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Carpenter syndrome: cone beam computed tomography pictorial review

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Abstract

Objective: To describe dentoalveolar findings in one pediatric patient with a very rare Carpenter syndrome or acrocephalopolysyndactyly type II, and using cone beam computed tomography (CBCT).

Case report: We found a syndromic oligodontia, upper canine transmigration, and an exceptional agenesis of four lateral incisors. We also described the fourth case in the literature of a single solitary lower incisor on the midline, and the first case ever illustrated on CBCT.

Conclusions: We proposed and illustrated the use of the system of progressive numbering of teeth on CBCT axial views to better understand complex dental clinical situations such as syndromic oligodontia.

Keywords: Carpenter syndrome, acrocephalopolysyndactyly type II, CBCT, oligodontia, single solitary lower incisor

Introduction

Carpenter's syndrome or acrocephalopolysyndactyly type II is an entity arising from a pleiotropic disorder with autosomal recessive inheritance [1-8] that was first described in the early 20th century. It is part of a large family of acrocephalosyndactyly including, among others, syndromes of Apert, Crouzon, Jackson-Weiss, Pfeifer and Saethre-Chotzen [1]. It is mainly distinguished from other typical syndromes by the presence of pre-axial polydactyly of the feet [1-8]. More than 70 cases have been already described in the literature but the prevalence of the disorder is known to be one in one million live births [3, 8].

Genetics

Carpenter's syndrome is an autosomal recessive disorder, which implies that both maternal and paternal alleles are affected, and therefore presents at least parental heterozygosity, although some sporadic cases have been described. Most of the cases described therefore concern families with several affected members [1, 4]. The origin of the mutation has been found to be either a mutation in RAB23 on chromosome 6p12.1-q12 [4, 5, 8] or in MEGF8 [3, 8], so there are two types of Carpenter syndrome [3]. Type I Carpenter originates from a mutation in the RAB23 gene, which codes for a Rab-like protein, a GTPase involved in vesicle trafficking, and thus allows the movement of proteins to their predestined intracellular location [3-5, 8]. RAB23 regulates the Hedgehog signalling pathway that is essential for cell growth and specialisation [3-5, 8]. Type II Carpenter, originating from a mutation in the MEGF8 gene, is essential for the production of a protein with a function that is still unknown at present [3]. The majority of articles dealing with the subject, particularly on the genetic level, often mention only the RAB23 mutation, and therefore the type I [4, 5]. This mutation stands out in genomic sequencing, which has identified a range of homozygous mutations in the RAB23 gene, including the more well-known and widespread c.434T>A (p.L145X) [4, 5, 8]. Other genomically detected mutations include the non-exhaustive list of E48fsX7, Y78fsX30, E137X, C85R, M12K, V53fsX13, N121fsX4 and Y79del, some homozygous, some heterozygous associated with a heterozygous mutation of L145X (V53fsX13, C85R) [4, 5, 8]. There is therefore both genotypic and phenotypic variability in the syndrome, sometimes originating from a single SNP.

General symptomatology

Carpenter's syndrome has a wide phenotypic spectrum. Among the most common symptoms we can find craniosynostosis, which differs from other hereditary craniosynostoses [1-8] as it involves the fusion of the medial rather than the coronal sutures [5], and can affect both the sagittal and lambdoid or coronal sutures. This

craniosynostosis results in a secondary acrocephaly which is typical for the disease, in some cases even to a particular appearance called "cloverleaf skull" [3, 5, 8]. This malformation has long been considered responsible [1, 2, 5-7] for the intellectual and learning difficulties associated with it, so much that a craniotomy with remodelling of the cranial vault was recommended between 6 months and one year of age [2, 3, 7] in order to separate the early fused sutures. However, several children maintained their cognitive impairments, while others showed no developmental decline in intellectual ability compared to normal, despite the obvious deformities, suggesting primary brain abnormality in at least some affected patients [1-3]. The face and the cervical area may also be malformed, referred to in the literature as epicanthal folds, flat nasal bridge, malformed ears at the base, and a short neck [1, 2, 4, 6-8].

