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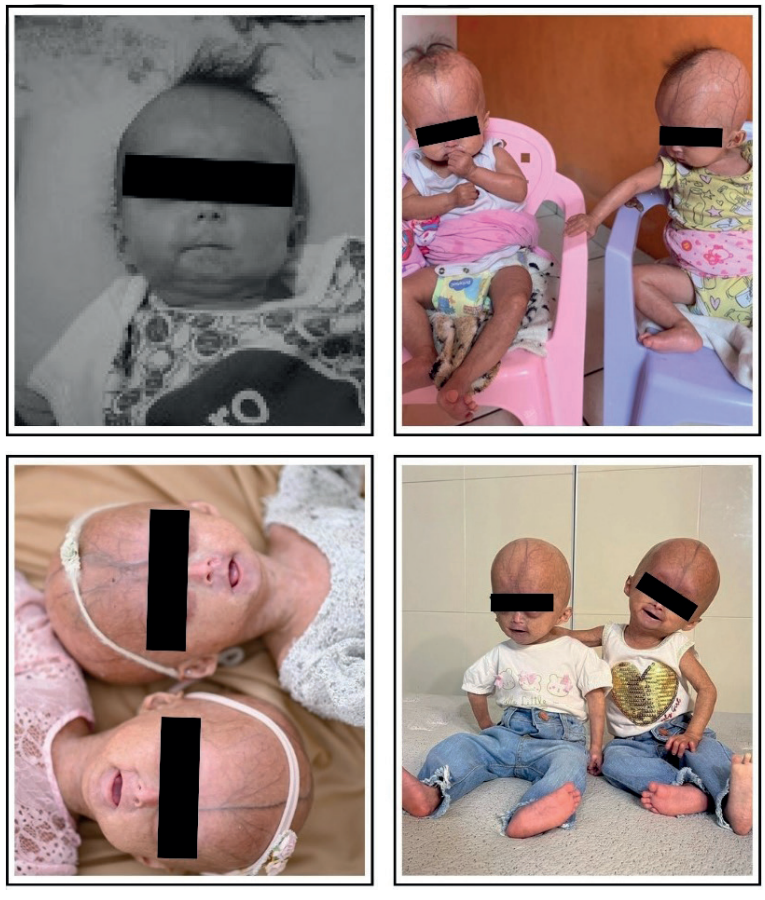

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Case Report

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Original Article

The effect of glycemic variability on DNA damage in children with type 1 diabetes mellitus

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ABSTRACT

Objective: The aim of this study was to determine the extent of DNA damage in pediatric patients with type 1 diabetes and the influence of glycemic variability on DNA damage.

Method: The study involved 50 patients under the age of 18 with type 1 diabetes and 21 healthy control individuals. The Medtronic iProTM2 Enlite Glucose Sensor® was implanted, and continuous glucose monitoring metrics were calculated, including standard deviation, glucose management indicator, coefficient of variation, time in range, time below range, and time above range. Blood samples were also taken to assess DNA damage and HbA1c levels.

Results: The mean age of children with type 1 diabetes was 13.69±2.99 years, and the male-to-female ratio was 30:20. DNA damage was found to be similar in patients with type 1 DM and in a healthy control group. However, among children with type 1 diabetes mellitus, head length, a measure of undamaged DNA, was significantly higher in patients with good glycemic control (HbA1c≤7.5%) than in those with poor glycemic control (HbA1c>7.5%). A positive correlation was observed between DNA damage parameters and % coefficient of variation, a marker of glycemic variability.

Conclusion: The correlation between the coefficient of variation and DNA damage demonstrates the critical importance of maintaining consistent glycemic management in diabetes.

Keywords: DNA damage, glycemic variability, type 1 diabetes

INTRODUCTION

Type 1 diabetes mellitus is one of the most common chronic systemic diseases in childhood and is a risk factor for long-term vascular complications.[1] There is a significant correlation between hyperglycemia and the risk of micro- and macrovascular complications in type 1 diabetes (T1DM). The hemoglobin A1c (HbA1c) is a surrogate marker for glycemia and reflects average blood glucose levels. Therefore, it is utilized as a target for metabolic control.[1-3] However, it is essential to note that HbA1c

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should not be used as the sole indicator of glycemic control and may not accurately reflect short-term changes in blood glucose levels.[4,5]

Individuals with similar HbA1c values may have different glycemic variability (GV), which may contribute to diabetes-related complications that are not related to the degree of HbA1c.[6,7] Compared to HbA1c, continuous glucose monitoring (CGM) provides information on daily and inter-day blood glucose fluctuations and the extent of these fluctuations.[8] Although various CGM metrics have been reported, utilizing all these indices in daily clinical practice is impractical. A report has been published on the standardization of CGM metrics, and ten metrics have been chosen for use in clinical practice.[8] The most useful metrics in clinical practice are number of days CGM worn (recommend 14 days), percentage of time CGM is active, mean glucose, glucose management indicator (GMI), glycemic variability (%CV, target ≤36%), time above range (TAR, % of readings >181 mg/dL), time in range (TIR, % of readings between 70–180 mg/dL), time below range (TBR, % of readings below 69 mg/dL).

All changes in the molecular integrity of DNA caused by endogenous and exogenous factors are referred to as 'DNA damage'. In patients with diabetes, there is an increase in the generation of reactive oxygen species and oxidative stress. Hyperglycemia has been identified as a major cause of increased oxidative stress leading to DNA damage.[9-11] Another causative factor that induces oxidative stress was found to be GV.[11-16]

Although there is a sufficient number of publications investigating both the relationship between oxidative stress and GV, and the link between hyperglycemia and DNA damage, no publication directly explores the relationship between GV and DNA damage.

Comet assay, also called the Single Cell Gel Electrophoresis Method (SCGE), is a fast, reliable, and quantitative method that can determine various types of DNA damage in cells.[17,18] DNAs are subjected to electrophoresis to move rapidly towards the anode. The migration speed increases according to the number of chain breaks in the DNA. This migration is like a comet. The amount of DNA damage is determined by the comet's tail length and the DNA density in the tail length. The longer the tail length, the more damaged the DNA.[17,18]

To the best of our knowledge, no research has been conducted to examine the association between glycemic variability and DNA damage in pediatric patients diagnosed with type 1 diabetes. This study aimed to investigate the relationship between DNA damage and CGM indices, particularly glycemic variability.

PATIENTS AND METHODS

Subjects

The study included 62 patients (24 males and 38 females) with T1DM who were being followed at the Department of Pediatric Endocrinology, Pamukkale University Faculty of Medicine. T1DM was initially diagnosed using the diagnostic criteria published by the International Society for Pediatric and Adolescent Diabetes (ISPAD 2022).[2] Twentyone age and gender-matched healthy controls were also enrolled.

The following criteria were used to exclude individuals from the study group: (i) children with acute infection and fever; (ii) children with type 1 diabetes in partial remission; (iii) children treated with any medication (except insulin) in the previous ten days; (iv) children who had been treated with oral vitamins in the previous month. The "partial remission" period was defined as insulin reduced to ≤ 0.5 IU/ kg per day and HbA1c <7%. Demographic and clinical data (duration of diabetes, diabetes treatment, and the presence of microvascular complications) were collected from medical records. Those with serum low-density lipoprotein (LDL) ≥100 mg/dL and/or triglycerides ≥150 mg/dL were considered to have dyslipidemia.[19]

The research group was separated into subgroups for a more extensive statistical analysis. According to coefficient of variation (CV) % values; those with CV<36% were considered stable, while those with CV≥36% were unstable. Patients with time in range (TIR) values above 70% were considered in the ideal target range, while those below 70% were considered to be in the suboptimal target range. Individuals with a mean HbA1c ≤ 7.5% were considered to have good metabolic control, whereas those with a value greater than > 7.5% were considered to have poor metabolic control. The Institutional Ethical Committee approved based on the Declaration of Helsinki's principles (number:60116787-020/59514). Each study subject provided informed consent.

CGM metrics

The Medtronic iProTM2, Enlite Glucose Sensor® was implanted, and continuous glucose monitoring (CGM) metrics were calculated, including standard deviation (SD), glucose management indicator (GMI), coefficient of variation (CV), time in range (TIR), time below range (TBR), and time above range (TAR). The participants wore the "Medtronic iProTM2, Enlite Glucose Sensor®" for seven days. TIR was defined as the proportion of time spent in the target range (70–180 mg/dL), TBR as the proportion of time spent below 70 mg/dL, and TAR as the proportion of time spent above >180 mg/dL. The CV % was

calculated as the SD of the glucose level divided by the mean glucose level.[8] CV% was considered as an indicator of glycemic variability.[8]

Blood samples

Blood samples were taken on the same day and immediately transported to the laboratories.

The HbA1c level was determined using the high-pressure liquid chromatography method (Tosoh G8 Bioscience, Inc., Tokyo, Japan).

Blood collection and lymphocyte isolation

All participants had their peripheral venous blood drawn into a 10-mL vacutainer tube containing K3EDTA, and lymphocytes were isolated using Histopaque-1077. Blood was diluted 1:1 with phosphate-buffered saline (PBS) and placed into the Leucosep tube directly. After that, it was centrifuged for 15 minutes at 800g and room temperature. Buffy coats were removed and washed with PBS twice.

Cell cryopreservation prior to comet assay

The cell suspension was centrifuged at 200g for 5 minutes, and the pellet was resuspended at 3105 cells/mL in freezing media containing 10% DMSO, 40% RPMI, and 50% fetal calf serum, as reported by Visvardis et al.[20] The cell suspension was transferred in aliquots of 2106 cells to plastic freezing vials. The vials were placed in a Cryo 1°C freezing container, then immediately into a -80°C freezer to achieve a cooling rate of 21°C/min, and then kept at -80°C.

