région des trois ou quatre premiers arcs branchiaux durant la période du développement de la face externe. Les malformations de la langue correspondent à des défauts de structure présents à la naissance et survenant au cours de l'embryogenèse. Les malformations les plus communes sont:

1. Aglossie
2. Microglossie, qui est souvent combinée à d'autres anomalies ou syndromes, tel le syndrome de Moebius
3. Macroglossie, qui est communément associée au crétinisme, au syndrome de Down, au syndrome de Hunter, au syndrome de Sanfilippo et à d'autres types de retard mental
4. Langue accessoire
5. Langue longue
6. Langue bifide, condition très usuelle chez des patients présentant le syndrome orodigitofacial
7. Glossite rhomboïde médiane (?)
8. Thyroïde linguale.

Les malformations sont analysées et discutées.

MOTS CLEFS:

Développement - Malformations - Défauts - Syndromes - Langue.

## INTRODUCTION

The development of the tongue, begins as known, in the floor of the primitive oral cavity, when the human embryo is three to four weeks old, during the period when the external face develops. More specifically, the tongue develops from the region of the first three or four branchial arches [3, 7, 12, 13, 14].

Malformations of the tongue, are structural defects, present at birth and happening during embryogenesis. Developmental anomalies or defects may be major or minor, single or multiple, depending on their size, site and effect.

Tongue arises from four swellings which are located on the ventral wall of the primitive pharynx and appear independent [7, 12, 13, 14].

The tuberculum impar is the first swelling to appear. (It is also called median tongue bud) and it forms between and caudal to the mandibular arches. The two lateral tongue buds are developing soon after on the ventral ends of the same arches. These buds grow in size and merge with each other and with the median tongue bud, forming the anterior two thirds of the tongue. On this part of the tongue, all the papillae are developed. The posterior one third of the tongue arises from the hypobranchial eminence, a median elevation which forms caudal to the median tongue bud between the ventral ends of the 2nd, 3rd and 4th branchial arches [13].

## AIM OF THE STUDY

The aim of this study was to review developmental malformations of the human tongue, which take place when the human embryo is in utero and to describe some of the most common syndromes, which are associated with these tongue malformations.

## REPORTS

Developmental malformations, or defects may be major or minor, single or multiple, depending on their size and site of expression. Their incidence varies from country to country and from author to author [3, 6, 16]. It is referred that more than 20% of congenital defects in man result from simple Mendelian dominant or recessive inheritance and a further 10% from extrinsic teratogens, such as viruses, drugs and environmental factors, radiation etc. [16]. About 10% of defects may be the result of major chromosomal anomalies. Developmental defects can be classified on purely anatomical grounds, such as defects of the face, skull, limbs etc, but where biochemical changes accompany the defects and make a discrete nosological entity, it is often easier to regard them as true biochemical disorders [16].

The most common malformations of the tongue combined with syndromes associated with them, are expandly discussed in this review article. Malformations of the tongue, which are involved in congenital syndromes are classified in the following categories, while a small number of them is not classified in any categorie. These are:

1. *Aglossia*
2. *Microglossia*
3. *Tongue hemiatrophy*
4. *Tongue hemihypertrophy*
5. *Macroglossia*
6. *Long tongue*
7. *Accessory tongue*
8. *Ankyloglossia*
9. *Cleft or bifid tongue*
10. *Glossitis rhombica mediana (?)*
11. *Lingual thyroid*
12. *Non classified syndrome*

TABLE I:  
Congenital syndromes associated with Aglossia.

---

<b>AGLOSSIA</b>
1. Aglossia-Adaktyla syndrome
2. Occulo-auriculo-vertebral syndrome or Goldenhar's syndrome

---

## 1. AGLOSSIA

This malformation is probably due to failure of development of the lateral lingual swellings of the mandibular arch. It is extremely rare and only a few cases have been reported in living children [18]. The first case was reported early in the eighteenth century (1718) by Jessieu [16, 18]. A case was then reported with multiple deformities besides aglossia. The subject presented malformations of both hands and severe anomalies of the right foot [18]. Other investigators referred some other cases of aglossia, combined with other malformations such as hypoplasia of the mandible, median harelip, cleft palate, remnants of a buccofaryngeal membrane in some cases, while irregular dentition accompanied the deformities. In cases that subjects survive, the manner of swallowing may improve after the first months.

