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Pros and Cons of Amelogenesis Imperfecta in the GARBA IV Hemi-Mandible, Melka Kunture, Ethiopia

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Abstract: Background: Recently, Le Cabec et al. (2021) contested the identification of Zilberman et al. (2004), of Amelogenesis Imperfecta (AI) Type II/III in the Garba IVE *Homo erectus* child hemi-mandible and attributed the lack of contrast between enamel and dentin in this specimen to a unique form of diagenesis. Objectives: To assess the basis for their conclusions in view of the fact that the Le Cabec et al. (2021) study relates to a genetically and clinically distinct condition - Hypoplastic AI, and does not relate to the Type II/III AI syndrome th.at Zilberman et al. described. Method: The authors analyzed the Le Cabec et al. article and compared their findings with the radiological and clinical findings in Amelogenesis Imperfecta Type II/III. Results: Le Cabec et al. (2021) presented detailed scans and synchotron study that replicate and support the findings of Zilberman et al. (2004); in showing lack of differentiation between enamel and dentin - typical of Amelogenesis Imperfecta Type II/III condition - together with excellent preservation of enamel micromorphology and clearly defined pulp chambers and pulp canals. Moreover, chemical corrosion results in loss of tissue whereas there is no evidence of this in Garba IVE. Conclusion: The authors contend that the findings in Le Cabec et al. (2021) are characteristic features of Type II/III AI as initially diagnosed by Zilberman et al. (2004), and best account for the similarity seen in radio-opacity of enamel and dentin.

Keywords: Fossil Teeth, Mineralization, Enamel Formation, Mutations, Dental Pathology, Diagenesis

1. Introduction

Non-syndromic Amelogenesis Imperfecta (AI) is an inherited defect of dental enamel formation. This condition shows both clinical and genetic heterogeneity in which any or all of the main stages of amelogenesis may be affected, resulting in deficiencies in the integrity and quantity of the matrix and or extent of mineralization.

Witkop [1] identified four main types of AI and subdivided them into 14 variants based on severity of expression and Mendelian inheritance. Type I Hypoplastic AI, is a quantitative defect in which the matrix formed is fully mineralized but is reduced in quantity. The expression of this condition varies in severity, ranging from surface pitting, to complete absence of enamel that may result in reduced dimensions of the teeth. In AI Types II and III, which are qualitative defects, the matrix is of normal thickness but is incompletely mineralized. Type II Hypomineralized AI, is the least severe form of AI and is characterized by soft, usually opaque enamel that wears down rapidly, while its radio-density is similar to that of dentin. In Type III Hypocalcified AI, the enamel is orange-yellow at eruption and sensitive to touch and temperature change. It is rapidly lost once the tooth erupts leaving only dentin. while on radiographs the enamel may appear to be even less dense than dentin. In Type IV Hypocalcification-Hypomineralization AI, all stages of odontogenesis are affected, so that these teeth are also taurodont and the enamel formed is both deficient in quality as well as degree of mineralization.

Mutations in at least seven genes, each with numerous variants, have now been identified as responsible for AI.

Together with variation in the pattern of inheritance i.e. autosomal recessive, dominant or X-linked, it may be expressed in phenotypic variation even between siblings [2-8]. For example, Katsura [9] cites at least four genes with mutations (KLK4, MMP20, C4orf26, and Wdr72) as specifically associated with Hypomineralization AI.

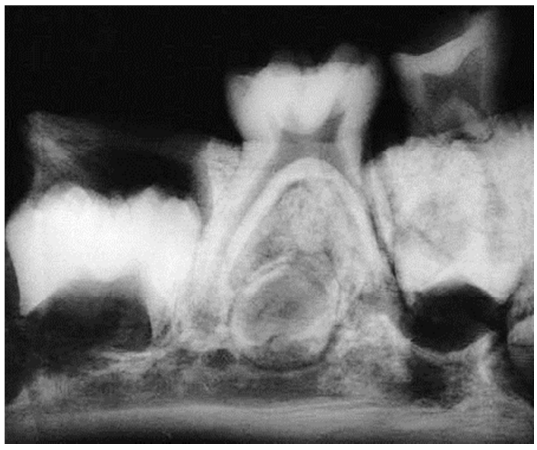
2. Methods

2.1. The Specimen

Garba IVE (MK 81 Garba IVE 0043; henceforth GAR IVE) is the fragmented right hemi-mandible of a 2.5-3.5 year old child, attributed to *Homo erectus*, and dated to ~1.7 Ma [10-12]. Both right deciduous molars are fully erupted. The first deciduous molar is severely worn with the occlusal surface sloping steeply from the mesial to distal cusps, where more than half the crown height has been lost in the distal area. Such severity of wear is highly unusual in a child of this young age, taking into account that this molar erupted only 12-16 months before death. The second deciduous molar just reached occlusion and the tips of the cusps are already worn [10, 11, 13].