Comet assay

The assay was carried out according to the protocol described by Nandhakumar et al.[18] To summarize; the vials were collected and immersed in a 37°C water bath until all ice was melted. The thawed cells were transferred immediately to conical centrifuge tubes containing 15 mL of pre-chilled thawing medium composed of 50% fetal calf serum, 40% RPMI, and 10% dextrose. To perform the comet experiment, cells were centrifuged at 200g for 10 minutes at 4°C, and the pellet was resuspended in ice-cold PBS pH 7.3.

The comet assay was done in alkaline conditions using a modification of Singh et al.[17] Cells were suspended in 1% low melting point agarose in PBS, pH 7.4, and pipetted 100 µl onto a frosted glass microscope slide pre-coated with 1% average melting point agarose. After 10 minutes on ice, the agarose was allowed to set, and the slide was placed in a lysis solution (2.5 M NaCl, 100 mM Na2 EDTA, 10 mM Tris, NaOH to pH 10.0, and 1% Triton X-100) at 4°C for 1 hour to remove cellular proteins.

After placing slides in an electrophoresis tank, they were allowed to soak for 30 minutes in an alkaline buffer (0.3 M NaOH and 1 mM Na EDTA) to unwind DNA strands and reveal alkali labile spots (alkali unwinding) before electrophoresis. After 30 minutes, electrophoresis at 25 V, 300 mA for 30 minutes at the same temperature was done. The slides were carefully removed from the electrophoresis buffer and put on a staining tray at the end of the 30 minutes. The slides were washed three times with the neutralizing buffer for five minutes each (0.4 M Tris-HCl, pH 7.5). The slides were then observed using the fluorescence staining process. Each slide was coated with 50 mL of ethidium bromide stain and covered with a clean coverslip. Before examining the slides, the excess pigment was wiped off the back and edges of the slides. A fluorescent microscope with an excitation filter of 515–560 nm, a barrier filter of 590 nm, and a magnification of 20 was utilized to visualize ethidium bromide-stained slides. To limit the likelihood of cellular DNA damage, all stages, starting with lymphocyte isolation, were performed under yellow light. Microscopically, slides were analyzed using Comet IV Computer Software (Perceptive Instruments, United Kingdom)

Statistical methods

Statistical Package for Social Sciences (SPSS) version 20.0 software was used for statistical analyses. Data were examined for normality. For continuous variables, Data with normal distribution were expressed as mean ± SD, as a median and interquartile range of non-normal distribution. Categorical variables were expressed as frequencies and proportions.

Mann-Whitney's U-test assessed differences in measured parameters between control and patient groups. The significance level was considered as $p< 0.05$. Correlation analysis was performed by using Spearman's correlation coefficient.

RESULTS

Twelve children were excluded from the trial because they had removed the CGM sensor due to local side effects (pruritus, discomfort) or due to sensor incompatibility or inadequate sensor data (<70%). The remaining 50 patients had a mean duration of diabetes of 4.39 ± 2.39 years and an HbA1c of 9.2 ±2.1%. Table 1 summarizes the clinical characteristics of all patients. None of the patients had micro- or macrovascular complications. Fourteen patients (29.8%) had dyslipidemia. Among those with dyslipidemia, 64.3% (n=9) had elevated triglycerides, 21.4% (n=3) had elevated LDL, and 14.3% (n=2) had elevated LDL and triglycerides together.

Table 1. Clinical and laboratory findings of the entire group			
	Control (n=21)	**T1 DM (n=50)**	***p***
Age (year)	13.16±3.78	13.69±2.99	0.57
Female/Male	20/11	30/20	0.33
Prepubertal/Pubertal	6/15	14/36	0.96
Weight SDS	-0.25±1.50	0.02±1.20	0.40
Height SDS	-0.02±1.27	-0.04±1.09	0.92
BMI SDS	-0.28±1.24	1.19±5.66	0.43
DNA damage parameters			
Head length (µm)	30.18±2.22	30.43±3.10	0.74
Tail length (µm)	36.07±7.03	32.52±9.79	0.14
Tail intensity (%)	25.10±10.63	20.78±11.56	0.15
Tail moment (µm)	4.89±2.99	3.92±3.55	0.28
Tail migration (µm)	21.02±7.67	17.34±9.93	0.24
BMI: body mass index, SDS: standard deviation score, T1 DM: type 1 diabetes.			

Table 2. Comparison of DNA damage parameters among subgroups divided according to metabolic control, coefficient variation %, and time in range %			
	HbA1c ≤% 7.5 (n=11)	**HbA1c > %7.5 (n=39)**	***p***
Head length (µm)	32.28±2.43	29.88±3.09	**0.02**
Tail length (µm)	31.12±7.24	32.94±10.47	0.59
Tail intensity (%)	16.86±9.18	21.95±12.05	0.20
Tail moment (µm)	3.19±2.48	4.13±3.81	0.44
Tail migration (µm)	15.18±7.78	17.99±10.49	0.41
	CV % <36 (n=14)	**CV % ≥36 (n=36)**	
Head length (µm)	30.65±3.11	30.35±3.14	0.77
Tail length (µm)	30.10±9.52	33.42±9.86	0.30
Tail intensity (%)	17.48±12.70	22.01±11.05	0.23
Tail moment (µm)	3.23±4.23	4.17±3.29	0.42
Tail migration (µm)	14.66±9.74	18.34±9.95	0.25
	TIR > %70(n=11)	**TIR < % 70 (n=39)**	
Head length (µm)	30.88±3.16	30.30±3.11	0.59
Tail length (µm)	33.21±13.95	32.32±8.41	0.79
Tail intensity (%)	20.88±17.08	20.76±9.67	0.97
Tail moment (µm)	4.58±5.69	3.72±2.7	0.48
Tail migration (µm)	17.58±14.66	17.27±8.31	0.93
HbA1c: hemoglobin A1c, CV: coefficient variation, TIR: time in range.			

Comet assay parameters indicating DNA damage did not differ between the diabetes and control groups (Table 1). However, when DNA damage was compared between diabetes subgroups, head length, an indicator of intact DNA, was found to be higher in the good metabolic control group than in the poor metabolic control group (Table 2). There was no difference between the subgroups that were separated according to CV % and TIR % (Table 2). DNA damage did not differ between those with hyperlipidemia and those without it.

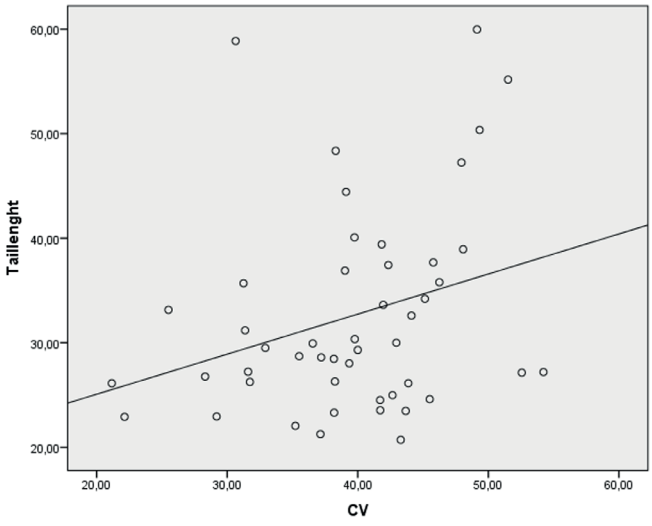

Figure 1. The correlation between coefficient variation (CV) % and tail length

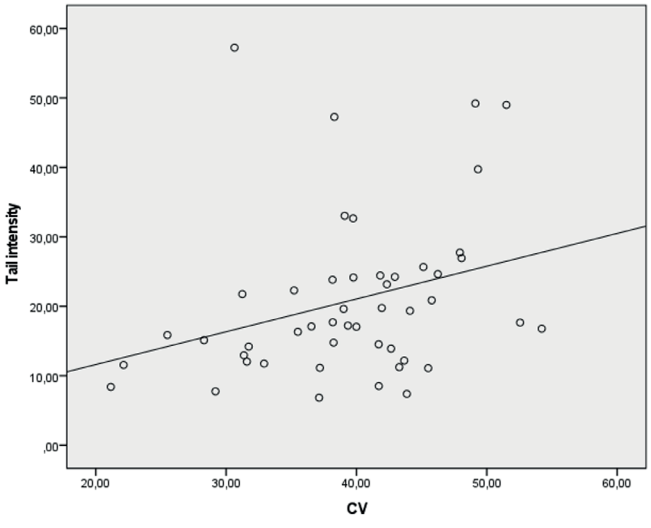

Figure 2. The correlation between coefficient variation (CV) % and tail intensity

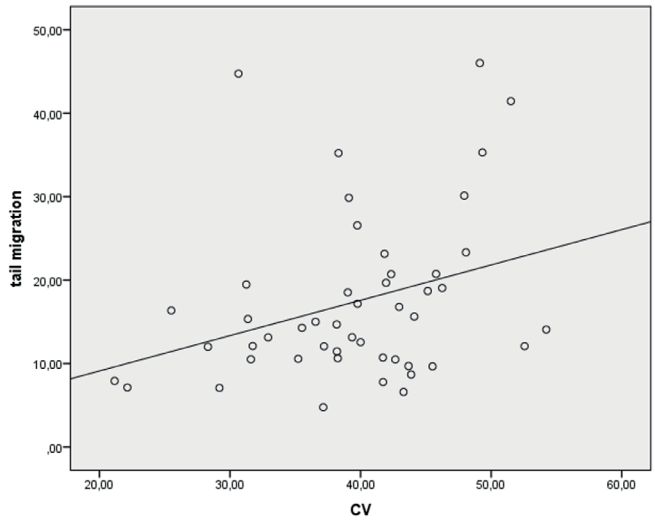

Figure 3. The correlation between coefficient variation (CV) % and tail migration

CV%, a marker of glycemic variability, was positively correlated with tail length, tail density, and tail migration, which are indicators of DNA damage (r= 0.29, p=0.04; r= 0.30, p=0.03; r=0.32, p=0.02, respectively) (Figure 1, 2, 3 and Table 3).