Kettner in 1907 was the first investigator who referred the association of aglossia with adaktylia [16].

*Aglossia-Adaktyla* (Table I) is described as a very rare syndrome, in which hypoplastic mandible, gum and dental abnormalities are associated by a very greatly reduced or absent tongue as well as a variable absence of digits and limb bones. The syndrome is not inherited on a genetic basis [16].

Partial aglossia is sometimes described in *Goldenhar's syndrome* or *occulo-auriculo-vertebral dysplasia* (Table I), which is accompanied by high arched palate or cleft-palate in some cases, while dental malocclusion is evident [16].

## 2. MICROGLOSSIA (Table II)

This malformation is combined with many congenital syndromes, while it is described as a not so rare one. It is often combined with glossopalatine ankylosis.

*Faciocardiomelic dysplasia*, includes in its symptoms microglossia and glossoptosis, combined with micrognathia. In this syndrome which is an autosomal recessive, inheritance is suspected, while parenteral consanguinity is present [6, 16].

TABLE II:  
Congenital syndromes associated with Microglossia.

---

<b>MICROGLOSSIA</b>
1. Microglossia-glossoptosis syndrome or Robin's syndrome or Robin's-Lenstrup syndrome or Pierre Robin syndrome or anomalad
2. Oromandibular-limb-hypogenesis syndrome
3. Peromelia and Micrognathia (Hanhar's syndrome)
4. German's syndrome
5. Congenital facial displegia or Moebius syndrome
6. Hypoglossia-Hypodaktylia syndrome
7. Faciocardiomeic dysplasia

---

Hypoglossia with microstomia and micrognathism is described in *Oromandibular-limb hypogenesis syndrome*, which is expressed due to some unknown teratogens, while it is not due to a single gene inheritance. It is possible to be multifunctional [6, 10].

Microglossia with glossoptosis is also characterizing the *Pierre Robin syndrome* or *anomalad* or *Robin's syndrome* or *Robin's-Lenstrup syndrome* or *Micrognathia-glossoptosis syndrome*. The cardinal features of the syndrome are micrognathism, cleft-palate and glossoptosis. Sometimes the micrognathia is of so extreme degree, so that tongue musculature is not allowed for full support. In Pierre Robin's syndrome familial incidences have been reported and an X-linked and an autosomal dominant transmission have been suggested. Most cases are sporadic, while oligohydramnios is most indicated. Whenever in Pierre Robin's anomalad, glossoptosis, cleft palate and micrognathia are combined with eye, ear, skeletal and cardiac defects, the syndrome is called Pierre Robin's anomalad [6, 16].

*Peromelia and micrognathia of Hanhar's syndrome*, presents severe micrognathia with microglossia in some cases. It is a very rare sporadic disorder, possibly multifunctional [6].

*German's syndrome* in which growth retardation is present, micrognathism, high-arched palate and microglossia are characterizing the syndrome [6].

*Moebius syndrome* or *congenital facial displegia*, atrophy of tongue due to lack of hypoglossal innervation is present. Muscle weakness remains from infancy to adulthood. Sexes appear to be equally affected. Hypoplasia of the mandible and the anterior half of the tongue are frequent. In this syndrome hypoplasia or agenesis of the nuclei of VI and VII cranial nerves happens very often [6, 16].

In *Hypoglossia-hypodactylia syndrome*, severe hypoplasia of tongue is observed, while sublingual muscular ridges may be enlarged. In this syndrome, submaxillary and sublingual glands are hypertrophic. This fact occurs possibly due to unknown intrauterine result. It is a very rare disorder in which most cases are sporadic [6, 16].

### 3. TONGUE HEMIATROPHY (Table III)

This deformity usually is an anatomic structure as a feature of craniofacial microsomia [3], condition where the three major features are auricular, mandibular and maxillary hypoplasia. The musculature of the soft palate and the tongue is occasionally less developed on the affected side. There is also observed an hypoplasia or aplasia of the parotid gland, unilateral or bilateral [3].

In *Progressive hemifacial atrophy* or *Parry-Ronberg's syndrome*, atrophy of one half of the tongue is distinguished [6, 16].

TABLE III:

Congenital syndromes associated with tongue hemiatrophy, tongue hemihypertrophy.