2.2. Analyses

Radiographs of the hemi-mandible showed little if any differentiation between the density of the enamel, dentine and bone (Figure 1) (see figure 2a from Zilberman et al.). Scanning electron microscopy (SEM) analyses of epoxy replicas of the teeth showed no evidence of hypoplasia on the smooth surfaces of the first deciduous molar or second deciduous molar, typical findings in Type II/III Hypocalcified or Hypomineralized AI [2], and was accordingly identified by Zilberman et al. as an early case of Type II/III AI [13]. The difference between these two types reflect the stage/or stages of amelogenesis involved as the mineralized content increases from ~30% to 60% and finally to 95%, differences that are expressed in the rate of wear, but are sometimes difficult to distinguish clinically since these phenotypes often overlap in degree of severity [4, 5].



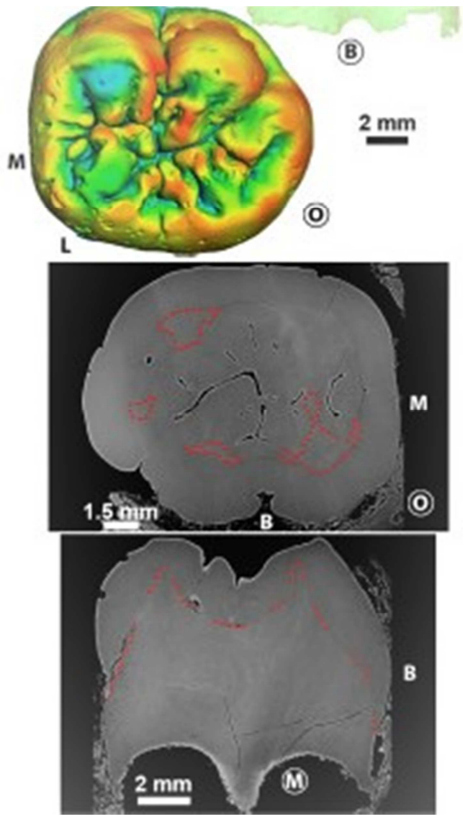
Note the loss of contrast between enamel and dentin In Garba IVE teeth.

Figure 1. *Figure 2a from Zilberman et al. 2004.*

3. Discussion

Two other publications have described the GAR IVE fragment since Zilberman et al. [13] examined and published it, and both have accepted our initial diagnosis [10, 14], and only the recent study by Le Cabec et al. [15] has disputed this. A careful reading of their text suggests that they did not relate to our diagnosis of a Type II or III Hypocalcified/Hypomaturation AI, but rather incorrectly attributed to us a diagnosis of a Type I or IV Hypoplastic AI which is a completely different condition.