DNA damage parameters did not correlate with age, diabetes duration, HbA1c %, or serum lipid levels.

DISCUSSION

This study aimed to investigate the association between GV and DNA damage in young patients with type 1 diabetes. Although there was no difference between individuals with stable CV% and those without in terms of DNA damage parameters, we observed a positive correlation between the CV% and DNA damage parameters, including tail length, intensity, and migration.

In subgroup comparisons based on HbA1c, a marker of hyperglycemia, the only difference among the DNA damage parameters was in head length. There was no correlation between Hba1c or mean glucose values and DNA damage. These findings suggest that glycemic variability, rather than hyperglycemia, maybe a more potent factor in inducing DNA damage.

It is well known that hyperglycemia causes oxidative stress, which promotes the development of diabetic vascular complications. Glycemic variability also stimulates oxidative stress.[11,12] It has even been reported that glucose fluctuations have a more

Table 3. Correlation between DNA damage parameters and CGMS data in patients with type 1 DM

		Mean glucose	HbA1c%	TIR %	TAR %	TBR%	GMI%	SD	CV%
Head length	r*	0.00	-0.1	0.07	-0.03	-0.12	0.00	-0.04	-0.10
	p	0.98	0.48	0.62	0.83	0.39	0.97	0.77	0.48
Tail length	r*	-0.12	0.09	0.04	-0.09	0.18	-0.12	0.03	0.29
	p	0.39	0.95	0.77	0.53	0.20	0.39	0.79	**0.04**
Tail intensity	r	-0.12	0.22	0.02	-0.07	0.19	-0.12	0.06	0.30
	p	0.40	0.88	0.88	0.61	0.17	0.40	0.68	**0.03**
Tail moment	r	-0.14	0.05	0.08	-0.11	0.13	-0.14	-0.00	0.25
	p	0.33	0.73	0.57	0.42	0.35	0.33	0.99	**0.08**
Tail migration	r	-0.11	0.01	0.01	-0.07	0.21	-0.12	0.05	0.32
	p	0.42	0.92	0.89	0.60	0.15	0.41	0.70	**0.02**

HbA1c: hemoglobin A1c, CV: coefficient variation, GMI: glucose management indicator, SD: Standard deviation, TIR: time in range, TAR: time above range, TBR: time below range.

significant effect on inducing oxidative stress than continuous, sustained chronic hyperglycemia.[13,21]

It is unclear why glucose variability is a greater driver of oxidative damage than chronic hyperglycemia. One of the possible explanations is based on the tumor suppressor gene p53. Enhanced oxidative stress activates p53 phosphorylation.[22] Liu et al. reported that high levels of glucose activate the tumor suppressor gene p53 in human endothelial cells. The study demonstrated that activation of p53 leads to an increase in the expression of other genes that are involved in apoptosis.[23] This process persists even after achieving normoglycemia, called as "metabolic memory".[23,24] Schisano et al. reported that fluctuations in glucose induce a higher transcriptional activity of p53 than constant hyperglycemia.[25]

Several studies have reported a significant increase in DNA damage in patients with diabetes.[9-11,16,26-28] These studies have investigated the association between oxidative stress, hyperglycemia, and DNA damage in diabetes mellitus, but they were limited to adult populations, with most participants having type 2 diabetes.[9,11,16,27-30] However, only a few clinical trials have studied DNA damage in children with T1DM.[10,26] DNA damage was found to be increased in children with T1DM, and the enhanced oxidative stress resulting from hyperglycemia has been shown to cause DNA damage.[10,26] No reports have been conducted on children regarding DNA damage and glycemic variability. Therefore, our study contributes to the literature in this field, and more research is needed in this area.

In the current study, we did not find any difference in DNA damage between the control group and the group of diabetic patients. Consistent with our research, some studies did not report increased DNA damage among diabetic patients compared to healthy controls.[29-31] Varvarovská et al.[31] demonstrated increased oxidative stress but unchanged DNA damage in children with T1DM compared to healthy controls. On the other hand, DNA repair capacity was increased. The authors attributed this to increased stimulation of DNA repair capacity due to the stimulation of oxidative stress.

Anderson et al.[30] offered the following possible explanation for this situation; the damage must exceed a certain level to trigger DNA repair mechanisms. Regular exposure to oxidative damage in people with diabetes may keep DNA repair mechanisms dynamic. In healthy people, unstimulated lymphocytes may not be competent in DNA repair and, therefore, accumulate small amounts of DNA damage.[30] Aging may be another explanation. Numerous studies have examined the association between DNA damage and aging. They found that aging was related to a lower ability for DNA repair.[32,33]

In our study, among children with T1DM, we didn't find a correlation between DNA damage and HbA1c %. On the contrary, we found a shorter head length in the poor metabolic control group compared to the good metabolic control group, which is associated with greater DNA damage. Although most of these studies have shown an association between HbA1c, hyperglycemia, and DNA damage[10,11,16,27], there is also one study that did not report an association between HbA1c, duration of diabetes, complications, and DNA damage.[9]

In summary, unaltered DNA damage in children with T1DM may be explained by increased DNA repair mechanisms due to

chronic stress, shorter duration of disease, or young age-related high repair mechanisms.

Study limitations

The main limitation of this study is the short duration of the CGM wearing time and the small number of the study population. Due to economic issues, patients received only one CGM sensor (for seven days). Second, although participation in the study was offered to all patients, those who were already using CGM technology declined to enter the study because they refused to wear a device other than their CGM device. Additionally, some individuals with good metabolic control did not want to wear a CGM because they already had good blood glucose regulation and did not want to put extra effort into the study. Unfortunately, this condition may be viewed as a selection bias, which may have influenced our understanding of the link between HbA1c and CGM measures. These associations may be valid in patients with good metabolic control and low CV%.

CONCLUSION

In conclusion, we found that glycemic variability, assessed by CV%, is associated with DNA damage in children with type 1 diabetes, even when DNA damage is not enhanced compared to healthy controls.

Ethical approval

This study has been approved by the Pamukkale University Non-Interventional Clinical Research Ethics Committee (approval date 02.07.2019, number 60116787-020/59514). Written informed consent was obtained from the participants.

Author contribution

Surgical and Medical Practices: GG; Concept: GG, SAA; Design: SAA; Data Collection or Processing: GG, BÖ; Analysis or Interpretation: ÖKE, MTA, EKT, VK; Literature Search: GG, SAA, EKT; Writing: SAA. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Original Article

Upper airway obstruction and nocturnal enuresis in children: Why is it important?

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ABSTRACT

Objectives: Nocturnal enuresis (NE) is a common urological complaint among children. The most common cause of obstructive airway disease in children is enlarged tonsils and adenoids. Although the relationship between the presence of NE and sleep disorders is unclear, some studies show that enuresis improves after airway obstruction is resolved. We aimed to investigate the relationship between upper airway obstruction and NE in children.

Methods: Between September 2020 and June 2021, 66 pediatric patients diagnosed with persistent NE were included in the study. A total of 57 healthy patients were included in the control group. The presence of snoring and apnea, the presence of Attention-Deficit/Hyperactivity Disorder (ADHD)/social adjustment disorder, academic achievement, and family members' history of NE were asked through questionnaires filled out by the families. An upper airway examination was done with a flexible nasopharyngoscope.

Results: The mean ages of the study patients and healthy controls were 8.32±2.1 and 8.18±2.3 years. The female/male ratio was (25/41) and (33/24), respectively. Of the case group, 62.1% were male, and 78.8% were under nine years old. The frequency of snoring/apnea in children with enuresis was 27.3%, while it was 19.3% in the control group (p=0.299). It was found that more enuresis developed in children with high BMI (p=0.044). Family history was higher in the NE group than in the control group, but it was not statistically significant (p=0.173).

Conclusion: Nocturnal enuresis is commonly associated with obstructive sleep apnea. Upper airway obstruction, obesity, and male gender are important risk factors for NE.

Keywords: Adenoid Vegetation, Children, Nocturnal Enuresis, Tonsillar Hypertrophy, Upper Airway Obstruction.

INTRODUCTION

Nocturnal enuresis (NE) is a common urological complaint among children.[1] According to the definition of The International Children's Continence Society, enuresis (synonymous with intermittent nocturnal incontinence) refers to discrete episodes of urinary incontinence during sleep in children ≥5 years of age.[2] Its prevalence is about 5-10%.[1,3] Several aetiologies have been researched for nocturnal enuresis, but its pathogenesis is still unclear.[4] Reduced functional bladder capacity, detrusor overactivity, nocturnal polyuria, release, and immaturity of the sleep mechanism have been implicated.[5] Enuresis is seen in patients without bladder dysfunction, and lower urinary tract complaints are defined as monosymptomatic nocturnal enuresis. This disease is described in children older than five years.[1,3]

Sleep problems in childhood with enuresis have been studied for a long time. The relationship between the presence of enuresis

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and sleep disorders is not clear. There are some hypotheses about the association of nocturnal enuresis with obstructive airway disease because it may resolve after corrective operation for the disease. The most common cause of obstructive airway disease (OAD) in children is enlarged tonsils and adenoids that block the airway and obstruct breathing during sleep.[6]

Studies are showing that self-esteem is impaired in children with nocturnal enuresis. Low self-esteem is a risk factor for psychiatric disorders and social adjustment problems. Therefore, when treated appropriately, later psychological disorders can be prevented. In addition, studies emphasize that it is important to start treatment early in these children.[7] Also, studies show that children affected by enuresis tend to have a worse sleep quality when compared to unaffected children.[8] These data show that enuresis is associated with an increased risk for learning disabilities, intellectual disability, and worse school performance.[9]

We aimed to investigate the relationship between upper airway obstruction and enuresis and its possible risk factors in children.