TONGUE HEMIATROPHY
1. Progressive hemifacial atrophy or Parry-Romberg syndrome
TONGUE HEMIHYPERTROPHY
1. Congenital hemifacial hyperplasia

### 4. TONGUE HEMIHYPERTROPHY (Table III)

Is observed in congenital hemifacial hypertrophy [1, 3, 8] a clinical condition in which hyperplasia of the facial features of one half of the face is obvious.

### 5. MACROGLOSSIA (Table IV)

Macroglossia is a condition commonly associated in infancy and childhood with cretinism and generally with types of mental retardation, although it has to be emphasized that it can occur in otherwise normal children [18]. It is also agreeable that tumors, such as lipomas, hemangiomas or lymphangionas enlarge the tongue. Tongue also may be enlarged in certain cases of generalized muscular hypertrophy. Idiopathic muscular macroglossia may be the only malformation of the body or may be associated with other anomalies of the gastrointestinal tract [18].

TABLE IV:

Congenital syndromes associated with macroglossia.

MACROGLOSSIA
1. Exomphalos-macroglossia-gigantism syndrome or Beckwith's syndrome or Beckwith-Wiedemann syndrome
3. Neurofibromatosis syndrome
4. Generalized gangliosidosis (GM <sub>1</sub> )
5. Hyalinosis cutis et mucosae or Lipoid proteinosis or Urbach Wiethe syndrome
6. Mannosidosis
7. Mucopolysaccharidosis I-H or Hurler's syndrome
8. Mucopolysaccharidosis I-S
9. Mucopolysaccharidosis II or Gargoylism or Hunter's syndrome
10. Mucopolysaccharidosis III
11. Mucopolysaccharidosis VI A&B or Maroteaux - Lamy syndrome
12. Pycnodysostosis or Osteopetrosis
13. Pud's syndrome
14. Trisomy 21 syndrome or Down's syndrome or Mongolism
15. 4p+ syndrome
16. 7p+ syndrome
17. Cloverleaf Skull or Tri-Lobed Skull or Kleeblattchader syndrome
18. Soto's syndrome

*Exomphalos-Macroglossia-gigantism syndrome* or *Beckwith's syndrome* or *Beckwith-Wiedeman syndrome*. In this syndrome macroglossia and exomphalos show a significant association, while a high birth weight is a feature of the syndrome. The syndrome includes facial nevus flammeus, diaphragmatic anomalies, some times urogenital deviations and ear lobes. A visceromegaly is also related to the syndrome [6, 18].

In *Multiple mucosal neuroma syndrome*, lingual neuromas are present, while other mucosal neuromas are less common. Investigators also describe an asthenic body build. This condition is thought to be a neurocristopathy that is hyperplasia and/or neuroplasia of neural crest elements [16].

*Neurofibromatosis syndrome* or *Von Recklinhausen's disease*, may produce enlargement of the tongue [18].

Although oral involvement is not common, neurofibromas are varying in numbers on face and tongue [6].

Macroglossia is a defect present in *Type II Generalized Gangliosidosis (GM<sub>1</sub>)*, a rare autosomal recessive, not related to any ethnic group. Large mouth and gingival hyperthrophia are existing together with macroglossia [6].

Another rare autosomal recessive syndrome is the *Hyalinosis cutis et mucosae*, in which tongue becomes large, thick and bound to the floor of the mouth, while the dorsum of the tongue loses its papillae. Bullous or pustular lesions may develop on skin, especially on the face region. The lesions may be covered with small yellowish white nodules, vary sometimes. Oral tissues may be infiltrated with yellowish white plaques [6].

In *Mannosidosis* [6, 16], another autosomal recessive, mental and growth retardation is observed, combined with flat nose, teeth widely spaced, coarse facial features and macroglossia.

In *Mucopolysaccharidosis J-H* or *Hurler's syndrome*, an autosomal recessive condition, with frequent parental consanguinity, large tongue and open mouth are frequently present. Apathetic facies, flat nasal bridge, broad nasal tip, large and protruding lips, small widely spaced teeth are symptoms associated with the syndrome [6, 16].

Another autosomal recessive, which is associated with large tongue, as well as square jaw and broad mouth, is *Mucopolysaccharidosis I-S* or *the Scheie's syndrome* [6, 16].