The other main symptoms of the disease, present in the vast majority of cases, are external genital malformations [1-4, 6-8] such as testicular hypoplasia, malformation of labia majora or internal malformations such as cryptorchidism, which are predominant in males [3, 6, 8]. We can find also postnatal obesity [3, 6, 8] which tends to increase with the age, and which mainly affects the face, proximal limbs, the neck and the trunk [2]. Patients may also present with umbilical hernia [2, 3, 5-7] and cardiac malformations [2-7]. These are multiple and include IVC, AIC, transposition of the great vessels, tetralogy of Fallot, persistent ductus arteriosus, and pulmonary artery stenosis [2-7]. Limb deformities including digital membranous symbrachydactyly and pre-axial polysyndactyly of the feet have also been reported [1, 2, 8].

Other symptoms have been reported with less frequency. Some abnormalities were associated with the musculoskeletal system such as genu valgum possibly associated with lateral displacement of the patella, varus equinus clubfoot, kyphoscoliosis, and coxa valga [1-3, 5, 6]. Other symptoms were more specific, and include auditory disturbances [3] up to bilateral neurosensory loss [2], cerebral atrophy or even anencephaly [1] in some stillborns. Some brain disorders are lethal, others such as hydrocephalus or ventriculomegaly require peritoneal shunt surgery [5,7].

Patient may also present with accessory spleens, opacity and microcornea, optic atrophy [2], large thumbs, clinodactyly of the little finger [2], camptodactyly or duplication of the proximal phalanx of the thumb [2]. Some additional sporadic disorders have been described: pyloric stenosis requiring pyloromyotomy [7], bicornuate uterus [6], duplication of the superior vena cava, acetabular hypodevelopment, coccygeal sacral agenesis, situs inversus [3, 4] or dextrocardia alone [3].

Dentoalveolar symptomatology

The oral manifestations at the bony level present enlarged alveolar ridges with excessive bone formation and their dimension is below the norm [1]. Dental arches are formed normally, sometimes with a strongly hollowed palate [2], but with the width considerably below the norm [1]. At the dental level, molar agenesis is

described [1] but may affect the whole dentition [1], and thus will result in retention of the deciduous dentition [1]. The teeth that are formed will eventually erupt on the arch, but with significant delay in eruption [1] compared to a classic eruption time. This delay in dental eruption may be related with the excess of tissue that generates the broad ridges [1]. This delay in eruption is the main explanation for the difference between the dental age, and the current age of the patient, although it is not the only causal factor [2]. The teeth show marked attrition and erosion [1].
At the level of cranio-maxillofacial area, the main symptom is the presence of the acrocephaly which can result from the fusion of any suture, sometime showing the pathognomonic image of a "cloverleaf skull". The flat nasal bridge, epicanthal malformations, and low implantation of the auricles can be present [1].

Treatment

The treatment is not curative but consists mainly in the surgical rehabilitation of the various malformations that may be associated with the syndrome. The most frequently performed corrections are: the reshaping of the abnormal skull, the removal of extra fingers and the separation of fused toes. Less commonly, various elective surgeries such as pyloromyotomy, genital or ocular surgery are performed. Outside the surgical sector, ophthalmological follow-up may be advisable in the case of orbital disorders, strict dietary follow-up, cardiac follow-up, follow-up with a speech therapist or occupational therapist [3].