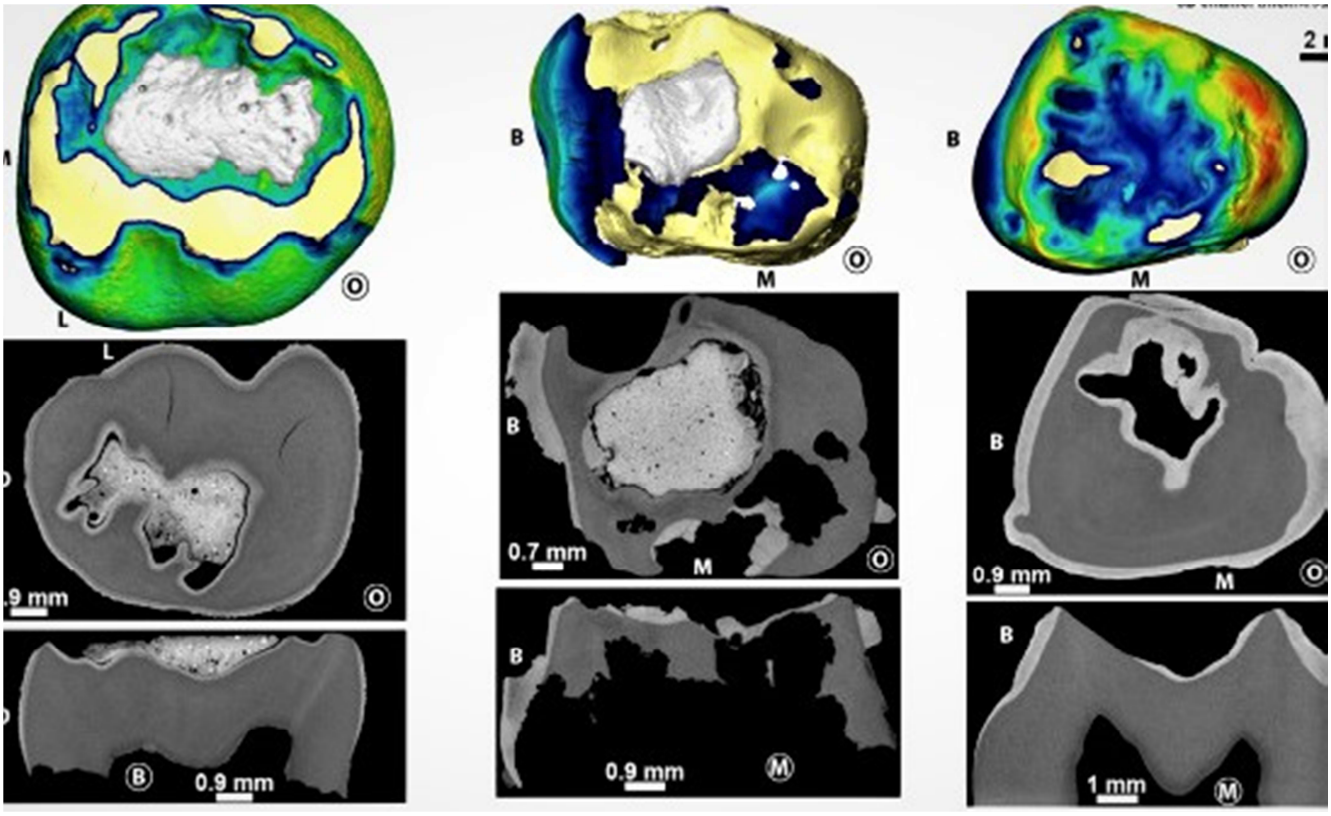
Thus, Le Cabec et al. [15] (pg. 23088) write: "Amelogenesis imperfecta encompasses a group of developmental conditions altering the enamel structure and making teeth fragile. The main diagnostic criteria may involve a marked reduction in enamel thickness frequently concerning both deciduous and permanent teeth, enamel pits or linear hypoplasia not associated with any noticeable developmental defects in the other dental tissues, a brown coloration of the enamel, or taurodontism." This sentence highlights that their study was directed to test for evidence of Hypoplastic AI in the GAR IVE specimen i.e. defects typical of Type I or Type IV of Witkop's classification. They did not investigate or look for features characteristic of Type II or III AI, the condition diagnosed by Zilberman et al. [13], a condition characterized by Hypomineralized /Hypocalcified AI without taurodontism and expressed in varying degrees of severity [8, 16].



Note loss of contrast between enamel and dentin.

Figure 2. *Figure 5a from Le Cabec et al 2021.*

The study carried out by Le Cabec et al. on GAR IVE focused on the ultrastructure of the developing permanent unerupted first molar crown. Le Cabec et al. [15] describe this specimen, shown in figure 5a of their article, (Figure 2) as showing "a loss of contrast between bone, enamel and dentine, and the enamel- dentine junction being barely visible in some places", page 23089 and figure 4d in their article, (Figure 3). These features are indeed characteristic of teeth from individuals with a clinically confirmed diagnosis of hypocalcified/hypomineralized AI [7, 8, 13], but this fact is ignored by them. Instead, they write (pg. 23095): "By definition, AI should affect enamel formation in all the teeth of both generations which is clearly not the case in GAR IVE". But this is exactly what was observed in GAR IVE- both deciduous molars and permanent first molar are affected. "Severe attrition does not belong to the suite of manifestations defining the hypoplastic forms of AI, but rather in the hypocalcified and hypomaturation AI. In the latter forms, enamel may prematurely chip away even before tooth emergence which is not the case in GAR IVE (pg 23095)". We agree entirely regarding the difference in susceptibility to attrition between the hypoplastic and hypomineralized forms but reiterate that this is not pertinent to the debate since we never claimed that we diagnosed hypoplastic enamel in this tooth (AI Type I) or the extremely severe form of hypomineralization identifed as Type IV AI. Rather, as they state, severe attrition does occur in Hypocalcified/Hypomatured AI, which is the condition we attributed to the GAR IVE specimen.