METHODS

A total of 66 patients (41 males, 25 females) with the diagnosis of persistent enuresis who attended the outpatient clinics of the pediatric department of Alanya Alaaddin Keykûbat University Medical Faculty Hospital between September 2020 and June 2021 were included in the study. Ethical approval was obtained from the Alanya Alaaddin Keykûbat University prior to the study. Written informed consent was obtained from all children's parents. Cases with complaints such as daytime urinary incontinence, sudden urgency to go to the toilet/incontinence before reaching the toilet, intermittent urination, straining while urinating, persistent constipation, secondary enuresis, mental retardation, and chronic disease were not included in the study. The control group included 57 healthy patients (24 males, 33 females) with no enuresis symptoms. The presence of snoring and apnea, the presence of ADHD (Attention-Deficit/Hyperactivity Disorder)/social adjustment disorder, academic achievement, and family members' own history of enuresis were asked through questionnaires filled out by the families. The survey questions were developed by reviewing the relevant literature on the subject. The questions were reorganized in accordance with the purpose of the study.[10,11] Then, an upper airway examination was performed with a flexible nasopharyngoscope in each group. Tonsil hypertrophy and adenoid vegetation were classified from 0 to 4 according to the tonsil to oropharynx and adenoid to nasopharynx ratio 1; 25%, 2; 25–50%, 3; 50–75%, or 4; 75–100%.[12] The Body Mass Index (BMI) percentage was calculated by measuring the height/weight of the children in the outpatient clinic, and they were divided into three groups, namely normal weight (5th-84th percentile), overweight (85th-94th percentile), and obesity (≥95th percentile), according to their BMI.[13]

All analyses were performed using the IBM SPSS Statistics Version 22.0 statistical software package (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corporation). Categorical variables were expressed as numbers and percentages, whereas continuous variables were summarized as mean and standard deviation. The differences between the categorical variables were compared with the chi-square test, and the differences between the groups were compared with the Mann-Whitney U test. It was accepted as the statistical significance level ($p < 0.05$).

RESULTS

Sixty-six patients diagnosed with enuresis in the pediatric age group and 57 healthy control groups were examined prospectively. The mean ages of the study patients and healthy controls were 8.32 ± 2.1 and 8.18±2.3 years. The demographic characteristics of the groups are presented in Table 1. Of the enuresis group, 62.1% were male, and 78.8% were under nine years old. While the frequency of snoring/apnea in children with enuresis was 27.3%, it was 19.3% in the control group, and the difference was not statistically significant (p=0.299). Family history was higher in the enuresis group than in the control group but was not statistically significant (p=0.173).

When the patients were classified according to their BMI values, the percentages of normal weight, overweight and obese patients in the control group were 87.7% (50), 8.8% (5) and 3.5% (2), respectively, while in the enuresis group they were 69.7% (46), 16.7% (11) and 13.6% (9), respectively. Our BMI results of sick children supported that more enuresis was observed in overweight and obese children, and it was statistically significant (p=0.044). Although family history was present in 18.2% of children with enuresis, it was not statistically significant. (p=0.231). When we evaluated the presence of ADHD and social adjustment disorder, we found no difference between enuresis (10.6%) and the control group (10.5%) (p=0.989). While low academic achievement was 22.7% in enuretic children, it was 12.3% in the control group. However, this difference was not statistically significant—(p=0.132) (Table 1).

DISCUSSION

Nocturnal enuresis is one of the common problems encountered in childhood. At the same time, it causes psychosocial problems and a decrease in academic achievement, and with this aspect, it becomes a source of serious emotional distress and anxiety for

Table 1. Demographic characters of control and case group and comparison of results between groups

	Case Group (n=66)	Control Group (n=57)	p
Age (year) (Mean±SD)	8.32±1.57	8.18±1.56	0.547
Gender female/male)(%)	25(37,9%) / 41(62,1%)	33(57,9%) / 24(42,1%)	0.027
Familial history of nocturnal enuresis (%)	18.2	10.5	0.231
Academic Achievement (%)	87.7	77.3	0.132
ADHD (%)	10.5	10.6	0.989
Snoring/Apnea (%)	19.3	27.3	0.299
Tonsillar Hypertrophy (%)	35.6	54.5	0.479
Adenoid Vegetation(%)	22.8	37.0	0.019
Septum Deviation (%)	24.6	18.2	0.388
Allergic Rhinitis (%)	12.3	16.7	0.493

ADHD: Attention-Deficit/Hyperactivity Disorder.

families.[10] It is known that patients with enuresis in childhood are at risk for polyuria in adulthood.[14] Similarly, childhood enuresis plays a predictive role in anxiety and depression in adults at older ages.[15] In this respect, treatment of nocturnal enuresis and the underlying risk factors are important.

The incidence of NE in the population is not known exactly. While its prevalence was found to be 12.6% in studies in Turkey, it was reported that it was most commonly observed in the 5-12 age group.[16] The prevalence of enuresis tends to decrease with age. Literature data indicate that enuresis nocturna is detected more frequently in boys.[17] In our study, the mean age of children with nocturnal enuresis was 8.3 years. Of these, 62.1% were male, and most (78.8%) were under nine years old. Our findings support that nocturnal enuresis is observed more frequently at early age periods and in boys. In this regard, it was found to be compatible with general literature information.[18]

It is known that having a family history of enuresis increases the risk.[19] If one of the parents has a history of enuresis, the risk of developing enuresis in the child is 43%, while the risk of developing enuresis in the child is 77% if both parents have a history of enuresis.[20] Several loci on chromosomes 12,13 and 22 have been identified in some studies.[19] This positive correlation suggested that genetic factors may play a role in enuresis.[21] In our study, although we found a family history in 18.2% of the children with enuresis, we did not find a link to the probability of developing enuresis in children (p=0.231). However, we think that parents may not be able to answer this question correctly due to social concerns, which may have affected the results.

Although a relationship has been shown between nocturnal enuresis and obesity, this issue is still unclear.[22] Overweight and obese children are generally thought to be fed an unhealthy diet, and because of this diet, the functional development of the bladder is prevented.[23] In a study, it was reported that while enuresis was observed in 9% of normal children, this rate reached 30% in obese children.[24] In their study, Ma et al. reported that there is a link between obesity and enuresis and that there is a low response to treatment in overweight and obese children.[25] Our results supported that more enuresis was observed in overweight and obese children (p=0.044).

NE is a disease that affects patients' social lives and academic achievement. A study found that the academic achievement of children with enuresis was significantly lower than that of healthy children.[26] In psychological analysis tests performed in children with enuresis, it was thought that incomplete intellectual maturation and an underlying ADHD might cause low academic achievement.[27] In a study, it has been reported that children with enuresis have more anxiety and feel depressed.[28] In a large study of 331 children, the presence of enuresis was statistically significantly increased in those with ADHD compared to normal children.[17] These data suggest that enuresis has an impact on academic achievement. On the other hand, some literature data also states no significant difference in academic achievement in children with primary enuresis compared to healthy children.[19] When we evaluated the presence of ADHD in our study, we did not detect any difference between enuresis and the control group (p=0.989). However, in terms of academic achievement, we showed that children with enuresis had a lower success rate (22.7%) than the control group (12.3%) (p=0.132). These findings were also similar to the literature.[9]

It is known that nocturnal enuresis may accompany diseases such as constipation, obstructive sleep apnea (OSA), urinary tract infection, and bladder dysfunction.[22] The coexistence of sleep disorder and enuresis has been revealed in previous studies.[29] Both bladder filling and detrusor contractions are strong stimuli for awakening. However, the fact that impending voiding does not trigger awakening in children with enuresis suggests that this is a sleep-related problem. It is thought to be related to the incomplete development of the brain in children and the immaturity of the sleep center in the hypothalamus.[30] In addition, it was thought that increased urinary output due to increased brain natriuretic peptide (BNP) secretion in children with OSAS may be among the other causes of enuresis development.[31] Snoring and enuresis are thought to be two entities that are seriously related to each other.[29] Although our data showed that the frequency of snoring/apnea increased in children with enuresis (27.3%), these findings were not statistically significant (p=0.299).

Adenotonsillar hypertrophy (ATH) is the most common cause of OSA in the pediatric age group and also the most common cause of upper airway obstruction associated with enuresis. Upper airway obstruction is usually not the primary cause of enuresis, but it leads to enuresis in children.[8] The hypothesis about the link between the two conditions is that persistent arousal stimuli from the airways lead to paradoxically raised arousal thresholds in order to preserve sleep. As a result, it is thought that the child, whose bladder is full, cannot interrupt his sleep and develops enuresis. In a study, a significant relationship was found between septal deviation, adenoid hypertrophy, and enuresis, but they did not find a significant relationship between the presence of allergic rhinitis and tonsillar hypertrophy.[32] Therefore, correcting sleep disorders and indirectly correcting NE is the expected response in children with ATH. Another study showed that enuresis improved in 40% of children with enuresis with ATH and septal deviation after necessary surgery.[6] These data suggest that pathologies causing upper respiratory tract obstruction may be involved in the etiology of enuresis.

The relationship between the presence of allergy and enuresis has not been fully elucidated. Abdollohi-Fakhim et al. stated that they did not find a relationship between enuresis and allergy.[33] However, data show that allergic rhinitis causes sleep disturbance, affects sleep quality, and poses a risk in terms of nocturnal enuresis and obstructive sleep apnea.[34] In our study, 16.7% of children with enuresis had accompanying allergic rhinitis. However, there was no statistical significance compared to the control group (p=0.493).

Again, adenoid hypertrophy was significantly higher in children with enuresis (47%) (p=0.019). Especially in children with enuresis, severe adenoid vegetation was detected at a higher rate. However, this situation was not statistically significant (p=0.269). When evaluated in terms of tonsillar hypertrophy, there was no statistically significant difference between tonsillar hypertrophy and enuresis, although enuresis was observed more in children with severe tonsillar growth (22.7%). These results seem similar to the literature.[6,32]

There are two main limitations to our work. First, we used a questionnaire instead of the polysomnography test to detect sleep disorders. The other limitation is that children with ATH were not questioned whether there was a correction operation or not. Therefore, questioning only for symptoms and lack of follow-up of patients partially weakened the power of our study.

