Craniofacial characteristics and genotypes of amelogenesis imperfecta patients

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SUMMARY The aims of the study were to identify craniofacial characteristics in patients with the rough hypoplastic amelogenesis imperfecta (AI) phenotype and to evaluate whether craniofacial variables are related to a mutation in either of the two genes associated with AI, enamelin (*ENAM*) and amelogenin (*AMGX*).

Eight children (five males and three females) with rough hypoplastic AI phenotype, aged 6.5–15 years, from three families and their parents (three males and three females) were examined clinically, radiographically, and genetically. Seventeen variables were measured on lateral cephalometric radiographs in AI affected (n = 11) and AI unaffected (n = 3) members. Craniofacial measurements were statistically analysed using a Student's *t*-test. In all 14 individuals, mutation analysis of the *ENAM* and *AMGX* genes was performed by direct sequencing of the coding region.

All Al affected patients had hypoplastic enamel with a rough surface and malocclusions. In the vertical plane, all Al children presented an anterior and/or posterior open bite (OB). Craniofacial analysis confirmed increased vertical relationships, with increased vertical jaw relationships and higher values for gonial angle. In two Al affected families, A and B, the same heterozygous *ENAM* g.8344delG mutation was confirmed, while in the third family, neither *ENAM* nor *AMGX* mutation was found.

All patients with rough hypoplastic Al had a moderate to severe malocclusion with increased vertical dimensions regardless of the presence or absence of the *ENAM* g.8344delG mutation. As an OB requires appropriate timing of therapy, it is important to diagnose these patients as early as possible.

Introduction

Amelogenesis imperfecta (AI) is an inherited disorder with alterations in the quality and/or quantity of the dental enamel, with widely varying phenotypes and genotypes. Although the AI enamel phenotypes can be broadly divided into hypoplastic, hypocalcified, and hypomaturated, there are many subtypes of these main entities. Three main types based on the predicted defective developmental mechanism are, in hypoplastic AI, a secretion of the extracellular matrix, in hypocalcified AI crystallite nucleation and growth, and in hypomaturated AI protein processing and crystallite growth. The classification, most in use, based predominantly on clinical manifestations and the mode of inheritance (autosomal dominant, autosomal recessive, or X-linked) distinguishes between 14 subtypes of AI (Witkop, 1988).

By definition, AI deformities are limited to conditions, which selectively disrupt the amelogenesis process (Witkop, 1988). On the other hand, there are reports that AI enamel alteration can be accompanied by craniofacial characteristics, such as malocclusions [e.g. anterior open bite (AOB)] (Ravassipour *et al.*, 2005; Poulsen *et al.*, 2008), taurodontism (Gjørup *et al.*, 2009), in combination with a syndrome (e.g.

tricho-dento-osseous syndrome; Price *et al.*, 1999; Pavlič *et al.*, 2007a), or systemic diseases (e.g. kidney disease; Pindborg, 1982).

Malocclusion, especially a dental or skeletal open bite (SOB), is frequently observed in AI patients. A SOB malocclusion is variably expressed in AI affected individuals, depending on the AI type and kindred (Cartwright et al., 1999; Ravassipour et al., 2005). An AOB as well as a deep anterior overbite have been reported in AI subjects (Poulsen et al., 2008). An AOB was found in 40 per cent of individuals with AI (Persson and Sundell, 1982), in 26 per cent of subjects with AI but in none of their unaffected relatives (Cartwright et al., 1999), in 42 per cent of AI individuals and 12 per cent of unaffected family members (Ravassipour et al., 2005), and in 24 per cent of AI individuals with a further 20 per cent of AI individuals diagnosed with vertical dysgnathia, defined as a maxillary to mandibular plane angle greater than 34 degrees (Rowley et al., 1982). On the other hand, the prevalence of Class III and Class II division 1 malocclusions is similar in subjects with congenital tooth anomalies as in the general population (Basdra et al., 2001).