Case report

We present the cone beam computed tomography (CBCT) (I-CAT) radiographic images of one Carpenter's syndromic patient. This is a young patient of 8 years and 8 months, whose images were found retrospectively in our University Clinics CBCT database.
The dentition is in full transition. The transition is more advanced in the maxilla than in the mandible, as we observe the persistence of one single deciduous tooth (n°63) (Figure 1) in the maxilla against four deciduous teeth in the mandible (n°74, n°75, n°84, n°85) (Figures 8, 9). We can also observe the agenesis of teeth n°12, n°22, (Figures 1-4, 5A, 6A, 7A), n°25 (Figures 1-4, 6A, 7A, 7C), n°32, n°42 (Figures 8-11), as well as n°31 or n°41 (Figures 8-11). We note the presence of a single mandibular central incisor, centred on the symphysis (Figures 8-11). The patient also had a large nasopalatine canal with nasopalatine cyst (Figure 6C). Tooth n°13 is in transmigration, and it is distal to the tooth n°14 (Figures 3, 4, 5B, 5C).

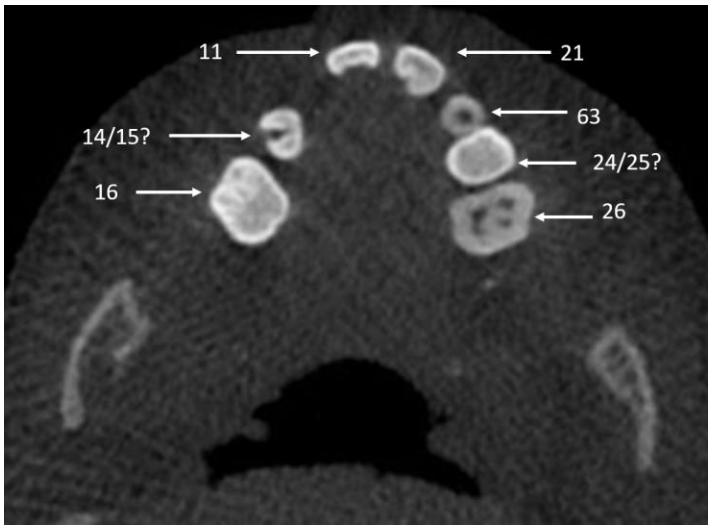

Fig. 1. I-CAT CBCT. Axial view through the incisal edge of the teeth n°11 and 21. Absence of upper lateral incisors right (n°12) and left (n°22), of right upper canine (n°13), and of one upper premolar right (n°14/15?) and left (n°24/25?).

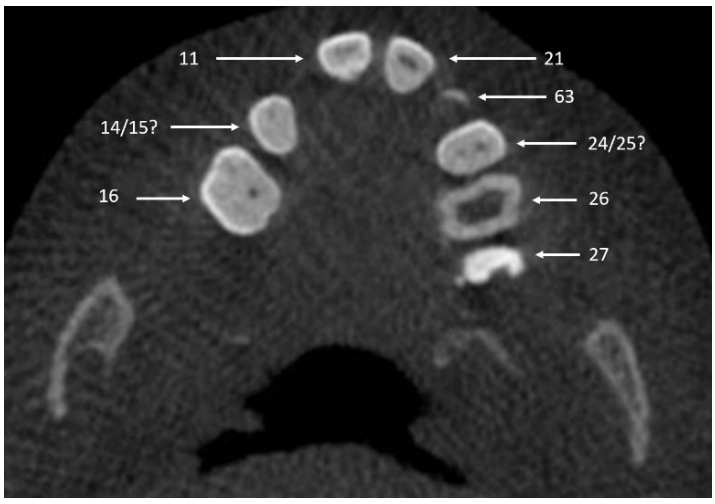

Fig. 2. I-CAT CBCT. Axial view through the crown of the teeth n°11 and 21. Absence of upper lateral incisors right (n°12) and left (n°22), of right upper canine (n°13), and of one upper premolar right (n°14/15?) and left (n°24/25?).

