Acta Scientific Dental Sciences (ISSN: 2581-4893)

Volume 6 Issue 7 July 2022

Research Article

The Effect of Congenital Cytomegalovirus on Tooth Development and Mineralization

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DOI: 10.31080/ASDS.2022.06.1401

Received: May 17, 2022

Published: June 09, 2022

Abstract

Objectives: To analyze dental development and mineralization of teeth from girls affected by congenital CMV.

Materials and Methods: Deciduous and permanent dentitions of three girls with congenital CMV infection were analyzed. X-rays and plaster impressions were taken during routine dental treatment. MD dimensions of the deciduous and permanent teeth were performed using a digital caliper and compared to teeth size of normal girls. On deciduous teeth of one girl, the relative content of elements in enamel and dentin were analyzed and compared to normal girls.

Results: The MD dimensions of the deciduous teeth and the early developing permanent teeth showed true microdontia (smaller than mean-2SD). The relative concentration of elements in both enamel and dentin showed hypomineralization and increased organic ions concentration.

Conclusions: Congenital CMV affect the development and mineralization of deciduous and permanent teeth. The teeth showed true microdontia and hypomineralization.

Clinical Relevance: True microdontia as observed in deciduous and early erupting permanent teeth in girls affected by congenital CMV, is due to smaller tooth germ. Clinical and orthodontic evaluation and treatment are necessary in order to obtain a normal occlusion. The hypomineralization may pose a higher carious risk for the children affected by congenital CMV.

Keywords: Cytomegalovirus (CMV); Microdontia; Hypomineralization; Tooth Germ

Abreviations

CMV: Cytomegalovirus; CNS: Central Nervous System; MD: Mesio-Distal; CEJ: Cemento-Enamel Junction; SEM: Scanning Electron Microscopy; EDS: Energy Dispersive X-ray Spectrometer; SD: Standard Deviation

Introduction

Cytomegalovirus (CMV) is the most frequent cause of congenital viral infections in humans, and the most common cause of major birth defects [1].

About 2% of live born infants are congenitally infected with CMV. About 10% of this group has symptoms after birth, and most of the infants will exhibit subsequent abnormalities of the Central Nervous System (CNS): microchephaly, mental retardation, deafness and blindness [1-4].

About 40% of children with CMV has induced birth defects and 5% of CMV infected asymptomatic infants also exibit enamel hypoplasia and enamel hypocalcification of their teeth. In many cases, the enamel might be absent and affected teeth tend to wear down rapidly or to fracture [5]. Although, these distinc defects of amelogenesis are mostly reported in deciduous dentition, enamel defects may also be expected in the permanent dentiton, since active CMV infection persist in many infants for 6-18 months postnatal [6]. Based on tests of specific Human CMV immunoglobulin G, and Immunoglobulin M antibodies, it was suggested that CMV may be a potent aetiologic factor in development of cleft lip or palate [7].

Studies on mice who were infected with CMV found that mouse CMV induced changes in signaling pathways. It delayed, but did not completely interrupt, tooth morphogenesis. These changes are similar with the Amelogenesis Imperfecta phenotype seen in some CMV infected children [6,8].

Enamel formation is a complex and highly regulated process. Deciduous human teeth begin calcification at 14-18 weeks in utero and complete enamel formation by first year of life [9]. Enamel hypoplasia may be defined as an incomplete or defective formation of the organic enamel matrix of teeth and it is quantitative enamel defect, having reduced thickness of enamel [10].

The presence of enamel defects is highly dependent on conditions occurring during critical time of enamel formation and mineralization. Dental enamel defects have been associated with a broad spectrum of etiologies including genetic and epigenetic factors such as systemic, local and environmental factors. Systemic conditions such as perinatal or prenatal illnesses, low birth weight, regular antibiotic consumptions, malnutrition, celiac disease and respiratory disorders like asthma are associated with enamel defects.

The aim of this research is to present data on tooth size, development and mineralization from three girls with congenital CMV infection.