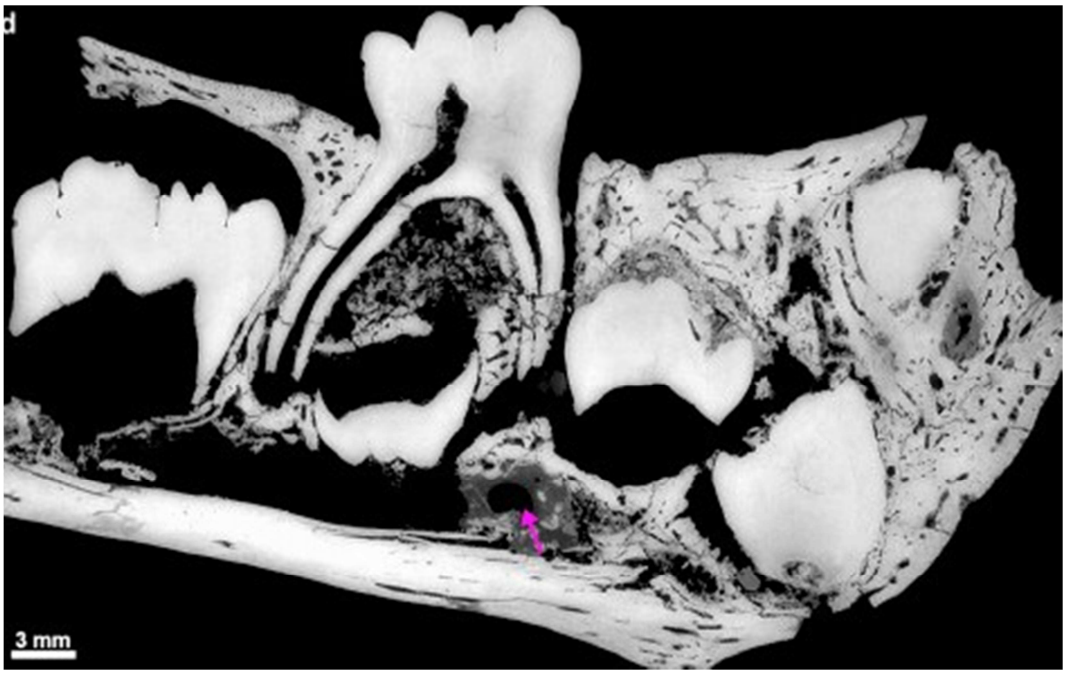


Note the clear contrast between enamel and dentin in modern teeth with hypoplastic AI type I.

Figure 3. *Figure 5b-d from Le cabec et al 2021.*

Le Cabec et al. (Figure 4) (see page 23091, figure 4d, and supplementary data) reported that enamel thickness of the first permanent molar of GAR IVE was thicker than that of three modern teeth with AI. However, their modern controls were a third permanent molar from a female with Hypoplastic AI (diagnosed both clinically and genetically) and two deciduous molars with non-specified AI (Figure 3) (see figure 5b-d, pg. 23091 and supplementary data), but which also appear to be affected by Hypoplastic AI based on the data they present. In all three control teeth, the enamel thickness is reduced but there is clear differentiation between enamel and dentin as typical of the Hypoplastic form of AI, while in GAR IVE (Figure 1) (see figure 5a, pg 23091) the enamel is thick but the radio-opacity of enamel and dentin is similar. Thus, the fact that le Cabot et al. [15] find no reduction in enamel thickness in the Garba molar does not detract from our diagnosis, while their finding of similarity in enamel and dentine radiopacity reinforces ours diagnosis based on radiographs and clinical cases. Moreover, in both studies, the erupted and unerupted teeth showed similar radiolucency of enamel and dentin in deciduous and permanent first molars. However, since le Cabot et al. did not relate correctly to our diagnosis, they attributed the lack of contrast between enamel and dentine as due to to a unique form of diagenesis resulting from taphonomic processes. To the best of our knowledge, a diagenetic signature such as this