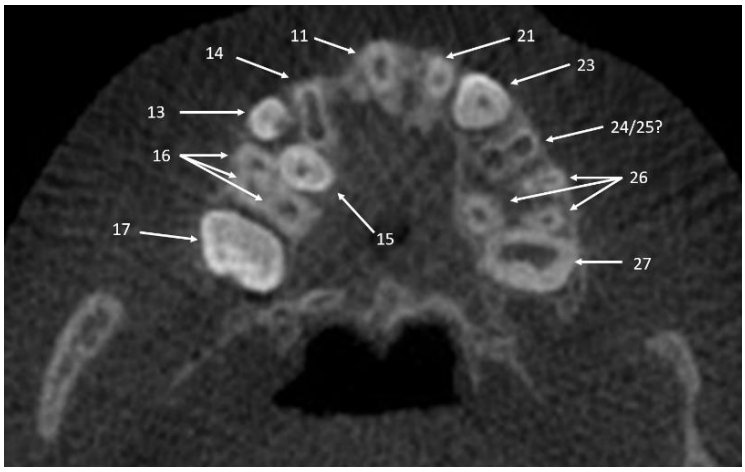

Fig. 3. I-CAT CBCT. Axial view through the roots of the teeth n°11 and 21. Confirmed agenesis of upper lateral incisors right (n°12) and left (n°22). Transmigration of the tooth n°13 vestibular and distal to the tooth n°14. Tooth n°14 in rotation with its distal side toward vestibule. Tooth n°15 positioned on palatine side between the roots of the tooth n°14 and the mesiovestibular root of the tooth n°16. Agenesis of the left upper premolar (n°24 or n°25 missing).

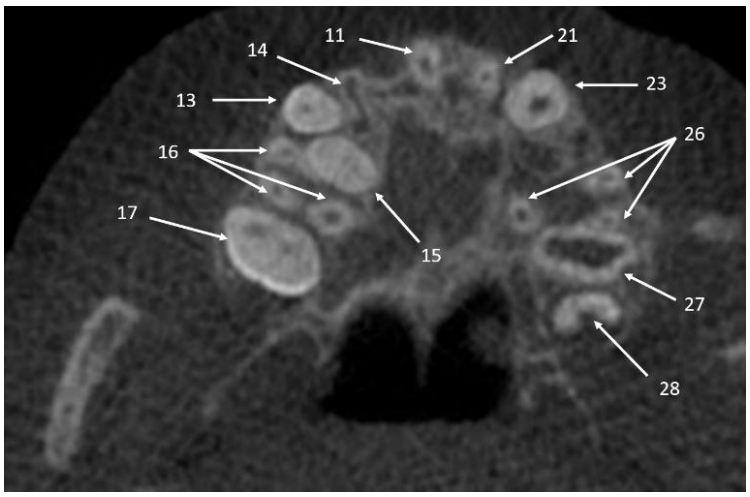

Fig. 4. I-CAT CBCT. Axial view through the apices of the roots of the teeth n°11 and 21. Confirmed agenesis of upper lateral incisors right (n°12) and left (n°22). Transmigration of the tooth n°13 vestibular and distal to the tooth n°14. Tooth n°15 positioned on palatine side between the roots of the tooth n°13, n°14, and the mesiovestibular root of the tooth n°16. Agenesis of the left upper premolar (n°24 or n°25 missing).