The aetiology of a malocclusion in AI patients is unclear. An open bite (OB) may result from an abnormal tongue position caused by tooth sensitivity, a deep anterior overbite due to collapse of the posterior occlusal segments, or both malocclusions may be the features of AI itself (Seow, 1993). AI individuals display statistically significant differences in cephalometric parameters, especially those of families with the X-linked mode of inheritance and with autosomal inherited generalized thin hypoplastic AI (Bäckman and Adolfsson, 1994). On the basis of these findings, it seems that the frequent association of malocclusion in AI, especially an AOB, is caused by a genetically determined anomaly of craniofacial development rather than by local factors influencing alveolar growth.

The aim of this study was to identify craniofacial characteristics of AI affected and unaffected patients of three families with rough hypoplastic AI. Additionally, the *ENAM* and *AMGX* gene were sequenced in order to find possible genetic correlations with the craniofacial characteristics.

Subjects and methods

Study design and sample

Written consent from all participants was obtained prior to inclusion. The study was approved by the Slovenian Committee for Medical Ethics.

Patients diagnosed with rough hypoplastic AI were selected from all children referred from 1995 to 2008 to the University Dental Clinic. The patients were diagnosed by one author (AP). The following clinical information was recorded: age, gender, quality and quantity of enamel, family history, and any known syndromes or systemic diseases. For all assessments lateral cephalogram was also available.

Eight children (five males and three females) with rough hypoplastic AI phenotype, aged 6.5 to 15 years, from three families (Figure 1) and their parents (three males and three females) were examined clinically, radiographically, and genetically. None of the patients had metabolic or endocrine defects, generalized systemic diseases, syndromes, or fluorosis. On the basis of clinical and



Figure 1 (A) Pedigree of three generations of family A segregate with autosomal dominant amelogenesis imperfecta (AI; Pavlič *et al.*, 2007b). The filled symbols denote AI affected individuals. An asterisk indicates individual examined clinically and genetically. (B) The pedigree of family B identified AI affected individuals of two generations. The history data of the third generation (indicated with a question mark) were indecisive and clinical examination was not possible. In AI affected members from families A and B, the same heterozygous *ENAM* g.8344delG mutation was associated with AI. (C) AI affected members of family C designated as II-8, III-13, and III- 14 are indicated by filled symbols. Family members indicated with an asterisk were clinically and genetically examined, yet no mutation in *ENAM* or *AMGX* gene was found. History data on the pedigree of family C were uncertain and clinical or genetic examination of other family members was not possible (P < 0.05).

radiographic examination [dental pantomogram (DPT) and lateral cephalogram], malocclusions and craniofacial characteristics were evaluated.

Radiographic assessment

The lateral cephalograms were taken for all patients in the same conventional cephalostat (Orthophos CD; Siemens Sirona, Bensheim, Germany) with the subjects in the standing position, the teeth in maximum intercuspation, and the Frankfort horizontal plane parallel to the floor. The distance from the focus to the median plane of the patient's head was 150 cm, and the median plane-film distance was 10 cm.

Tracing and computing technique

The cephalograms were scanned (ScanMaler i900; Microtek, Hsinchu, Taiwan) at 300 dots per inch and digitized. The landmarks were traced by one person (MM) using the cephalometric analysis software (Quick Ceph Systems, Inc., San Diego, California, USA). The magnification of 10 per cent was taken into account in the linear measurements. Cephalometric analysis consisted of 17 variables (Table 1; Figure 2).

Error of the method

The measurements were carried out twice, by the same person (MM) with the second measurement repeated after a 1 month interval. Error analysis was performed using a paired *t*-test. There was no statistically significant difference between the two cephalometric analyses (P > 0.05). Data were analysed

Variable	Definition		
Dental			
Inclination of the upper incisor to the palatal plane	UIE-UIA/ANS-PNS (°)		
Distance from the upper incisive edge to	UIE ⊥ N–A (mm)		
N–A line			
Inclination of the lower incisor to the mandibular plane	LIE-LIA/Go-Gn (°)		
Distance from the lower incisive edge to N–B line	LIE \perp N–B (mm)		
Intericisal angle	UIE-UIA/LIE-LIA (°)		
Vertical skeletal relationships			
Vertical jaw relationship	ANS-PNS/Go-Gn (°)		
Mandibular inclination	S–N/Go–Gn (°)		
Maxillary inclination	S-N/ANS-PNS (°)		
Gonial angle	Me–Go–Ar (°)		
Björk's polygon	N-S-Ar-Go-Me (°)		
Sagittal skeletal relationships			
Sagittal position of the maxilla	S–N–A (°)		
Sagittal position of the mandible	S–N–B (°)		
Sagittal relationship of the jaws	A–N–B (°)		
Cranial base angle	N–S–Ba (°)		
Mandibular position	S–N–Pg (°)		
Wits appraisal	A'–B' (mm)		
Articulare angle	Go–Ar–-S (°)		