CONCLUSION

Nocturnal enuresis is commonly associated with obstructive sleep apnea. Upper airway obstruction, obesity, and male gender are important risk factors for NE. The low academic achievement of children with NE is a striking phenomenon. In addition, we think that the evaluation of children presenting with enuresis in terms of upper respiratory tract obstruction is important as a step of treatment.

Ethical approval

This study has been approved by the Alanya Alaaddin Keykubat University Faculty of Medicine Clinical Research Ethics Committee (approval date 14.08.2020, number 2020/22-21). Written informed consent was obtained from the participants.

Author contribution

Surgical and Medical Practices: HG, ŞG; Concept: AK, HG; Design: AK, HG, ŞG; Data Collection or Processing: HG, ŞG; Analysis or Interpretation: AK, HG; Literature Search: AK, HG; Writing: AK, HG, ŞG. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Case Report

Unprecedented report: First female monozygotic twins as carriers of Hutchinson-Gilford progeria syndrome

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ABSTRACT

Hutchinson-Gilford Progeria Syndrome (HGPS) is a rare genetic condition characterized by premature aging resulting from an autosomal mutation in the LMNA gene. This article presents a groundbreaking instance of the first female monozygotic twins affected by HGPS, originating from Brazil, highlighting the exceptional nature of this case.

Keywords: Hutchinson-Gilford progeria syndrome, monozygotic twins, female, progeria

INTRODUCTION

Hutchinson-Gilford Progeria Syndrome (HGPS) is an exceedingly rare condition characterized by premature aging. It arises from a spontaneous autosomal mutation in the LMNA gene, which is responsible for producing the Lamina A protein. This protein plays a crucial role in maintaining the structural integrity of the cell nucleus. However, due to the mutation, cellular instability ensues, leading to various abnormalities in nuclear morphology, dysregulated gene expression, deficiencies in deoxyribonucleic acid (DNA) repair, telomere shortening, and genomic instability, resulting in the impairment of the cell's ability to proliferate. The primary manifestation of HGPS is the early onset of aging-related features, which become evident in the affected individuals. As the condition progresses, complications arising from atherosclerosis, such as myocardial infarction, stroke, and heart failure, become a significant cause of death. Unfortunately, individuals diagnosed with HGPS typically have a life expectancy that extends only into their teenage years or early twenties.[1,2]

Progeria was first described in 1886 by Hutchinson and confirmed by Gilford in 1904. It occurs sporadically, with an incidence of 1 in every 8 million live births, and its diagnosis is merely clinical, based on physical manifestations.[3] According to data from the Progeria Research Foundation in March 2023, an estimated 193 children live with progeria, encompassing both HGPS and Progeroid Laminopathy. Progeroid Laminopathy refers to cases wherein individuals have mutations in the lamin pathway but do

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not produce progerin, the characteristic protein associated with HGPS. Since the foundation's inception in 2001, 373 Progeria cases have been registered.[4] To date, the only reported instance of monozygotic twins affected by progeria has been documented in the study conducted by Viégas et al.[5] However, this present work introduces a groundbreaking discovery — the first case of female twins affected by progeria, specifically Hutchinson-Gilford Progeria Syndrome. Notably, both twins have undergone laboratory confirmation, which involved the collection of genetic material. This significant finding expands our understanding of progeria and highlights the importance of further exploration in diverse populations and gender-specific presentations of the syndrome.

CASE REPORT

We present the case of female monozygotic twins born through vaginal birth at 32 weeks of gestation in Boa Vista, Roraima, Brazil. The maternal history involves a healthy Brazilian woman, 38 years old, who has had ten natural deliveries from different relationships, with no complications during pregnancy, although she did not receive prenatal care. The father is a healthy 27-year-old Brazilian man and the twins' sole father. Both parents met while working in a mine in the Amazon rainforest.

At birth, no syndromic features were observed in either twin. However, when the twins reached four months, the family noticed a progressive onset of hair loss, changes in skin thickness, prominent veins in the cranial region, and difficulty gaining weight. Concerned about their health, the twins were admitted to the hospital at six months of age due to suspected pneumonia and malnutrition. Given their low weight and the presence of phenotypic changes, their pediatrician initiated a comprehensive clinical investigation. Karyotype analysis, among other tests, was conducted to identify any underlying abnormalities. However, the results of the tests did not reveal any apparent irregularities. At nine months of age, during a pediatric consultation at the Reference Center for Women's Health, located in the capital of Roraima–Boa Vista, the twins were clinically diagnosed with Hutchinson-Gilford Progeria Syndrome (HGPS). The diagnosis was based on the progression of the HGPS phenotype becoming more evident over time. The twins exhibited characteristic features associated with HGPS, including accelerated aging, craniofacial abnormalities, and vascular changes.

In their concern for their children's health and in search of guidance and support, the family turned to the Progeria Research Foundation (PRF). In June 2023, genetic testing confirmed the diagnosis of HGPS in the twins, detecting c.1968+1 G>C heterozygous mutation in the LMNA gene. This gene variant is associated with Hutchinson-Gilford progeria, which exhibits autosomal dominant inheritance, alongside various clinical phenotypes associated with both autosomal dominant and autosomal recessive inheritance. This confirmation played a crucial role in initiating appropriate management strategies and exploring access to Lonafarnib, the only FDA-approved drug known to delay the disease's progression potentially.[6]

The anthropometric measurements of both twins fall below the normal range. As of November 2023, at the age of 2 years and six months, the twins weighed 4690 and 4350 grams, with heights of 64.9 and 61.9 centimeters, head circumferences of 42.3 and 41.8 centimeters, and Body Mass Index (BMI) values of 11.13 and 11.35 kg/m2, respectively. Additionally, both twins exhibit a global developmental delay relative to their age milestones. Early recognition of developmental delays is crucial as it allows for timely interventions and support, ultimately facilitating positive progress in their future development.

Anthropometric parameters vary significantly between individuals and change according to sex due to genetic potential and environmental factors. Specifically, in childhood and adolescence, body measurements change according to the growth and development stage, in other words, according to age and Tanner pubertal stage. Consequently, evaluating the normality of these measures becomes complex. In daily pediatric practice, scores like the Z-score are used to compare measurements with children of the same age and sex. Any alteration beyond three standard deviations from the mean is considered severe. Tables and charts for children of up to 5 years of age of both sexes can be freely downloaded from the WHO website (www.who.int/childgrowth/standards/en). Regarding the twins in the study, both girls have a Z-score < -3 for weight, classified by the WHO as very low weight for age, and for length, both have a Z-score < -3, classified as very short stature.

The proactive engagement of a multidisciplinary healthcare team is pivotal in overseeing the well-being and developmental progress of twins affected by Hutchinson-Gilford Progeria Syndrome (HGPS). Within this team, the pediatric neurologist assumes a central role in assessing the twins' overall developmental trajectory, particularly providing guidance on speech and social delays. Concurrently, the twins' nutritionist ensures they receive optimal nourishment to preempt malnutrition, even in the absence of current dietary challenges or restrictions. The physiotherapist adopts a proactive stance in advocating for recreational activities to bolster mobility, resulting in noteworthy enhancements to the twins' daily functioning. This includes engaging in intra-household activities utilizing familiar

toys introduced by the family in a playful manner strategically designed to stimulate cognitive and motor skills. Moreover, the recommendation of late afternoon walks has proven efficacious, effectively addressing early-onset walking challenges to foster improved mobility and independence as the twins progress through development.

Given the tropical climate and heightened sun exposure in Roraima, the twins' dermatologist maintains vigilant oversight of their skin health. Emphasis is placed on rigorous photoprotection and hydration regimens to mitigate the elevated risks of sunstroke and skin dehydration prevalent in the region. Diligent care management can effectively alleviate skin-related symptoms associated with HGPS, enhancing the twins' overall comfort and well-being. The collaborative synergy between the family, medical specialists, and the PRF underscores the imperative of early identification and intervention in HGPS cases. By harnessing available resources and exploring potential therapeutic avenues, the collective goal is to optimize the quality of life and long-term outcomes for these remarkable female monozygotic twins.

DISCUSSION

HGPS is a single sporadic autosomal alteration in the LMNA gene, which produces a defective Lamin A protein that cannot maintain cell nucleus stability.[7] This makes the cells unstable, which leads to the fatal process of premature aging. However, progeroid syndromes encompass a group of diseases, HGPS or not, that are characterized by signs of premature aging.[8]

Previously, it was only possible to diagnose HGPS using error-prone clinical information, as other progeroid syndromes existed. With the advent of genetic testing and gene identification, it is possible to make a more accurate diagnosis that may allow early medical intervention that favors a better quality of life for children.[4]

In November 2020, Lonafarnib was the first drug to receive US Food and Drug Administration (FDA) approval for Progeria and Progeroid Laminopathies.[6] Preclinical studies involving the farnesyltransferase protein inhibitor Lonafarnib, originally an experimental drug in oncology, resulted in better life expectancy in children with the disease and minimized the impact of cardiovascular events due to the syndrome.[9,10]

This work announces the first recorded case of female monozygotic twins with HGPS worldwide. Two Brazilian women residing in the capital of the state of Roraima, Boa Vista. Both were born 32 weeks premature and have been fighting for life ever since.

The use of mercury in gold mining is one of the main sources of methylmercury contamination in Brazil. Methylmercury exposure during pregnancy is indeed a concerning issue, as it has been associated with various complications and adverse effects on both maternal and fetal health.[11] Since the mother remained until the fifth month of pregnancy in the mining area, a place with high contamination with mercury, the question arises of the participation of this metal with the predisposition to the syndrome. Although there is currently no literature data directly linking HGPS to mercury exposure during pregnancy, Khan et al.'s work in 2019 demonstrated that mercury exposure could induce epigenetic alterations, leading to behavioral outcomes, atherosclerosis, and myocardial infarction, and miRNAs in the cervix of pregnant women are responsive to maternal mercury exposure, suggesting a novel pathway of influence. The same work has shown that mercury-induced epigenetic alterations in kidney tissues have revealed a significant disruption in renal function, with DNA methylation and histone post-translational modifications being the predominant types of mercury-induced epigenetic changes.[12] Indeed, it was postulated that exposure to adverse environmental factors during fetal life determines the chronic disease risk during adult life due to epigenetic alterations or changes in the genetic material.[3,4]

The physical characteristics of progeria begin to manifest themselves only from 4 months of age. The family suspected, based on this event, that they might have a syndrome. However, doctors were still determining what it could be since most of the tests requested had negative results.