*Mucopolysaccharidosis II* or *Hunter's syndrome* or *Gargoylism* [6, 16], is another mucopolysaccharidosis in which the general appearance in birth is normal and only after two or three years, the characteristic changes begin their appearance. The facies is coarse with depressed nasal bridge, noisy respirations and mucopurulent nasal discharge. The neck presents short and wide and irregular dentition, while thick lips and Macroglossia are present [16].

*Mucopolysaccharidosis III* or *Polydystrophic oligophrenia* or *San Filippo A & B syndrome* or *Sanfillippo-Harris syndrome* presents thick lips and mouth, frequently held open with noisy mouth breathing. In this condition macroglossia is appeared [6, 16].

In *Mucopolysaccharidosis VI* or *Maroteaux-Lamy syndrome*, a large tongue is also observed. The facies are also coarse, the nose large and there are also thick

lips [16]. Fissuring of the tongue is also distinguished [6].

In *Pycnodysostosis* or *Osteopetrosis acrolytica* or *Dysostosis petrosans*, macroglossia with grooved palate, various dental anomalies and persistence of the primary dentition is observed [6, 15].

In *oligophrenia -epilepsy- ichtyosis syndrome* or *Rud's syndrome*, together with other congenital anomalies, such as arachnodactylia, generalized muscular hypotonia, alopecia, strabismus, high arched palate and extreme dental caries, macroglossia is also present [6, 16].

Macroglossia often associates trisomies [6], such as:

*4p+ syndrome*, where mandibular prognathism with pointed chin and long philtrum are present.

*7p+ syndrome*, with cleft palate and micrognathism.

*21 Trisomy syndrome* or *mongolism* or *Down's syndrome*. In this syndrome protruding fissured tongue with hypertrophy of papillae is observed. Trisomy 21 accounts in 95% of Down's syndrome cases. About 3,5% exists due to transplantations and this type may produce familial mongolism. About 2% exists due to a mixture of cell lines referred to as mosaicism [6, 16].

In *Cloverleaf skull* or *Tri-Lobed Skull* or *syndrome Kleeblattschadel* [6, 16] macroglossia, unilateral microphthalmia, cleft lip and palate, colobomata, Meckel's diverticulum and patent ductus arteriosus are accompanied findings of the syndromes. Most cases have been reported in Germany, while the findings suggest a possible autosomal distribution [16].

*Soto's syndrome* is also connected with macroglossia [6, 16].

TABLE V:

Developmental malformations and associated syndromes in human tongue associated with Long tongue, Accessory tongue, Ankyloglossia.

---

LONG TONGUE.
1. Ehlers-Danlos syndrome
ACCESSORY TONGUE
ANKYLOGLOSSIA
1. Van der Wonde's syndrome or Murray's syndrome
2. Cryptophthalmos syndrome

---

6. LONG TONGUE (Table V)

A few cases have been described in the literature with extreme length of the tongue and extreme mobility.

In *Ehlers-Danlos syndrome*, subjects have hyperextensibility of their skin. They do easily touch the tip of their nose with their tongue [6, 9].

7. ACCESORY TONGUE (Table V)

Accesory tongue is a very rare malformation. A very few cases are referred in the literature [17]. In this condition, tongue is attached to the tonsil, or a process is arising from one side of the base of the tongue.

8. ANKYLOGLOSSIA (Table V)

Ankyloglossia is a common clinical manifestation in *Van der Wonde's syndrome* or *Murray's syndrome*. Among the findings associated with Van der Wonde's syndrome, syndactyly, symblepharon and absence of the upper lip incisors combined with ankyloglossia is observed. In *cryptophthalmos syndrome*, ankyloglossia is often described.

TABLE VI:

Congenital syndromes associated with Cleft or Bifid tongue

CLEFT or BIFID TONGUE
1. Oculo-auriculo-vertebral dysplasia or Goldenhar's syndrome
2. OFD I syndrome or oro-facial-digital syndrome or Gorlin-Psaume syndrome or Papillon Leage and Psaume syndrome or Dysplasia lingofacialis or orodigital-facial dysostosis or Papillon-Leage syndrome
3. OFD II syndrome or Mohr's syndrome
4. Cleft-palate-lateral synechia syndrome or CPLS syndrome
5. Focal dermal hypoplasia

9. CLEFT OR BIFID TONGUE (Table VI)

This condition is described in *oculo-auriculo-vertebral dysplasia* or *Goldenhar's syndrome*, which is associated with dental malocclusion, high-arched palate, or cleft palate. In this syndrome, partial aglossia instead of bifid tongue is also reported [6, 16]. Embryologically the syndrome is thought to derive from an abnormal mesoblastic development which affects the formation of branchial and vertebral systems [16].