using the Statistical Package for Social Sciences (version 15; SPSS Inc., Chicago, Illinois, USA).

Statistical analysis

The cephalometric variables were tested with a Student's *t*-test for equality of means between the following groups: AI affected children, AI affected parents, and AI unaffected parents. P values < 0.05 were considered statistically significant. Because of the small sample size, normality and equality of variances of the observed variables were carefully examined. All measurements were within acceptable ranges. A non-parametric Mann–Whitney test was also performed with similar results (except for gonial angle in both cases).

ENAM and AMGX mutation analysis

Genomic DNA was isolated from 10 ml of peripheral blood using the salting out procedure. The coding region and flanking intronic sequences of the *ENAM* and *AMGX* genes were amplified using 12 pairs of primers for *ENAM* (Hart *et al.*, 2003a) and 6 pairs of primers for *AMGX* (Kim *et al.*, 2004) with Ampli *Taq* GoldTM polymerase (Applied



Figure 2 Cephalometric landmarks registered on the lateral cephalogram of a 7-year-old amelogenesis imperfecta affected boy of family B. In Figure 1B, he is designated as III-4. A, perpendicular projection of point A on the occlusal plane (A'), anterior nasal spine (ANS), articulare (Ar), point B (B), perpendicular projection of point B on the occlusal plane (B'), basion (Ba), gnathion (Gn), gonion (Go), lower incisor apex (LIA), lower incisor edge (LIE), menton (Me), nasion (N), posterior nasal spine (PNS), pogonion (Pg), sella (S), upper incisor apex (UIA), upper incisor edge (UIE).

Biosystems, Norwalk, Connecticut, USA). Briefly, the amplification consisted of 35 cycles of denaturation at 94°C for 30 seconds, annealing at 56°C (AMGX 1, AMGX 2, and AMGX 7), 57°C (AMGX 3, AMGX 4/5, and AMGX 6) 58°C (ENAM 1–3, ENAM 4–5, ENAM 6, ENAM 7, and ENAM 10a), or 60°C (ENAM 1, ENAM 8, ENAM 9, ENAM 10b, ENAM 10c, ENAM 10d, and ENAM 10e) for 30 seconds, extension at 72°C for 40 seconds, followed by final extension at 72°C for 7 minutes. Amplicons were purified with the Qiagen extraction kit (Qiagen GmbH, Hilden, Germany) and directly sequenced using the Big Dye Terminator Sequencing Kit and ABI Prism[®] 310 Genetic

Analyser (Applied Biosystems, Piscataway, New Jersey, USA). The results were compared with normal sequences of the *ENAM* and *AMGX* genes (http://www3.ncbi.nlm.nih. gov, Accession number: AY167999 and AC002366).

Results

Subject characteristics

The phenotype of all AI affected patients from three unrelated families was generalized as rough hypoplastic AI (Figure 3A, 3C, 3E, and 3G). The thickness of the enamel



Figure 3 (A) A 9-year-old female from family A with rough hypoplastic enamel and an anterior open bite (AOB) with an overjet of 3.4 mm. A heterozygous *ENAM* g.8344delG mutation was confirmed. (B) No enamel was visible on the dental pantomogram (DPT) taken at 10 years of age; the enamel of both maxillary central and all mandible incisors was restored. (C) Her 6-year-old sister, with the same mutation confirmed, showed similar enamel aberration with an overjet of 4.5 mm. Regarding the patient's chronological age, the eruption of anterior teeth and a false AOB must be taken into consideration. (D) No enamel was visible on the DPT of the same child at 6.5 years of age; the enamel of the first right permanent maxillary incisor was restored with composite. (E) A 13-year-old girl from family B, with rough hypoplastic enamel and the same heterozygous *ENAM* g.8344delG mutation, had an Angle Class III malocclusion, a bilateral posterior open bite and negative overjet incisor relationship. (F) No enamel was visible on the DPT. (G) A 10-year-old boy from family C had thin enamel with rough was evident on the DPT, either on the primary or permanent teeth or on developing tooth buds.