Materials and Methods

Patients examined

- ML, a 5-year-old girl was referred from a community dental clinic to the pediatric dental clinic at Barzilai Medical University Center, Ashkelon, for dental examination. She was referred on the grounds that the teeth had a strange color, and multiple carries lesions. Past medical history revealed congenital CMV and preterm birth at 25 weeks. At birth she suffered from respiratory distress syndrome, bronchopulmonary dysplasia, necrotizing enterocolitis stage 3, intraventricular hemorrhage bilateral grade 3, and sepsis. She underwent partial resection of small intestine/distal jejunostomy and closure of stoma of small intestine. CNS involvement included- porencephalic cyst fronto-parietal, retinopathy and hearing impairment and developmental delays. She is under daily treatment with Depalept and Valporal. The extra oral examination showed bilateral cochlear implants. The intraoral examination showed a spaced deciduous dentition with missing lower left incisor, open bite, and microdontia. The teeth showed a yellowish discoloration with extensive carious lesions on the upper incisors and lower molars. The dental treatment was performed under general anesthesia, due to extensive dental treatment needs and lack of cooperation. Clinical figures (Figure 1), upper anterior and bite-wings X-rays (Figure 2), and plaster impressions (Figure 3) were taken for measurements of MD dimensions of the teeth.
- YA, an 11-year-old girl was referred to our clinic due to dental esthetic problems. Past medical history revealed congenital CMV infection with normal development. The clinical intra oral examination revealed mixed dentition with very small teeth and carious free dentition. A panoramic X-ray (Figure 6) was performed, and during routine dental treatment 6 deciduous teeth were extracted (Figure 7,8). The panoramic X-ray showed short roots of permanent incisors, restricted MD dimensions at the CEJ (Cemento-Enamel Junction) of lower

and upper second deciduous morals and first permanent molars and single root maxillary first permanent molars.

- MA, a 17-year-old girl was referred to our clinic due to lack of cooperation on dental examination and multiple carious lesions. Past medical history revealed congenital CMV infection in utero, deafness, deaf mutism, pervasive developmental disorder and implant placement of cochlear prosthetic device. The intra-oral examination revealed permanent dentition with extensive carious lesions. During dental treatment, under general anesthesia, bitewings (Figure 4) and plaster impressions (Figure 5) were taken.

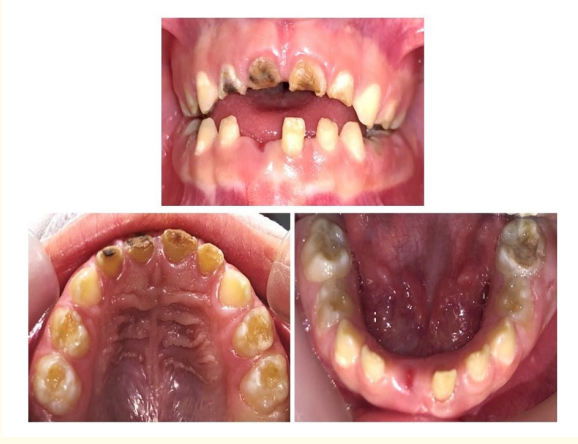

Figure 1: Clinical views of ML. Note the yellowish color of the deciduous teeth.

Figure 3: Plaster impressions of ML dentition.

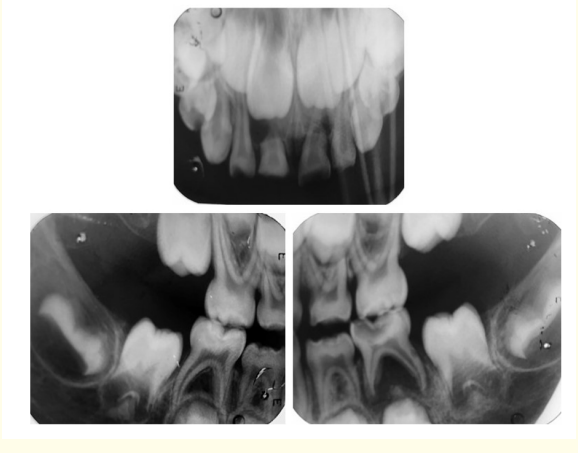

Figure 2: X-rays of ML. Note the reduced MD dimensions of the first permanent molars.

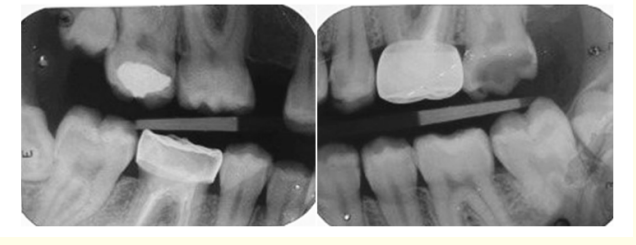

Figure 4: X-rays of MA. Note the mesial inclination of the right lower third molar.

Figure 5: Plaster impressions of MA dentition.