*Orofacial digital syndrome* or *orodigital-facial dysostosis* or *OFD I syndrome* or *dysplasia lingofacialis* or *Papillon-Leage syndrome* or *Gorlin-Psaume syndrome* or *Papillon-Leage and Psaume syndrome* [6, 16]. In this syndrome which occurs only in females, various oral abnormalities are included. Lobulation of the tongue, cleft palate, hyperplastic frenula between muccobuccal folds, associated with facial anomalies and digital malformations are present. The OFD I syndrome appear to be inherited as an X-linked dominant occuring in females while it is lethal to males [16].

In *OFD II syndrome* or *Mohr's syndrome* [6, 16], which is a very rare one, the tongue is lobulated with two or three clefts and nodular hamartomata are present at the base of the clefts in many cases. This syndrome occurs in both sexes and may be diagnosed in birth. Lobulate tongue usually exists with midline cleft of the upper lip while bilateral hallulal polysyndactyly and other digital anomalies appear very often. Congenital conductive hearing loss, is sometimes present. The syndrome is transmitted as an autosomal recessive.

*Cleft Palate-Lateral synechia syndrome* or *CPLS syndrome* [4, 6], which is described as a very rare one, synechia lateral to tongue, cleft palate and maxillary hypoplasia is observed.

In *Focal dermal hypoplasia syndrome* or *Goltz syndrome*[6], all affected subjects are female (X-linked dominant gene with lethality in males). In this syndrome multiple oral lesions are observed, such as cleft lip, high arched palate, median cleft of tongue, double lingual frenula, hemihypoplasia of tongue, absence of labial sulcus and hypertrophy of gingiva.

TABLE VII:

Developmental malformations of human tongue

GLOSSITIS RHOMBICA MEDIANA (?)
LINGUAL THYROID

10. GLOSSITIS RHOMBICA MEDIANA (Table VII)

This condition is described to be a developmental malformation. It is believed [17], that this anomaly is due to the persistence of the tuberculum impar which in the embryo forms the pharyngeal floor between the first pair of branchial arches.

The typical lesion consist of a rhomboid plaque which may extent anterior to the sulcus terminalis, slightly raised from the oral surface [2, 5]. As anti-fungal therapy and, above all, suppression of tobacco may reduce this anomaly, some authors [17] call in question its character of developmental malformation.

### 11. LINGUAL THYROID (Table VII)

This condition is due to the incidence of thyroid gland elements in the area of the foramen caecum. The lesions usually are median in position, immediately posterior to the foramen caecum and sitting on a broad base, varying in colouring from red to purple [17].

TABLE VIII:

Syndromes and malformations non classified in the previous categories

- 
1. MELKERSSON-ROSENTHAL syndrome
  2. COFFIN-LOWRY syndrome
  3. RILEY-DAY syndrome
  4. ANGIOOSTEOHYPERTROPHY  
or Klippel-Trenaunay-Weber syndrome
  5. FISSURED TONGUE syndrome
- 

### 12. NON CLASSIFIED SYNDROME (Table VIII)

The following syndromes that we found in the international litterature, are not classified in the typical tongue malformations, providing differential lesions (Table VIII).

#### *MELKERSSON-ROSENTHAL syndrome.*

In this syndrome, «lingua plicata» (folded tongue) is observed in one third of the cases. It may also be loss of taste and a slight visual disturbance prior to paralysis [6].

#### *COFFIN-LOWRY syndrome.*

In this syndrome, X-linked dominant inheritance is described. Affected males show full syndrome, while affected females have milder findings. It is believed to be a lysosomal storage disorder.

Hypodontia in which conical incisors erupt, open mouth and a very deep central lingual groove as well as, thickened lips with protruding lower lip is also observed [6].

#### *RILEY-DAY syndrome or FAMILIAL DYSAUTONOMIA.*

It occurs mainly in Ashkenazi Jews. It is a rare autosomal disorder, in which the tongue provides with decreased fungiform papillae, as well as with decreased numbers of circumvallate papillae [6].