was significantly reduced, the teeth were a yellowish colour, and the enamel surface was rough. DPT examination showed no enamel visible on the primary or permanent teeth (Figure 3B, 3D, 3F, and 3H). All permanent teeth were present, either erupted or as tooth buds.

All patients exhibited a malocclusion. In the vertical plane, an AOB was observed and the overjet was increased in family A, a POB and negative overjet were present in family B, and an AOB and POB in family C (Table 2). In the sagittal plane, Angle Classes I or II (families A and C) and Angle Class III (family B) were present.

Craniofacial characteristics

The main differences in cephalometric variables between the AI affected and unaffected subjects were in the vertical plane. The mean values and standard deviations in the group of AI affected children, AI affected parents, and AI unaffected parents in vertical jaw relationship, maxillary inclination, and gonial angle are shown in Figure 4A, 4B and 4C, respectively. Statistically significant differences were found when the vertical jaw relationship, maxillary inclination, and gonial angle of AI affected children versus unaffected parents (P = 0.047, P = 0.005, and P = 0.017, respectively) and all AI affected versus AI unaffected parents (P = 0.033, P = 0.011, and P = 0.008, respectively) were tested. No differences were found when comparing AI affected children versus AI affected parents (P = 0.559, respectively).

ENAM and AMGX mutation analysis

Sequencing of the *ENAM* gene revealed heterozygous mutation g.8344delG in all four siblings and their father in family A (Pavlič *et al.*, 2007b) and the same heterozygous *ENAM* mutation in both siblings and their mother in family B. No mutation, either *ENAM* or *AMGX*, was identified in any member of family C.

Discussion

The University Dental Clinic is a tertiary referral centre for the whole of Slovenia (roughly 2 030 000 inhabitants). All referred and included patients in this study had the rough hypoplastic AI phenotype combined with increased vertical dimensions.

An OB is uncommon in the general population. Its prevalence varies between ethnic groups, approximately 2 per cent in British teenagers (Rowley et al., 1982), 16 per cent in Afro-American children (Rowley et al., 1982), and 3-7 per cent in the general population in the USA (Ravassipour et al., 2005). The prevalence of AI is even lower: 0.014 per cent in the USA (Witkop, 1957), 0.08 per cent in Israel (Chosack et al., 1979), 0.04 per cent in Sweden (Sundell and Valentin, 1986), and 0.72 per cent in the Swedish area of Vaskerbotten (Bäckman and Holmgren, 1988). As the prevalence of an OB and AI is low, the probability of these two conditions occurring by chance in the same patient is very small. Moreover, clinical studies show that the prevalence of an OB in AI affected individuals is much higher than in the general population (Persson and Sundell, 1982: Cartwright et al., 1999: Ravassipour et al., 2005).

Skeletal morphology is variably expressed in AI affected individuals and depends on the AI type and mode of inheritance (Cartwright *et al.*, 1999). AI patients with an autosomal dominant mode of inheritance have significantly different cephalometric parameters indicative for an OB (Bäckman and Adolfsson, 1994), while in individuals affected with localized hypoplastic AI subtypes, an OB is never present (Ravassipour *et al.*, 2005).

No data are reported in the literature on the prevalence of rough hypoplastic AI. Generalized hypoplastic AI is associated with multiple allelic mutations in *ENAM* or *AMGX* (Wright, 2006). In AI individuals, with mutations confirmed in either *ENAM* or *AMGX*, an OB occurs more

Table 2 Data of rough hypoplastic amelogenesis imperfecta (AI) affected children. AOB, anterior open bite; POB, posterior open bite.