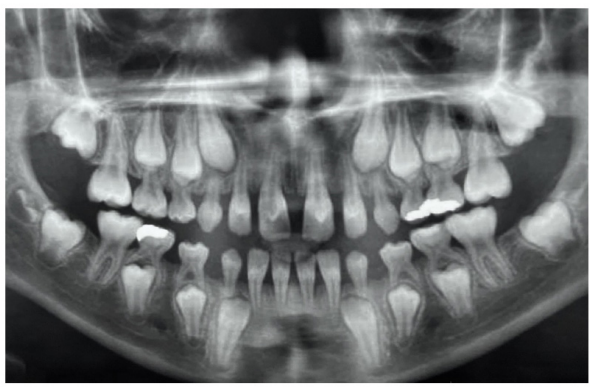

Figure 6: Panoramic X-ray of YE. Note the restricted MD dimension at the CEJ of second deciduous molars and first permanent molars and the single root of upper first permanent molars.

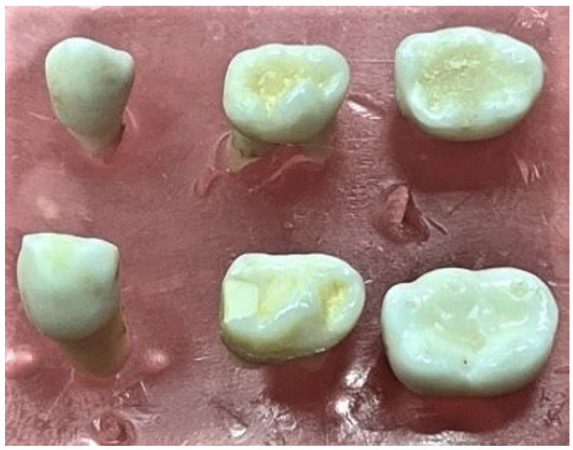

Figure 7: Lower deciduous teeth of YE (upper row) in comparison to normal girls.

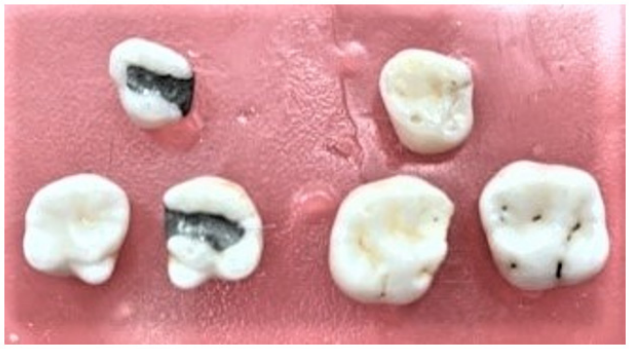

Figure 8: Upper deciduous teeth of YE (left) in comparison to normal girls.

Measurements of teeth

On the plaster models of ML and MA, mesio-distal dimensions of the teeth were performed using an electronic digital caliper (Max-Cal from NSK) to the nearest 0.01mm. The measurements of first permanent molars of ML were taken from the bite-wings x-rays, after comparing the measurements on the plaster impressions with the measurements of the same teeth on bite-wings X-rays. The mesio-distal measurements for YA teeth were taken on

the extracted deciduous teeth and compared to the dimensions on the panoramic X-ray. The measurements taken from the plaster models and the bite-wings X-rays showed similarity up to ±0.1mm. The dimensions of the other deciduous and permanent teeth of YA were taken from the panoramic x-ray. The results were compared to mean measurements of teeth of normal girls [11,12].

Tooth components measurements

On ML bite wings and YE panoramic X-rays, maximal enamel thickness on the mesial aspect was taken using the digital caliper and compared to normal girls.

Ion components

Extracted deciduous teeth of YA (lower deciduous canine first and second molars and upper first molar and 2 second molars) and match-paired deciduous teeth of normal girls, were invested in epoxy resin (Epofix Resin) and sliced along a bucco-lingual plane using Isomed 1000. On the canine the slice was performed through the cusp tip, parallel to the long axis of the tooth, and on the molars through the mesial cusps, parallel to the long axis of the tooth. The sections were observed using a scanning electron microscope (SEM- FEI, Quanta 200, Eugene, OR) under high vacuum mode, without coating. Using energy dispersive X-ray spectrometer (EDS) ion analyses were carried out for prenatal enamel (close to the cusp tip), postnatal enamel (close to the CEJ) and for dentine. The location of the ion analyses was identical in YA teeth and normal teeth. The relative ion concentration of calcium, phosphate, oxygen, carbon and nitrogen were determined from a rectangle with a minimum of 8000 counts.

Results

Table 1 shows the normal MD diameter of deciduous teeth of girls, compared to our CMV affected girls (ML and YE). The MD diameter of the deciduous teeth showed true microdontia (smaller than mean minus 2SD) [10,13] except for lower deciduous canines of ML and upper first deciduous molars of YE that were smaller than mean minus 1SD but larger than mean minus 2SD.