In one of the routine consultations with the pediatrician, at nine months of age, both received the clinical diagnosis of HGPS based on clinical experience and the characteristic phenotypes of premature aging.

The twins periodically carry out several multidisciplinary follow-ups with health professionals to maintain their well-being. Initially, there was a significant barrier, as the professionals were unaware of HGPS, and the caregiver stated that he often needed to explain the syndrome based on previous research carried out for self-knowledge of the subject. From these searches on internet sites, the family found information about PRF. They contacted the institution that instructed them on the collection of genetic material for laboratory confirmation of HGPS, in addition to clarifying doubts about the drug Lonafarnib.

The family has great positive expectations with the test result confirming HGPS and is anxiously awaiting PRF's response to the possible use of the farnesyltransferase protein inhibitor since the drug helps to minimize this effect of vascular stiffness, allowing for a longer life expectancy.[9]

Figure 1 represents the twins' clinical journey, showcasing the changes in their physical appearance and syndromic features as they age.

All the information presented in this article, including laboratory tests and photos, was provided by the family to the researchers through formal written consent. Moreover, the family has requested to disclose the twins' social media, such as their Instagram account (https://www.instagram.com/elis_e_eloa/), YouTube channel (https://www.youtube.com/@Elis_e_Eloa), and TikTok page (https://www.tiktok.com/discover/elis_e_eloa), which allows interested individuals to follow the twins' routine. The twins are public figures virtually, accompanied by their caregiver (brother) on these platforms. By sharing their experiences, the family aims to raise awareness about HGPS and provide insights into the daily lives of individuals living with this rare genetic disorder.

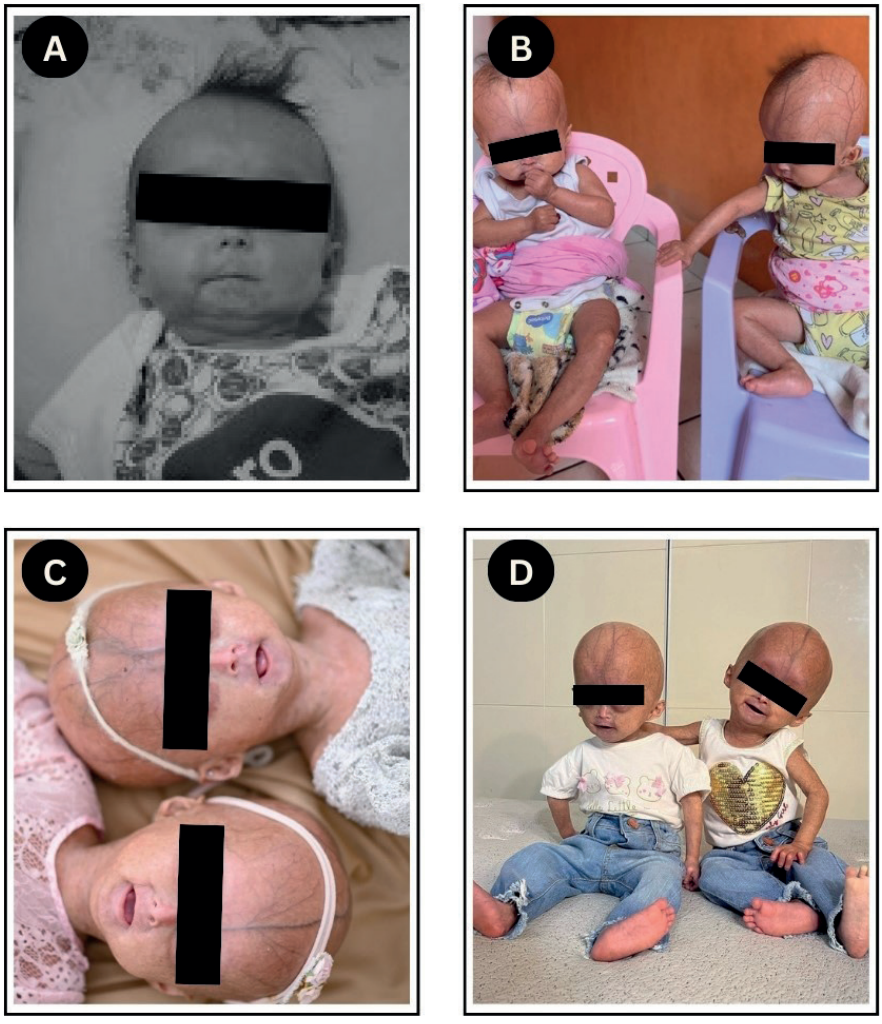

Figure 1. Progression of alopecia and syndromic characteristics in female monozygotic twins affected by HGPS.

(A) One of the twins at an early age with only a few phenotypic manifestations. The child still has preserved hair at 12 months of age, indicating an early phase in the development of the syndrome. **(B-C)** Both twins are at a later stage of development (15 months of age). They exhibit changes characteristic of HGPS, including vascular alterations, noticeable hair loss, and low weight. These manifestations highlight the progression of the disease over time. **(D)** HGPS Twins in February 2024 at three years old with the syndrome's full range of phenotypic characteristics evident.

HGPS: Hutchinson-Gilford Progeria Syndrome Hutchinson-Gilford Progeria Syndrome

CONCLUSION

This is the first confirmed case of progeria in female twins in the world, an extremely rare syndrome with premature cellular aging as a hallmark. The diagnosis is made according to clinical aspects and confirmed by laboratory tests from the genetic material, which are very difficult in some poor and underdeveloped regions. There is currently no cure, but there is a drug treatment, approved in 2020 by the FDA, capable of delaying the impacts of the syndrome, which therapy can be supported by the Progeria Research Foundation (PRF).

Ethical approval

This study has been approved by the Federal University of Roraima (approval date 01.08.2023, number 99168103204). Written informed consent was obtained from the participants.

Author contribution

All authors collected information and analyzed the results. All authors also contribute to writing and reviewed and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Case Report

Management of avulsion-induced external root resorption of permanent maxillary left central and lateral incisors - a one-year follow-up case report

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ABSTRACT

The presented case elicits the successful management of external root resorption in an avulsed permanent central and lateral incisor due to failure to initiate root canal treatment (RCT) at the right time and prolonged splinting. A 13-year-old female child reported a complaint of pain in her upper anterior teeth region. The child gave a history of avulsed 21 and 22, which was replanted. External inflammatory root resorption in (21 and 22) and peri apical abscess (11) was noted in the radiograph. External inflammatory root resorption was treated endodontically with corticosteroid-antibiotic medicaments and obturated with mineral trioxide aggregate (MTA). Obturation was done only after restoring tooth stability and symptom resolution. Replacement resorption was noted radiographically during the follow-up visit. This case underscores the importance of meticulous endodontic care and adherence to treatment timelines, providing valuable insights for clinicians managing similar challenging cases.

Keywords: Tooth avulsion, incisor, root resorption, mineral trioxide aggregate, intracanal medicament

INTRODUCTION

Dental avulsion is defined as the total displacement of the tooth from its alveolar socket. This phenomenon is observed in 0.5% to 16% of all dental traumas, with the permanent maxillary central incisor being the predominantly affected tooth in instances of dental avulsion.[1] The ideal course of action for maximizing a tooth's survival after avulsion is prompt replantation during the first 20–30 minutes of the damage. However, this may not be possible in all situations where prompt management immediately may be compromised. In these situations, the pulp and periodontal ligament (PDL) complexes' ability to recover is significantly influenced by the storage media utilized, the length of time the tooth is left outside the socket (the extra-alveolar period), and how it is treated during this time. Ultimately, these aspects play a pivotal role in determining the prognosis of the treatment.[2] Immediate replantation leads to various pulpodentinal responses. These responses include the formation of various reparative dentines, such as regular tubular and irregular dentin. Osteodentin, irregular immature bone, or lamellate bone is also included in this spectrum. In some instances, there might be indications of internal resorption, and pulp necrosis may occur in more severe cases.[3] Similarly, PDL healing can take a variety of paths, including healing with normal PDL, replacement resorption, external inflammatory resorption, or surface resorption.[4] The guidelines for prompt treatment and

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management of avulsed permanent teeth have been given by The International Association of Dental Traumatology (IADT). Generally, splinting is done for two weeks if no associated alveolar bone fracture is seen. If so, the period of splinting may be prolonged to 4-6 weeks. Endodontic management of the avulsed tooth, if planned intra-orally after replantation, should be initiated within two weeks of replantation.[5] The postponement of the commencement of Root Canal Treatment (RCT) can impact the vitality of the remaining PDL, as the necrotic pulp has the potential to release toxins through different pathways, including lateral canals and the apical foramen.[6]

The primary aim of this article was to document and visually depict the successful management of avulsed permanent teeth after one year of replantation with external root resorption due to prolonged splinting and failure to initiate RCT. Furthermore, the case report explains the successful management of severe external inflammatory root resorption and follow-up, drawing upon a meticulous review of pertinent literature in the field.

CASE REPORT

Patient information

A 13-year-old female patient reported to the Department of Pediatric and Preventive Dentistry with the chief complaint of pain in the upper anterior teeth region. The patient gave a dental history of avulsed maxillary left permanent central (21) and lateral incisor (22) two years back and luxation of the maxillary right permanent central incisor (11) due to a road traffic accident. Both the teeth (21,22) were carried in the dry environment within 1 hour, and the patient had undergone replantation treatment previously elsewhere for avulsed 21 and 22 two years back, followed by splinting at the time of replantation itself. There were no dental records of previous pre-treatment status and management of root surface before replantation. The patient was currently symptomatic with pain and no history of swelling previously. No relevant medical or family history was present.

