

Osteogenesis Imperfecta type III: A report on the unusual phenotypic features of six individuals of Cape mixed ancestry heritage.



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ABSTRACT

Osteogenesis imperfecta type III (OMIM 259420) is a severe autosomal recessive disorder in which frequent fractures and progressive limb and spinal deformity result in profound physical disability. The condition is heterogeneous and dentinogenesis imperfecta (DI) is an important syndromic component of some types of OI III. Other maxillofacial and dental manifestations also have significant implications in terms of management.

The prevalence of Osteogenesis imperfecta type III (OI III) as a category of the inherited connective tissue disorders in South Africa is of paramount importance. Although autosomal recessive (AR) OI is rare worldwide, it has emerged that the frequency of OI III is relatively high amongst the indigenous Black African population of South Africa. A review of the literature revealed a paucity of information regarding the dental and craniofacial manifestations of the disorder in this ethnic group. For these reasons, the central theme of this report is the identification, documentation and analysis of these features in five individuals with OI III in SA.

In an overall study, a total of 64 Black African affected persons were assessed. In a nested study five persons of Cape Mixed Ancestry (CMA) and three Indian individuals were investigated.¹

The five CMA patients had the phenotypic features of classical OI III, specifically severe fracturing, stunted stature, white sclerae and moderate to severe DI. Their general health was reasonably good and longevity was a major factor. One person, the prototypic OI III patient described in SA, was 61 years of age. Each of these individuals had massive mandibular prognathism with dental and skeletal Class III malocclusions.

ACRONYMS

AR: Autosomal Recessive

CMA: Cape Mixed Ancestry

DI: Dentinogenesis imperfecta

OI I: Osteogenesis imperfecta type I

OI III: Osteogenesis imperfecta type III

KEY WORDS

Craniofacial, Dental, Osteogenesis imperfecta

In South Africa, a developing country, the allocation of resources in terms of specialized dental facilities is limited. Socio-economic barriers also exist, restricting patient access to dental care.

The previously neglected dental and craniofacial abnormalities documented in this study emphasizes the importance of a raised level of awareness in terms of dental management and the possible challenges that may be encountered.

INTRODUCTION

Osteogenesis imperfecta (OI) is a heritable bone fragility disorder characterized by decreased bone quality and quantity and variable bone deformity.

Osteogenesis imperfecta type III (OI III) (OMIM 259420) is a severe autosomal recessive (AR) disorder in which frequent fractures, and progressive limb and spinal deformity result in profound physical disability. The condition is clinically and genetically heterogeneous, and maxillofacial and dental manifestations have significant implications in terms of management.

The historical evolution of knowledge concerning Osteogenesis Imperfecta (OI) has been chronicled in successive editions of Victor McKusick's magisterial book 'Heritable Disorders of Connective Tissue'.¹ In the mid nineteenth century, Lobstein documented the adult form of OI while Vrolik described the lethal infantile type. At the beginning of the 20th century, Looser of Heidelberg introduced the terms 'OI tarda' and 'OI congenita'.¹ These designations have remained in use in clinical medicine.

With the onset of clinical genetics in the 1960's, the autosomal dominant (AD) mode of inheritance of OI-tarda was well

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Table 1: Clinical Findings of Cape Mixed Ancestry persons

Affected Individual	Date of Birth	Age When Seen (Years)	Affected Relatives	Gender	No. of Fractures	Height (cm)	Mobility
CPT2	20/04/1952	63	5	F	>50	96	Chairbound
CPT3	02/05/1993	21	0	F	>50	93	Chairbound
CPT4	30/05/1986	28	0	F	>50	95	Walks with an aid
CPT5	30/05/1986	28	0	F	>50	95	Walks with an aid
CPT6	20/12/2001	13	0	F	>20	80	Chairbound

established. In OI-congenita, the consistent normality of the parents and the occasional recurrence in siblings was suggestive of autosomal recessive (AR) inheritance.² By the late 1980's, however, discoveries in collagen biochemistry and later in molecular biology conclusively indicated that OI-congenita resulted from new dominant mutations.^{3,4,5}

The prevalence of Osteogenesis imperfecta type III (OI III) as a category of the inherited connective tissue disorders in South Africa is of paramount importance. Although the autosomal recessive (AR) OI is rare worldwide, it has emerged that the frequency of OI III is relatively high in the indigenous Black African population of South Africa.⁶