Tooth	**Maxilla**	**i^1**	**i^2**	**c^1**	**m^1**	**m^2**
	Mean ± SD	6.48 ± 0.43	5.29 ± 0.43	6.48 ± 0.38	6.77 ± 0.44	8.59 ± 0.45
YE	Mean			5.33*	6.10*	7.29*
ML	Mean	5.35*	4.07*	5.17*	5.55*	6.56*
Tooth	**Mandible**		**i_2**	**c_1**	**m_1**	**m_2**
	Mean ± SD		4.68 ± 0.40	5.70 ± 0.40	7.37 ± 0.52	9.50 ± 0.40
YE	Mean			4.39*	6.42**	
ML	Mean		3.58*	4.58*	5.68*	7.8*

Table 1: Mesio-distal dimensions (mm) of deciduous teeth of CMV affected girls in comparison to unaffected girls.

Note: SD: Standard Deviation; i: Deciduous Incisor; c: Deciduous Canine; m: Deciduous Molar; MD: Mesio-Distal

*= < Mean-2SD, **= < Mean-1SD.

Table 2 shows the MD dimensions of permanent teeth of YE and MA (CMV affected girls) in comparison to normal girls. The upper and lower incisors, upper canine and upper first molar of YE showed true microdontia, smaller than mean minus 2SD, while lower first molars were smaller than mean minus 1SD. Upper and lower canines of MA showed true microdontia while upper laterals and first molar, and lower incisors, second premolar and first molar showed results similar or smaller than mean minus 1SD.

Table 3 shows the mesial enamel thickness of deciduous molars and first permanent molars of YE and ML in comparison to normal girls and the ratio of the enamel to MD dimensions of the teeth. The ratio of mesial enamel thickness was higher in CMV girls in comparison to normal, due to smaller tooth germ size, reflected by measurement of Dentino-Enamel Junction (DEJ) (maximal mesio-distal dimension).

Tooth	Maxilla	I^1	I^2	C^1	PM^1	PM^2	M^1
	Mean ± SD	8.67 ± 0.56	6.78 ± 0.64	7.67 ± 0.46	6.77 ± 0.37	6.53 ± 0.39	10.18 ± 0.58
YE	Mean	6.33*	4.75*	6.49*	6.14**	6.83	9.44**
MA	Mean	8.52	5.89**	6.46*	6.22**	6.06**	9.09**
Tooth	**Mandible**	**I_1**	**I_2**	**C_1**	**PM_1**	**PM_2**	**M_1**
	Mean ± SD	5.46 ± 0.34	5.92 ± 0.34	6.51 ± 0.37	6.93 ± 0.38	6.93 ± 0.41	10.29 ± 0.74
YE	Mean	4.49*	4.53*	6.54	6.64		9.47**
MA	Mean	5.14	5.47**	5.9*	6.4	6.59**	9.22**

Table 2: Mesio-distal dimensions (mm) of permanent teeth of CMV affected girls in comparison to unaffected girls.

Note: SD: Standard Deviation; I: permanent Incisor; C: Permanent Canine; PM: Premolar; M: Permanent Molar

*= < Mean-2SD, **= < Mean-1SD, MD: Mesio-Distal

	Tooth	normal	CMV	normal	CMV	normal	CMV
		MD	MD	Enamel	Enamel	Enamel/MD	Enamel/MD
YE	m^1	6.61	6.08	0.66	0.85	0.10	0.14
ML	m^1		6.56		0.66		0.10
YE	m_1	7.71	6.46	0.64	0.82	0.08	0.13
ML	m_1		5.68		0.72		0.13
YE	m^2	8.74	7.39	0.83	0.74	0.09	0.10
ML	m^2		6.83		0.74		0.11
YE	m_2	9.73	8.11	0.74	0.94	0.08	0.12
ML	m_2		7.80		0.76		0.10
YE	M^1	10.18	8.76	1.17	1.16	0.11	0.13
ML	M^1		8.76		1.01		0.12
YE	M_1	10.29	8.94	1.26	1.61	0.12	0.18
ML	M_1		8.95		1.10		0.12

Table 3: MD dimension (mm) of tooth germ (DEJ) and enamel thickness of CMV affected girls in comparison to unaffected girls.