Patient		Orthodontic assessment			Results of ENAM mutational analysisc		
Initials	Years	Family	AOB	РОВ	Overjet ^a	Angle Class ^b	
RS	15	A	+		+	L: II: R: II	Heterozygous g.8344delG
KS	13	А	+		+	L: I; R: II	Heterozygous g.8344delG
MS	9	А	+		+	L: I; R: II	Heterozygous g.8344delG
ES	6.5	А	+d		+	L: II; R: II	Heterozygous g.8344delG
TP	13	В		+	*	L: III; R: III	Heterozygous g.8344delG
AP	7	В			*	L: III: R: III	Heterozygous g.8344delG
HS	9	С	+	+	+	L: II: R: I	
BS	5	С	$+^d$			L: I; R: I	—

^aPositive overjet incisor relationship (increased incisor relationship) is marked with a plus sign and negative overjet (mandibular protrusion) an asterisk. ^bAccording to occlusion between the first permanent molars, L, left; R, right

^oReference sequencing for GenBank accession number AY167999, the A of the initiation for ATG is taken as +1.

^dRegarding chronological age, the eruption of the anterior teeth and a false AOB must be taken into consideration.



Al-unaffected

Figure 4 Mean values and standard deviations of the groups of amelogenesis imperfecta (AI) affected children, AI affected parents, and AI unaffected parents of: (A) vertical jaw relationships, (B) maxillary inclinations, and (C) gonial angles. In each of three variables, statistically significant differences are found when compared with AI affected children versus unaffected parents and AI affected versus unaffected parents (P < 0.05).

often (Ravassipour et al., 2005). An OB is frequently reported with ENAM g.8344delG mutation (Kida et al., 2002; Hart et al., 2003a; Kim et al., 2005; Pavlič et al., 2007b). An OB is also common with ENAM mutations g.4806A>C (Kim et al., 2005) and g.13185-13186insAG (Hart et al., 2003b; Pavlič et al., 2007b). Interestingly, in patients with homozygous ENAM g.13185-13186insAG mutation, generalized hypoplastic AI and a Class II malocclusion with an OB are present, while in those with heterozygous ENAM g.13185-13186insAG, only localized hypoplastic AI, with (Pavlič et al., 2007b) or without (Hart et al., 2003b) an OB is found. These observations suggest that the aetiology of malocclusions in AI individuals may be due to genetic rather than local factors. The gene(s) mutation(s) associated with AI enamel phenotype(s) may also be an important aetiologic factor in malocclusions.

Genotype-phenotype correlation was not possible due to the low prevalence of the disease and consequently the number of patients included in the study. AI patients from two unrelated families A and B had the same ENAM g.8344delG mutation with similar clinical presentation of rough hypoplastic AI and increased vertical dimensions. Loss of vertical dimensions in the AI affected father from family A is in accordance with the description of clinical problems in autosomal dominant rough hypoplastic AI (Wright, 2006). His dental status and occlusion, with only a few molars and premolars in situ, was most likely due to poor hard dental tissue preservation. All AI affected individuals from family C, with no mutation in either ENAM or AMGX coding region, had the same clinical phenotype of rough hypoplastic AI and increased vertical dimensions. It is possible that this may be due to an unidentified gene controlling ENAM or AMGX gene expression. On the other hand, it seems likely that more genes influence vertical craniofacial growth. Further genetic analysis of this family is warranted.

Conclusions

An increase in vertical dimensions was confirmed in patients with rough hypoplastic AI regardless of the presence or absence of the ENAM g.8344delG mutation. Early clinical recognition of increased vertical dimension in patients with rough hypoplastic AI is paramount for correct timing of orthodontic intervention.

Funding

National Agency for research grants (J3-9663, P3-0343, and P3-0374).

Acknowledgements

The authors would like to thank Dr M. Milačić for his kind advice in setting up the study and performing the cephalometric analysis. We would also like to thank Dr I. Verdenik for performing the statistical analysis and the genetic laboratory team of University Children's Hospital of Ljubljana and Dr M. Debeljak, Dr T. Hojnik, and Mrs J. Ferran for their valuable comments and expert technical assistance.

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