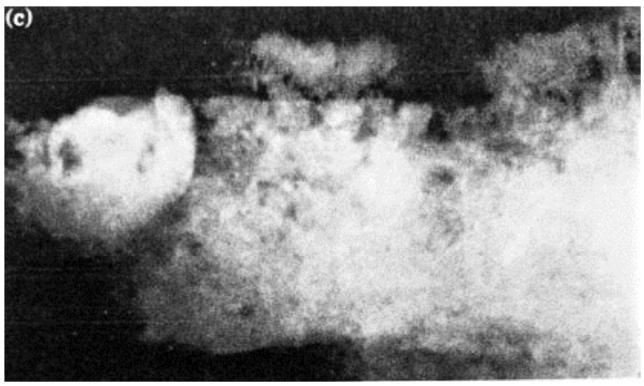
– that selectively affects enamel without affecting it micromorphorphology but leaves the bone and dentine unscathed- has not been documented elsewhere. They write (pg. 23094): "Garba IV is located in a volcanic area which was active during the Early and Middle Pleistocene. In this volcanic environment, chemical corrosion due to water acidity is better accounted for as a general cause of tissue alteration".



Note loss of contrast between enamel and dentin.

Figure 4. *Figure 4d from Le Cabec et al. 2021.*

Certainly, the mineral component of enamel, like that of dentin and bone undergoes changes in elemental composition during fossilization, with the nature and rate of changes dependent on the mineral content and pH of the surrounding sediments [17, 18], but tooth enamel is considered the most stable of all mineralized tissues and the least affected either by microorganisms or by mineral exchange during fossilization [17-20]. Their explanation that chemical corrosion of the enamel, followed by remineralization was the cause of loss of radio-opacity in the enamel is a hypothesis and unsupported by any evidence, but rather is at odds with their own findings. In fact, hypermineralization results in loss of contrast between dental components and bone, as observed in the Sterkfontein specimen SK55b (Figure 5) (see figure 2c from Zilberman et al.), where even spaces left by decay of soft tissue of the dental pulp, dental tubulae and bone trabeculi are completely mineralized. Chemical corrosion results in loss of surface integrity, seen firstly as intensive surface pitting varying in size and depth, and finally in dissolution (e.g., see ref 21, figures. 445-7; 943-5) [21]. This, in contrasts with Le Cabot et al.'s comment relating to the excellent preservation of surface morphology of the enamel in the Garba IVE specimen. Moreover, they note that the pattern of insect damage seen in the bones and dentin of this specimen is similar to that seen elsewhere in fossils from African Plio-Pleistocene contexts and so suggestive of a similar depositional environment of fossil teeth that display excellent contrast between enamel and dentine [22].



Note the effect of fossilization on SK 55b.

Figure 5. *Figure 2c from Zilberman et al. 2004.*

Finally, Le Cabec et al. [15] concluded by stating that "Following Zilberman et al.'s diagnostic, GAR IVE would most likely have been affected by the AI variant called "hypoplastic, pitted autosomal dominant type IA as defined by Witcop Jr (see page 23095)". This statement is incorrect and does not apply either to our study or to their own findings. Our paper was based on the clinical and radiologic evidence for a completely different type of AI in Garba IVE, and substantiated by comparison with a modern case of Hypomaturation/Hypocalcified AI now known to result from mutations in numerous genes. with different modes of inheritance and variable phenotypic expression [6, 8].

4. Conclusion

We propose that the conclusions reached by Le Cabec et al. were based on a misunderstanding. They appear to have confused our diagnosis of Types II /II Hypocalcified/Hypomineralized AI with Type I or Type IV AI, as shown by their reference to hypoplasia, taurodontism and pulp inclusions. This is a completely different condition than described by us. Moreover, their attempt to explain the lack of definition between enamel and dentine in terms of more intensive diagenesis in the mineral content of enamel versus that of dentine and bone, is not supported by their results on the synchotron study nor by their concluding remarks regarding the excellent preservation of micromorphology in the teeth. It is also unsupported by current understanding of the processes involved in fossilization. Most importantly, despite their conclusions, their results do not contradict ours but rather provide additional evidence to support our diagnosis of hypomineralized/hypocalcified AI in GAR IVE.

Author Contribution

UZ and PS wrote the main manuscript text. Both authors reviewed the manuscript.

Competing Interests

The authors declare no competing interests.

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