Note: MD: Mesio-Distal; m: Deciduous Molar; M: Permanent Molar

Table 4 shows the relative ion composition of prenatal, postnatal enamel and dentin in deciduous teeth of YE in comparison to normal teeth. The calcium and phosphate relative concentrations were lower in prenatal enamel, postnatal enamel and dentin of CMV teeth and the concentration of carbon and nitrogen were higher.

Discussion

Tooth formation is dependant upon a coordinated series of interaction between oral epithelium and neural crest derived ectomesenchyme. Final crown size is determined by two steps: the tooth germ size, reflected by the Dentino-Enamel Junction (DEJ) and the thickness of the enamel layer.

	Prenatal Enamel		Postnatal Enamel		Dentin	
Ion	**Normal**	**CMV**	**Normal**	**CMV**	**Normal**	**CMV**
C	4.169	4.685	5.076	6.607	10.898	13.561
N	4.152	5.585	4.608	6.007	13.97	14.262
O	46.19	45.899	45.082	45.485	42.98	43.287
P	13.373	13.238	13.224	12.498	9.765	9.097
Ca	32.115	31.594	32.009	29.402	22.386	19.793

Table 4: Ion components (MW%) of enamel and dentin of CMV affected girl in comparison to unaffected children.

Note: C: Carbon; N: Nitrogen; O: Oxygen; P: Phosphate; Ca: Calcium

In mice, CMV infection of neural crest-derived ectomesenchyme may interrupt the reciprocal interactions between epithelial and mesenchymal components. It seems that tooth morphogenesis may be severely delayed by CMV, and enamel defects may be the result of affected ectodermal derived ameloblasts [8].

Microdontia is used to describe teeth which are smaller than normal, outside the usual limits of variation (mean minus 2SD of the examined population). Three types of microdontia are recognized:

- True generalized microdontia - all the teeth are smaller than normal. Aside from its occurrence in some cases of pituitary dwarfism, this condition is exceedingly rare.
- Relative generalized microdontia - normal or slightly normal teeth are present in jaws that are somewhat larger than normal, and there is an illusion of microdontia.
- Microdontia involving single tooth - this is a rather common condition, and often effects maxillary lateral incisors and the third molars [10].

True generalized microdontia is a rare condition and it is often related to other syndromes such as Rieger anomaly, orofaciodigital syndrome (type 3), oculo-mandibulo-facial syndrome, and pituitary dwarfism [14-16].

The main findings in the deciduous and permanent teeth of the girls affected by congenital CMV was the reduced mesio-distal dimensions. All deciduous teeth measured showed microdontia, while in permanent dentition the incisors and first permanent molar were affected. The initiation of the primary dentition begins between 7-10 weeks in utero and calcifications begins between 13-23 weeks in utero. During the cap stage (morphogenesis of the tooth tissues) the CMV virus may affect the interaction between epithelial and mesenchymal components [8], resulting in reduced tooth germ, defined by the dentino-enamel junction. The apposition of enamel, the second stage of final crown formation was not affected by the CMV in these girls, and the ratio of enamel thickness to tooth germ dimensions was higher in the affected girls, due to smaller mesio-distal dimensions of tooth germ. No significant hypoplastic enamel was observed in the teeth of the affected girls examined, a general finding described in Stagno et al. 1982. In the CMV affected girl both prenatal and postnatal enamel and dentin of deciduous teeth showed reduced inorganic ions (calcium and phosphate) and higher concentrations of organic ions, implicating hypomineralization of enamel and dentin. The effect of the hypomineralization can be seen on figures 2 and 4 where extensive caries lesions were observed on deciduous and permanent teeth of the affected girls.

The true microdontia observed in congenital CMV affected girls will affect the arch length in permanent dentition, and a full orthodontic and clinical analysis have to be performed. The hypomineralization in deciduous and permanent teeth will affect carious attack, with the clinical result of significant caries lesions.

Conclusion

The CMV affects deciduous and permanent tooth development during pregnancy and up to 2 years after birth. Mineralization of the deciduous teeth is affected and more organic ions were detected in enamel and dentin, implicating that CMV affected organic matrix removal. The enamel in deciduous and permanent teeth

was similar to normal in thickness and no hypoplastic enamel was observed.

Acknowledgements

We want to thank Roxana Golan from the Isle Katz Institute for Nanoscale Science and Technology, Ben Gurion University of the Negev, Beer-Sheva for the work on the SEM and the EDS analysis of the ions content.

Compliance with Ethical Standards

Conflict of Interests

Dr Alisa Fatale, Dr Leibovitz Haviv Shirley and Dr Zilberman Uri declare that they have no conflict of interests.

Funding

No funding was obtained for this study.

Ethical Approval

Not Applicable.

Informed Consent

Not Applicable.

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