In South Africa and Zimbabwe OI III was found to be fairly common in the indigenous Black African population.⁶ The affected individuals originated from the Sotho, Pedi, Swazi, Zulu and Tswana linguistic groups among others and a ratio of OI I to OI III at 1 to 6 was estimated in this population group.³ It was suggested that the reason for this high prevalence is that the unaffected heterozygote may have a biological advantage in the African environment and that the mutation for OI III in Africa occurred more than 2000 years ago in West or Central Africa prior to migration to present day Southern Africa.⁷

Two doctoral studies which emanated from a collaboration between UWC Faculty of Dentistry and UCT Department of Human Genetics were carried out in the field of thin bone disorders, in particular Osteogenesis Imperfecta.

The aim of one PhD project undertaken in the late 1990's was to determine whether Dentinogenesis imperfecta (DI) is a diagnostic discriminant for OI and to ascertain the prevalence and severity of DI in various families with OI type I (OI I).^{3,8} In order to fulfil this objective, more than 400 patients with OI I were assessed.

In 2016, in another PhD, 72 individuals with a confirmed diagnosis of OI III were assessed. The focus of the study was to investigate and document the oro-dental features in affected Black African persons in SA. Five individuals of Cape Mixed Ancestry (CMA) heritage presented with the phenotypic characteristics of OI III. Three Indian persons with an unusual form of autosomal recessive OI were also investigated. A total of 72 individuals with the OI III phenotype were assessed.

The number of affected individuals that were included in these studies made up the largest series in the world.

The CMA group of affected individuals were phenotypically defined as having OI III with short stature and multiple fractures. They differed from the majority of the Black African persons with OI III by virtue of their longevity and presence of DI. Their molecular status also differed as they were negative for the determinant mutation in FKBP10 described in exon 5 which is frequently identified in Black African persons.⁹ For these reasons, the phenotypic, craniofacial and dental manifestations of this unique group of individuals are presented and discussed in this report.

AGE, GENERAL PHYSICAL CONDITION, DENTINOGENESIS IMPERFECTA AND MOLECULAR FINDINGS

Individuals are represented by alphabetical-numerical designations pertaining to the investigation centre and the chronological order in which they were assessed.

The affected persons examined at the University of the Western Cape (UWC) dental school were members of the Cape Mixed Ancestry population group and were designated CPT2, CPT3, CPT4, CPT5 and CPT6 (Figure 1 – Figure 10). Their clinical data are presented in Table 1.



Figure 1: CPT 2. Aged 22 years in calipers **Figure 2:** CPT 2. Aged 62 years. She is chairbound

Each person had limited oral opening and all their teeth were discoloured consistent with moderate to severe DI. Their sclerae were white in every instance and there was no hearing loss. None of the individuals had received bisphosphonate therapy.

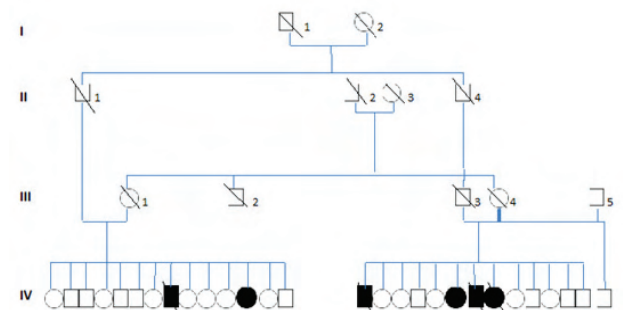


Figure 3: The Pedigree of the Kindred (Horan and Beighton, 1975). CPT 2 was the proband

Comment

It is of interest that all five affected persons were female. CPT 4 and CPT 5 were twins. The disorder occurred sporadically in the other affected individuals except in the family of CPT 2. The phenotypic features and radiographic manifestations of each patient are described in the brief case reports which follow.

CASE REPORTS

CPT 2

Forty-two years ago, affected individuals in five interrelated families were reported.^{15,20} These persons were the prototypic OI III affected persons described in South Africa. CPT 2, then 22 years of age and now aged 60 years (Figure 1 and Figure 2), was a member of one of these families. In one family, two of 14 siblings had OI while in the other, four of thirteen individuals were affected with OI. The original pedigree of the kindred is shown in Figure 3.