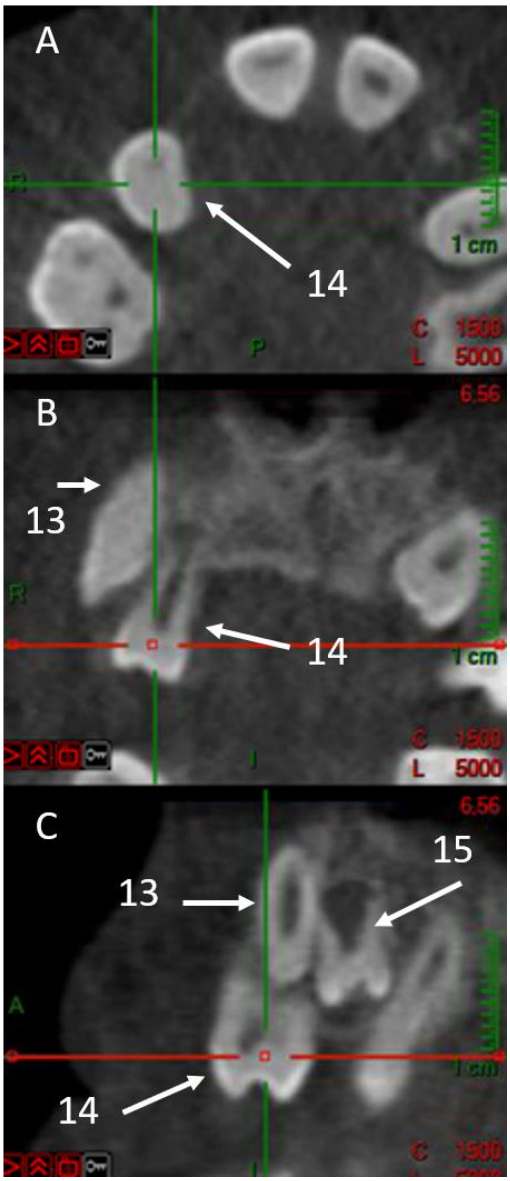

Fig 5. A. Axial view through the crowns of the teeth n°11 and n°21. Crown of the tooth n°14 on the arch. B. Coronal view. Tooth n°13 is impacted and vestibular to the tooth n°14. C. Sagittal view. Tooth n°14 is in rotation. Tooth n°13 is impacted above the roots of the tooth n°14. Tooth n°15 is impacted, and between the roots of the tooth n°13, n°14, and n°16.

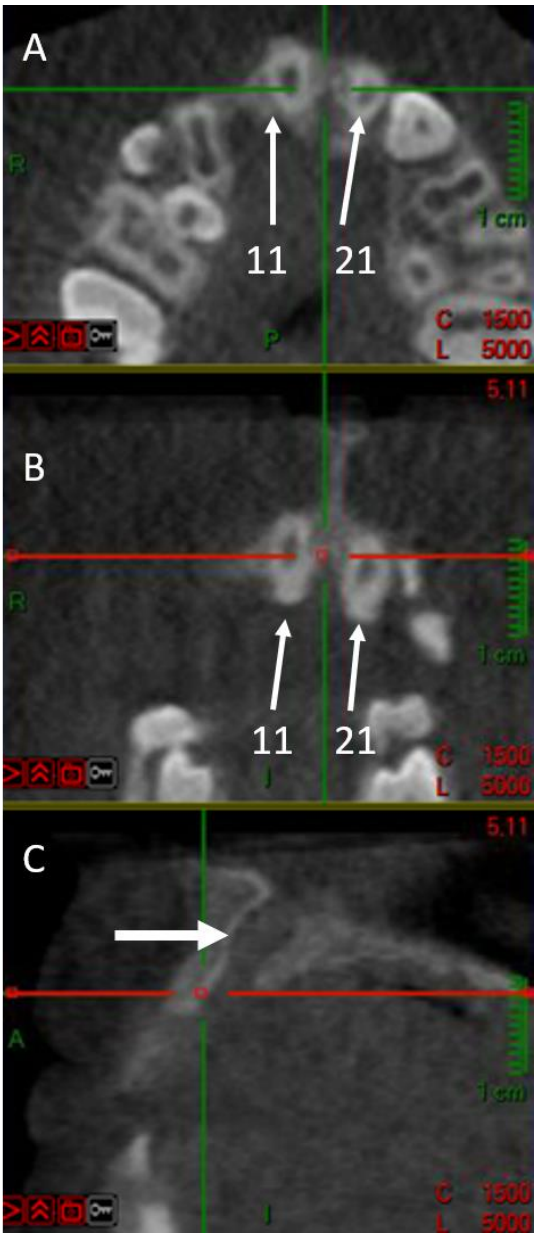

Fig. 6. A. Axial view through the roots of the teeth n°11 and n°21. Agenesis of the teeth n°12 and n°22. B. Coronal view through the roots of the teeth n°11 and n°21. C. Sagittal view. Arrow: nasopalatine cyst and large nasopalatine canal.