#### *ANGIOOSTEOHYPERTROPHY syndrome or KLIPPEL - TRENNANAY - WEBER syndrome [6].*

In this syndrome, angiomatosis of the tongue, and pharynx, associated with multiple hemangiomas of the body are present.

#### *FISSURED TONGUE syndrome [5, 11], where fissures on the tongue are very distinguished.*

### REFERENCES

- [1] Antoniadis, K., Letsis, I., Karakasis, D. — Congenital hemifacial hyperplasia. *British J. of Oral and Maxillofacial Surg.*, 26: 344-348, 1988.
- [2] Bain, J., Carter, Ph., Morton, R. — Colour Atlas of Mouth, Throat and Ear Disorders in Children. Lancaster, MTP Press Ltd, 14-15, 1985.
- [3] Converse, J.M., Mc Carthy, J.G., Wood-Smith, D. — Symposium on Diagnosis and Treatment of Craniofacial Anomalies. Louis, Toronto, London, The C.V. Mosby Co., 11-23, 1979.
- [4] Dinardo, N.M., Christian, J.M., Bennett, J.A., Shutack, J.G., Morganstorm, W.A. — Cleft palate lateral synechia syndrome. *Oral Surg. Oral Med. Oral Path.*, 565-566, 1989.
- [5] Eidelman, E., Chosack, A., Cohen, T. — Scrotal tongue and geographic tongue: Polygenic and associated trains. *Oral Surg. Oral Med. Oral Path.*, 42: 591, 1976.
- [6] Goodman, R.M., Gorlin, R.J. — The Face in Genetic Disorders. St. Louis, Missouri. The C.V. Mosby Co., 3-73, 90-165, 215-239, 262-263, 270, 280, 290-298, 304-321, 326-327, 370-377, 396-397, 400, 401, 402-487, 500-531, 1977.
- [7] Kerameos-Foroglou, Ch. — Human Histology and Embryology. Thessaloniki, Greece. Paratiritis, 1st ed. Vol. I, 233-300, 321-332, Vol. II, 475-477, 1987.
- [8] Khanna, I.M., Andrade, N.N. — Hemifacial hypertrophy. *Int. J. of Oral and Maxillofacial Surgery*, 294-297, 1989.
- [9] Kirk, F.L., Heidi, F.H., Kempt, K.K., Moline, D.D. — Dental Implications in Ehlers-Danlos syndrome. *Oral Surg. Oral Med. Oral Path.*, 431-435, 1990.
- [10] Kitamura, A, Inokuchi, T. — A case of oromandibular-digital hypogenesis syndrome. *J. of Cranio-Max.-Fac. Surg.*, 15: 291-293, 1987.
- [11] Kullqa-Mikkonen, A., Penttila, I., Kotilainen, S., Pyhakainen, E. — Haematological and immunological features of patients with fissured tongue syndrome. *British J. of Oral and Maxillofacial Surg.*, 25: 481-487, 1987.
- [12] Melfi, C.R. — Permar's Oral Embryology and Microscopic Anatomy. Philadelphia. Lea & Febiger. 8th edition, 36-39, 1988.

[13] Mjor, J.A., Fejerskov, O. — Human Embryology and Histology. Copenhagen, Munksgaard. 1st edition, 22-24, 1986.

[14] Provenza, V., Seibel, W. — Oral Histology: Inheritance and Development. U.S.A. Lea & Febiger, 418-426, 1986.

[15] Ruprecht, A., Wagner, H., Engel, H. — Osteopetrosis: Report of a case and discussion of the differential diagnosis. *Oral Surgery*, 674-679, 1988.

[16] Salmon, M.A. — Developmental Defects and syndromes. Great Britain HM+M. Publ. 1st ed., 1-5, 7-10, 40-49, 86-100, 115-147, 186-188, 236-237, 253-254, 264-266, 296-298, 317-359, 1978.

[17] Waal van der, I., Kwast van der, W.A.M. — Pathologie van de Mondholte. Utrecht/Antwerpen, Bohn, Scheltema en Holkema, 1981.

[18] Warkany, J. — Congenital Malformations. Chicago, Medical Publ. Inc., 3-11, 162-172, 327, 661-677, 1971.

**Address correspondence to:**  
Emmanouil-Nikoloussi, E.-N.,  
Aristotelian University of Thessaloniki (Greece).