These families shared the common CMA genetic heritage but there was specific information that they also had Black African, Scottish and Indian heritage. The fathers of the affected siblings were an uncle (II-1) and nephew (III-3) who married sisters (III-1 and III-4). Despite the reported absence of consanguinity, it can be assumed from pedigree data that the parents shared a considerable percentage of their genes. The parents and their progenitors were unaffected.

The Proband, CPT 2, had sustained several fractures by the age of two years and in early childhood had been institutionalized at a home for disabled children in Cape Town until 14 years of age. In 1975, at the age of 22 years, she was documented as being 105cm in height with severe scoliosis and pronounced bowing of the femora and humeri. At that time, she walked with the aid of long leg callipers and crutches (Figure 1) and she had minimal bluing of the sclerae.



Figure 4: CPT 2. An Intraoral picture. Her teeth are yellow and moderately translucent.



Figure 5: CPT 3 is chairbound and 90 cm in height. Mandibular prognathism is apparent and DI is evident in all her secondary teeth. Deposits of interdental calculus are obvious.

In 2014, person CPT 2 was re-examined by one of the authors and her clinical manifestations were documented. She was chairbound; 96 cm in height (Figure 2), her teeth were discoloured and showed mild features of DI (Figure 4). She gave a dental history of severely discoloured primary teeth and considers that her secondary teeth are less severely discoloured.

A cone beam CT was requested by a maxillofacial surgeon after CPT 2 was referred for an evaluation of pain in the region of her right TMJ which was exacerbated when chewing. She also experienced intermittent tingling and numbness in her right arm. Frequent sinus infections and nasal obstruction were also troublesome. Her hearing and mental faculties were normal.

CPT 3

CPT 3 was the only affected person in her family. Her non-consanguineous parents and a male sibling were normal. In 2014, at 21 years of age, she was 90cm in height, and was chairbound with severe scoliosis and pronounced bowing of her femora and tibia (Figure 5). She had slight difficulty hearing but her sclerae were normal.

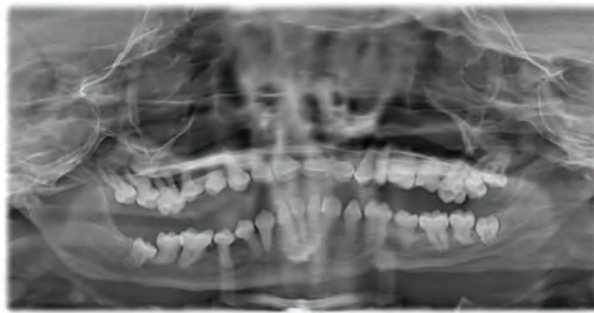


Figure 6: Panorex of CPT 3. The apparent image distortion is evidence of craniofacial abnormality and consequence difficulty with patient positioning. All teeth show features of severe DI. The lamina dura is absent and there is severe generalized osteoporosis of her craniofacial bones.

She gave a history of severe DI in her primary dentition and this was also evident in her secondary dentition (Figure 5). Deposits of interdental calculus were present and during oral prophylaxis, moderate gingival bleeding was observed.

As a young woman, she was understandably concerned about the appearance of her teeth and was referred to the Department of Restorative Dentistry at UWC. A previously obtained panorex radiograph was made available to the authors (Figure 6) and a CBCT was requested by the attending prosthodontist.



Figure 7: CPT 4 and CPT 5 are twin sisters, aged at 28 years. Marked kyphoscoliosis and prominent mandibular prognathism is evident.

The presence of DI in all of her teeth was confirmed on a panorex radiograph (Figure 6). Optimal radiographic images of any kind were impossible to obtain due to the difficulty of positioning her due to the short stature and chairbound situation.

CPT 4 and CPT 5

CPT 4 and CPT 5 are twin sisters (Figure 7) and are the only affected persons in their family. Their parents were unaffected and non-consanguineous. There was no history of the disorder in any of their parents' progenitors. The sisters were 93cm in height and both had marked kyphoscoliosis.