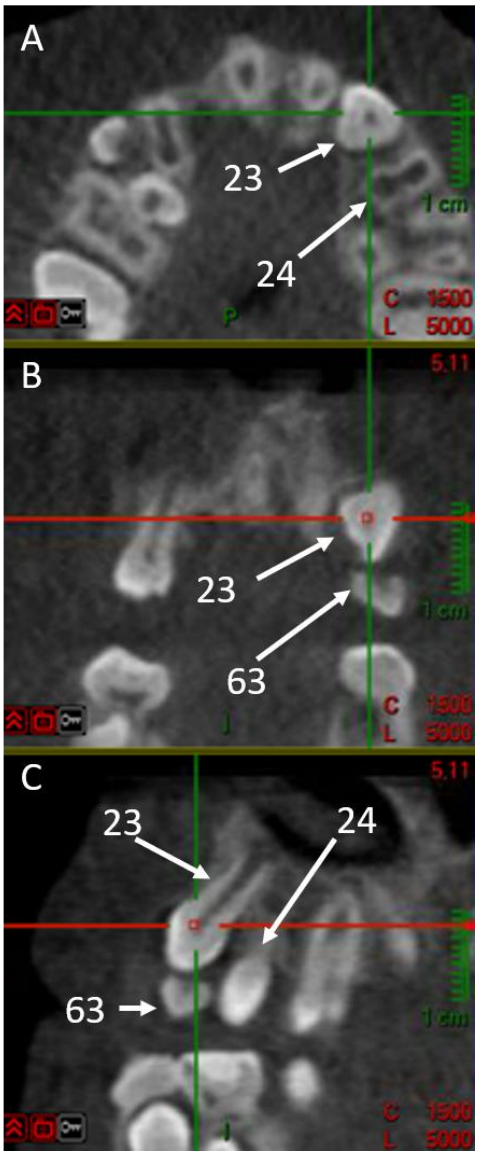

Fig. 7. A. Axial view through the roots of the teeth n°11 and n°21. Confirmation of the agenesis of the teeth n°12 and n°22, and of the tooth n°25. B. Coronal view. Presence of deciduous tooth n°63. Crown of the tooth n°23 in pre-eruptive state with the resorption of the tooth n°63. C. Sagittal view. Confirmation of the agenesis of the tooth n°25. Crown of the tooth n°23 in pre-eruptive state with the resorption of the tooth n°63.

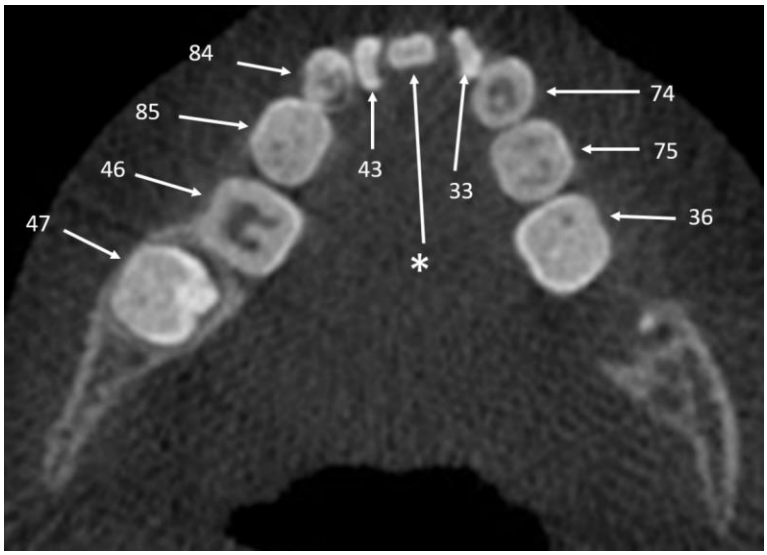

Fig. 8. I-CAT CBCT. Axial view through the lower canines edges. * Solitary central lower incisor. Teeth n°42 and n°32 are absent. Teeth n°33 and n°43 are in rotation and in close relationship with the solitary central lower incisor. Mixed dentition with presence of deciduous and definitive molars.