Clinical and radiographic findings

On further intraoral clinical examination, it was noted that splinting was present for the past two years in the maxillary anterior teeth region from maxillary right permanent canine (13) to maxillary left permanent canine (23) in the buccal surfaces (Figure 1A). The patient had tenderness on percussion in relation to 11, 21 and 22. Mild dis-coloration was present in 21 and 22. Periodontal probing depths were normal. Radiovisiography (RVG) revealed a radiolucent area involving the root surface and surrounding bone in relation to 21 and 22. Periapical radiolucency with widening of PDL space was present in relation to 11 (Figure 2A). Thus, external inflammatory root resorption was present in relation to 21 and 22, and periapical abscess in relation to 11 was noted.

Diagnostic assessment

Following clinical and radiographic examination, the pre-existing splint was removed to assess the vitality and mobility if present. Electrical and thermal pulp testing gave no response. 21 and 22 exhibited grade 2 and grade 1 mobility, respectively.

Timeline

Treatment was planned for a period of 6 to 12 weeks, from the start of access cavity preparation to obturation.

Case management

Therapeutic intervention

Endodontic management of 11,21 and 22 was planned. Before the commencement of the treatment, the prognosis of

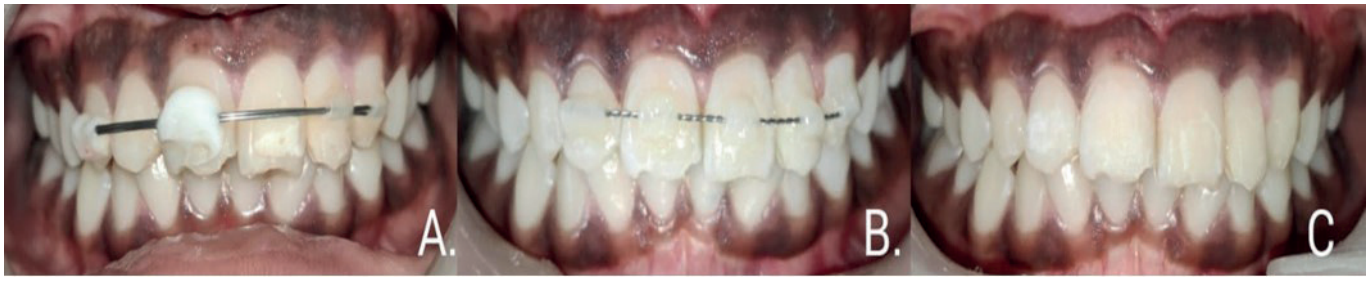

Figure 1. Clinical images: **A.** Pre-existing splint extending from 13 to 23 done two years back elsewhere without initiation of root canal treatment and failure to remove the splint at the appropriate time. **B.** Pre-existing splint was removed, and a flexible splint was placed from 13 to 23 for stabilization. **C.** Clinical image at the end of 12 months with no mobility or discoloration.

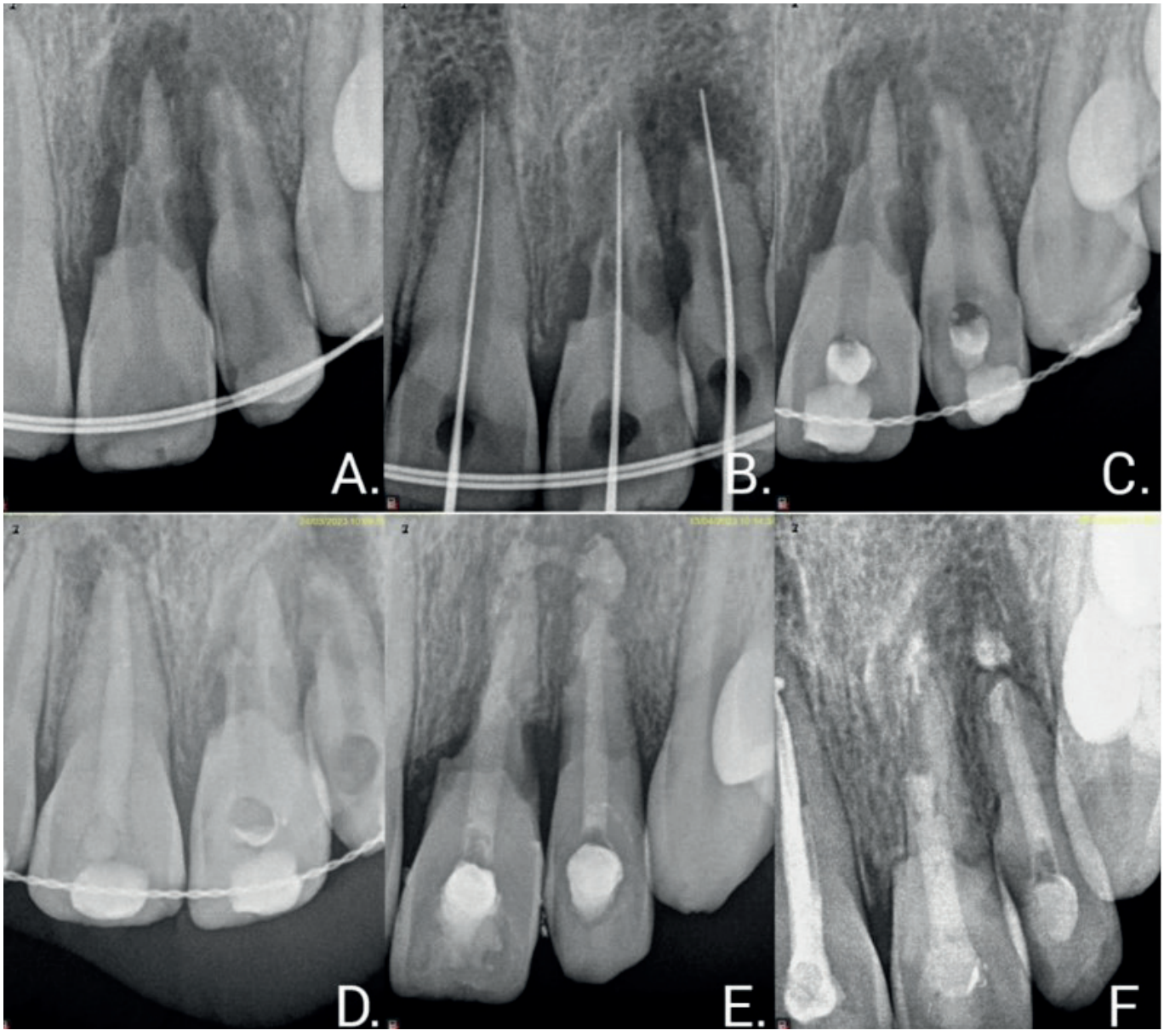

Figure 2. Radiographic image: **A.** Pre-operative radiograph **B.** Working length determination **C.** Intracanal medicament placement with CaOH placement in relation to 11 and a combination of Triamcinolone acetonide, doxycycline, and metronidazole placed in relation to 21 and 22 **D.** Splinting at the end of 14th day. **E.** After obturation. **F.** 12 months follow up.

endodontic management of 21 and 22 was explained to the patient and the parent due to severe external inflammatory root resorption, and written consent was obtained. Access cavity preparations were done in 11, 21, and 22. All three teeth were found to be non-vital with no purulent exudate from the canals. Canals were completely derided and irrigated using saline. Working length was determined for all three canals using 25mm 20, 40, and 35 size K file (MANI ® Kfiles Tochigi, Japan) (Figure 2B), and complete Biomechanical preparation was done in 11 using ProTaper NiTi rotary instruments (Dentsply Maillefer, Ballaigues, Switzerland). However, the conventional step-back technique was used with minimal preparation in 21 and 22 to preserve the remaining tooth structure. 1.25% sodium hypochlorite (Vensons India, Bangalore, India) was used for irrigation between instrumentation and finally rinsed with saline. The canals were dried using paper points, and Calcium hydroxide (Rc Cal, Prime Dental Pvt Ltd., Maharashtra, India) intracanal medicament was placed in 11 and temporized with Intermediate Restorative Material (IRM) (Dentsply Sinora, Charlotte, North Carolina, USA). A combination of triamcinolone acetate (Kenacort 0.1% buccal

paste, Abbott Healthcare Pvt. Ltd, Mumbai, India) doxycycline 100 mg (DOxy-T, Frankel Health care Pvt Ltd., Mumbai, India) and metronidazole 400 mg (Aristogyl, Aristo Pharmaceuticals Pvt Ltd., Mumbai, India) paste was prepared and was used as an intracranial medicament in 21 and 22 followed by temporization with IRM (Figure 2C). A flexible splint was placed from 13 to 23 for stabilization (Figure 1B). The patient was recalled after 14 days and was assessed clinically and radiographically (Figure 2D). The patient was completely asymptomatic, and the splint was removed. Mobility was reduced to grade 1 in 21 and 22. Radiographically, no changes were observed. Thus, the intracranial medicament was left undisturbed for six weeks. At the end of the sixth week, the intracanal medicaments in 21 and 22 were changed to CaOH. At eight weeks, the canals were re-entered and completely derided of their content. Canals were irrigated using 1.25% sodium hypochlorite followed by saline. Canals were dried, and 11 were obturated with 30 sizes 6% Gutta Percha (Dentsply Maillefer, Ballaigues, Switzerland) and AH plus sealer (Dentsply DeTrey, Konstanz, Germany). In 21 and 22, canals were dried using paper points, and mineral trioxide aggregate (MTA) (Angelus Dental, Londrina, Brazil) was placed at the apex till the predetermined apical stop (Figure 2E). The remaining part of the canals, both in 21 and 22 were obturated using MTA. After confirming the absence of voids in the obturation of 11, 21, and 22 using multiple-angle RVG, the access cavity was filled with type II Glass Ionomer Cement (GIC).