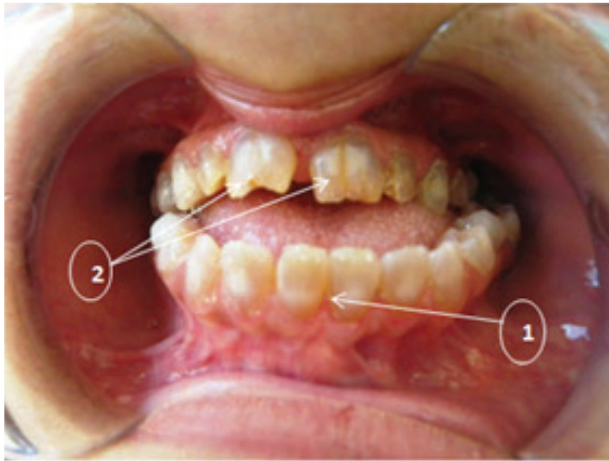


Figure 8: CPT 4. An intraoral picture. Clinical features of DI are evident in all her teeth. Minimal deposits of interdental calculus are observed (1) and enamel fractures (2) are present on teeth 11 and 21.

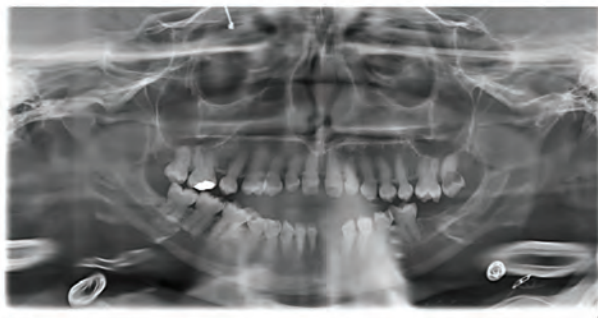


Figure 9: Panorex of CPT 5. The apparent image distortion is evidence of craniofacial abnormality and consequence difficulty with patient positioning. All her teeth show radiological features of DI. The lamina dura is absent.

They gave a history of severely discoloured primary teeth which fractured easily. At 28 years of age, they had prominent mandibular prognathism, an anterior open bite, severe DI and interdental calculus (Figure 8).

A panorex radiograph obtained in 2011 of CPT 5 showed features of severe DI (Figure 9).



Figure 10: CPT 6 Chairbound at the age of 13 years. Mandibular prognathism is evident. All her permanent teeth are affected with DI. Multiple cervical carious lesions (1) and interdental calculus (2) are present.

A CBCT image of both individuals was requested by a specialist prosthodontist and orthodontist, but as with the previous patients, optimal images were impossible to obtain due to difficulty with positioning.

CPT 6

At 13 years of age, CPT 6 is chairbound (Figure 10). She is the only affected person in her family. Her non-consanguineous parents are normal and there is no history of the OI in any progenitors. She has a younger unaffected female sibling. Her parents stated that she had a dental history of severe discolouration of her primary teeth with marked attrition and early loss. Her secondary teeth

were all moderately discoloured, translucent and multiple carious lesions were observed. Mandibular prognathism was also present.

Due to non-cooperation from CPT 6, it was impossible to obtain dental radiographs.

DISCUSSION

The four adult affected individuals of CMA heritage, namely CPT 2, CPT 3, CPT 4 and CPT 5 ranged in age from 21 years to 63 years and had severe physical deformities. They achieved an average height of 95cm and each of them had experienced 50 or more fractures. Although none of these individuals had received bisphosphonate therapy, longevity was a major feature. CPT 6 at age 13 years had already experienced 20 fractures and was chairbound.

A dental history of severely discoloured primary teeth with attrition and early exfoliation was reported by each of these persons. The colour of the crowns of their secondary teeth varied from yellow to brown and they were opalescent. There was chipping, fracture and focal loss of the enamel. Radiographic images confirmed the presence of bulbous crowns and almost complete obliteration of the pulp chambers. The roots of the teeth were thin and short.

Extensive dental intervention, management and appropriate referral was necessary due to the longevity of the individuals, the severity of the disorder and the extent of their DI.

These observations suggest that the underlying gene defect has the same or a similar effect on bone and dentine. In this cohort of affected persons, a positive correlation between the severity of the disorder and the presence and severity of DI was apparent. Several authors have documented the association between OI III and the expression of severe DI.^{4,10,11} These findings are, however, contrary to those observed in the Black African persons with the homozygous and compound heterozygous FKBP¹⁰ molecular genetic status and Indian persons with the unknown molecular status.

Permission to reproduce the photographs was granted.

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