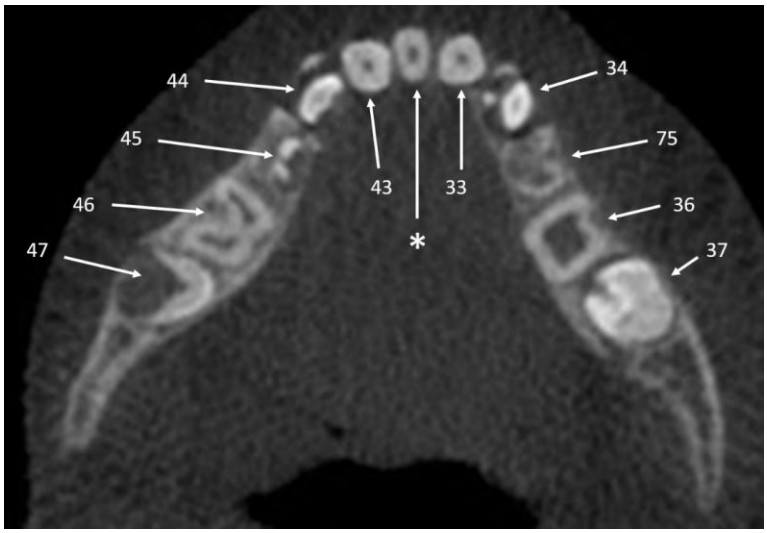

Fig. 9. I-CAT CBCT. Axial view through the crowns of the lower canines. * Solitary central lower incisor. Agenesis of the teeth n°42 and n°32. Teeth n°33 and n°43 are in rotation and in close relationship with the solitary central lower incisor. Mixed dentition with presence of deciduous and definitive molars.

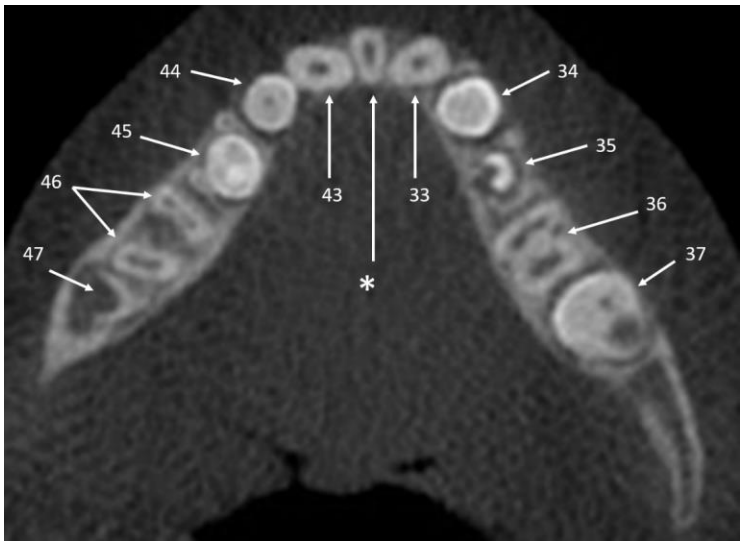

Fig. 10. I-CAT CBCT. Axial view through the roots of the lower canines. * Solitary central lower incisor. Agenesis of the teeth n°42 and n°32. Teeth n°33 and n°43 are in rotation and in close relationship with the solitary central lower incisor.

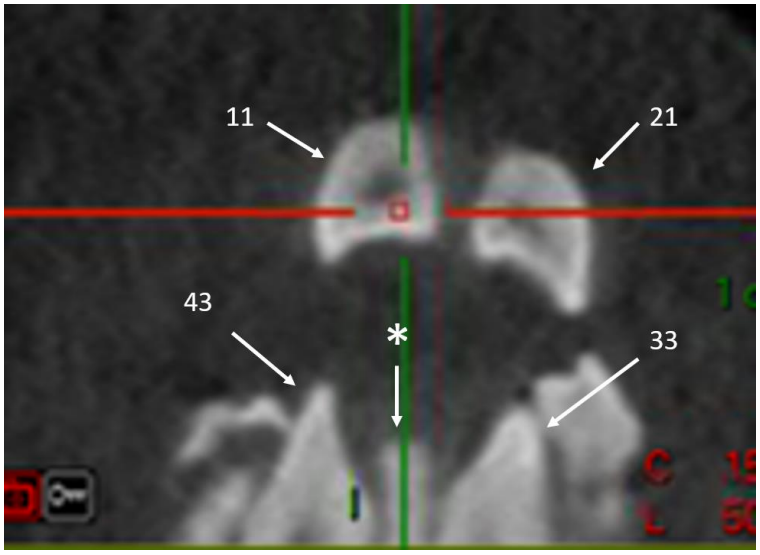

Fig. 11. I-CAT CBCT. Coronal view. * Solitary central lower incisor. Agenesis of the teeth n°42 and n°32. Teeth n°33 and n°43 are in rotation and in close relationship with the solitary central lower incisor.

Discussion

Syndromic oligodontia (six or more missing teeth) which is present here corresponds to the general description of Carpenter syndrome orofacial symptoms [1, 2]. Oligodontia is related to the presence of ectopic eruption and to tooth transposition/trasmigration because of the absence of neighbouring teeth to guide them into correct position or by lack of the place for the correct eruption [9]. In our case the agenesis of the lateral upper incisors, which is a frequent type of hypodontia [9], is related to the transmigration of the tooth n°13 (Figures 3, 4, 5B, 5C), and then to the palatine eruption of the tooth n°15 because of the lack of place for normal eruption for the tooth n°15 (Figures 3, 4, 5C, 6A, 7A). The agenesis of the second upper premolar (n°25) is less frequent in the literature (Figures 7A, 7C) [9].

The prevalence of missing maxillary lateral incisors falls within the range 0.79% to 2.6% [10]. The prevalence rate of missing mandibular incisors is less than 1% [11]. In our case the agenesis of four lateral incisors (Figures 1-4, 5A, 6A, 6B, 7A, 8-11) is an exceptional clinical situation and may be added to the oral findings related with the Carpenter syndrome.

There exist only 3 cases of single solitary lower incisor in the literature: in one patient with velocardiofacial syndrome [12], in three consecutive generations of Japanese family [13.], and in one pediatric patient with cervical dermoid cyst [14]. Here we present the fourth case of single solitary lower incisor, and it is the first case ever illustrated on CBCT (Figures 8-11). This also exceptional clinical finding may be added to the oral findings related with the Carpenter syndrome.

Finally, our case report illustrates the use of the system of progressive numbering of teeth on CBCT to better understand complex dental clinical situations such as oligodontia or hyperdontia. First, we start with numbering of teeth on successive axial view from upper/lower incisors edges to the apices of upper/lower incisor roots (Figures 1-4, 8-10) with the possibility to modify the numbering of a tooth during the procedure (Figures 1-3). Coronal and sagittal CBCT views serve to better understand situations of transmigration/transposition, teeth crowding on the arch, transition between deciduous and definitive dentition, and to affine the final numbering of the teeth (Figures 5, 7, 11).

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- **Informed consent**: the patient was exempted from the informed consent according to the ethical committee approval. All the images were anonymized, and no private data were provided allowing the patient's identification.

Authors contribution:

Author	Contributor role
Delroisse Adrien	Investigation, Methodology, Data curation, Validation, Writing original draft preparation, Writing review and editing
Olszewski Raphael	Conceptualization, Investigation, Methodology, Data curation, Resources, Validation, Writing original draft preparation, Supervision, Writing review and editing

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