Follow-up and outcome

At the end of the 12th week, GIC was changed to composite restoration, and 21 and 22 were firm and free of mobility. Both post-operatively and intra-operatively, the patient was informed about the poor prognosis of the teeth. The child was asked to avoid biting hard food onto the front tooth region and was instructed to take the food to the back and chew. Maintain a good oral hygiene by gently brushing and flossing. The patient was asked to avoid habits like nail-biting, chewing on pens, or using teeth to open packages. Properly Scheduled follow-up appointments to monitor the healing process and assess the stability of the tooth. The patient was periodically followed up at the 3rd, 6th, and 12th month. At the end of 12 months (Figures 1C and 2F), the patient was completely asymptomatic, and radiographic evidence of bone deposition was noted around 21 and 22, indicating replacement resorption and complete periapical healing with the formation of hard tissue around 11,21 and 22.

DISCUSSION

Injuries to the periodontal ligament (PDL) can trigger initial resorption cavities on the tooth surface. When coupled with exposed dentinal tubules, necrotic pulp, local toxins, and contamination, this process amplifies inflammatory resorption on the tooth surface, potentially advancing to the root canal and penetrating the dentinal tubules. Without intervention, heightened microbial virulence can lead to complete root resorption within a few months. Observable changes may manifest as early as 6-10 years; however, endodontic intervention at the right time can shift the condition from inflammatory resorption to replacement resorption. Radiographically, inflammatory resorption appears as cavities on the root surface with accompanying bone excavation. The affected tooth will exhibit looseness, extrusion, and sensitivity to percussion, accompanied by a dull note.[7,8] Prolonged splinting of avulsed teeth (>1 year) may lead to root resorption, impaired periodontal health, and compromised tooth stability.

Due to their biological properties, Corticosteroids can effectively suppress the body's inflammatory response. Consequently, they alleviate or eliminate pain associated with inflamed tissue.[9] According to the IADT guidelines, when opting for a corticosteroid or a combination of corticosteroid and antibiotic as an intracanal medicament for its anti-inflammatory and anti-resorptive properties, it is recommended to administer it promptly or shortly after the tooth's replantation. The medicament should be left in place for a minimum of 6 weeks.[5] Triamcinolone exhibits a controlled release pattern as it diffuses through the dentinal tubules and cementum, eventually reaching the surrounding periapical and periodontal tissues. The release profile is characterized by an initial burst, with approximately 30% of the medication being dispensed within the first 24 hours. Subsequently, the remaining seventy percent of the drug is steadily released over a more extended period, spanning 14 weeks. This sustained release mechanism allows for a prolonged therapeutic effect, contributing to Triamcinolone's anti-inflammatory and anti-resorptive actions in the targeted dental and periodontal regions.[10] Corticosteroids, along with antibiotics, have been known to have anti-inflammatory properties and reduce microbial load.

Boukpessi et al.[11] successfully treated traumatized immature permanent teeth by applying an MTA plug. Additionally, Al-Kahtani[12] demonstrated successful management of avulsed immature permanent teeth through reimplantation, followed by obturation with MTA. Kirakozova et al.[13] analyzed the impact of intracanal corticosteroids following delayed replantation. The findings indicated that corticosteroid treatment proved effective in addressing external root resorption. This suggests the potential therapeutic efficacy of corticosteroids in mitigating adverse outcomes associated with delayed replantation of teeth. However, corticosteroids may cause local effects like delayed wound healing and systemic effects, including

immunosuppression. Antibiotics can lead to microbial resistance and adverse drug reactions, such as allergies and gastrointestinal disturbances. In the present case report, failure to initiate endodontic management within two weeks of replantation, along with prolonged splinting for more than one year had led to the development of external inflammatory root resorption due to persistent immobilization and necrotic 21 and 22. Though the tooth was indicated for extraction, an attempt was made to arrest the resorption and endodontically manage the mobile teeth. With the arrest of inflammatory resorption, the surrounding bone can undergo progressive, transient, or internal tunneling replacement resorption depending on the amount of remaining vital PDL.[14] In the present case, progressive replacement resorption was noted in 21, and transient replacement resorption was noted in 22.

CONCLUSION

In summary, this case report illustrates the successful management of avulsed permanent teeth with external root resorption, emphasizing the crucial role of timely endodontic intervention. Despite a history of dental trauma, prolonged splinting, and delayed treatment initiation, a comprehensive approach involving corticosteroid-antibiotic medicaments and MTA obturation led to restored tooth stability, symptom resolution, and favorable radiographic outcomes after 12 months. This highlights the potential for successful outcomes in challenging cases through meticulous endodontic care and adherence to treatment timelines.

The approach employed here serves as a valuable reference for clinicians facing similar cases, emphasizing the potential for favorable results.

Ethical approval

The case was managed according to the guidelines of International Association of Dental Traumatology. Ethical clearence is not required as it is not a prospective research paper. Written and informed consent was obtained from the participant and parent.

Author contribution

Surgical and Medical Practices: PB, DS, SE; Concept: PB, DS, SE; Design: PB, DS, SE; Data Collection or Processing: PB, DS, SE; Analysis or Interpretation: PB, DS, SE; Literature Search: PB, DS, SE; Writing: PB, DS, SE. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Case Report

Life-threatening amlodipine and irbesartan poisoning in two adolescents: Extracorporeal life support is life-saving

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ABSTRACT

Calcium channel blockers (CCBs') and angiotensin receptor blockers (ARBs') are widely used in clinical practice and are easily available. Intoxication with these drugs results in life-threatening deep vasoplegic shock, making them particularly dangerous, especially for children. Here, we report two patients who ingested amlodipine and irbesartan for suicidal attempts and were unresponsive to all conventional treatments. They were placed on venoarterial extracorporeal membrane oxygenation (VA-ECMO) and hemodynamically stable immediately after extracorporeal life support (ECLS). Patients were successfully decannulated and extubated. CCB and ARB poisoning that are resistant to medical therapy can be treated by ECLS successfully.

Keywords: Amlodipine poisoning, irbesartan poisoning, vasoplegic shock, extracorporeal life support, children

INTRODUCTION

Amlodipine is a dihydropyridine calcium channel blocker (CCB) that blockades slow L-type calcium channels in vascular smooth muscle and pancreatic beta cells. Intoxication with amlodipine results in vasoplegic shock and myocardial depression. Sartans are antagonists of angiotensin-1 (AT1) receptors of angiotensin II (AII). Angiotensin receptor blocker (ARB) toxicity is associated with hypotension, acute renal failure, and deep hypokalemia. The elimination half-life of both drugs (31-46 hours for amlodipine and 11-15 hours for irbesartan) is prolonged in case of poisoning.[1,2]

Especially CCB overdoses are associated with high morbidity and mortality secondary to multiorgan dysfunction and catecholamine-refractory hypotension. The current medical treatments based on expert opinion and case reports aim to provide organ support. In patients with cardiogenic and distributive shock caused by massive overdoses of CCBs and ARBs, venoarterial extracorporeal membrane oxygenation (VA-ECMO) has the potential to improve the patient's hemodynamic status.[1-3]

CASE 1

A fifteen-year-old girl ingested amlodipine and irbesartan combined preparation 325 mg of amlodipine (6.5 mg/kg) and 9750 mg of irbesartan (195 mg/kg) for a suicidal attempt. She was lethargic and hypotensive on admission (60/40 mmHg). Mean arterial pressure was (MAP) 46 mmHg. She was limp with

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filiform pulses, hypothermic (35°C), and a capillary refill time of 4 seconds. Heart rate was 110 beats/min; respiratory rate was 25/min. The patient was intubated for increased work of breathing.

Despite she was started on high doses of norepinephrine (1.2 mcg/kg/min), epinephrine (1.2 mcg/kg/min), dopamine (15 mcg/kg/min), and terlipressin (25 mcg/kg/dose) remained hypotensive. Hyperinsulinemia/euglycemia therapy (infusion rate titrated up to 1 IU/kg/hour with target glucose level 100-200 mg/dL), calcium gluconate (1 mEq/kg/hour, target iCa^{++} level >1.5 mmol/L), 20% lipid emulsion (1.5 mL/kg bolus, then an infusion of 0.25 mL/kg/min for 30–60 minutes), and methylene blue (MB) (1mg/kg/hour infusion after 2 mg/kg loading dose) were started. A transthoracic echocardiograph showed left ventricular ejection fraction (LVEF) was 40%.

The patient was placed on VA-ECMO 10 hours after pediatric intensive care unit (PICU) admission. An arterial cannula (17 fr) was placed in the left femoral artery with a 12 fr distal perfusion cannula. The venous side of the circuit was inserted in the right femoral vein (21 fr). Heparin infusion started at 10 IU/kg/hour after a single 30 IU/kg bolus with a target activated clotting time (ACT) of 180-220 seconds. At 2nd hour of therapy, rapid improvement was observed in hypotension, and lactic acidosis resolved on the second day. Vasopressors were weaned on the second day of ECLS.

An acute ischemia developed at the arterial cannulation side (left foot) on the 3rd ECLS day. Doppler ultrasonography showed arterial thrombosis (left main and external iliac artery), the patient's hemodynamics were stable, and ECLS was terminated with thrombectomy at the 76th hour. The patient was extubated on day 4. Systemic heparinization continued with low molecular weight heparin (LMWH) 40 mg/day for ten days. The patient received arterial thrombosis prophylaxis with aspirin (3mg/kg/dose once daily). Enteral nutrition with a nasogastric tube is tolerated on the third day, and she started oral feeding on the seventh day. She was discharged from the PICU to an inpatient psychiatry unit 14 days later.

CASE 2

A 16-year-old girl with a history of depression attempted suicide with approximately 280mg of amlodipine (4,7 mg/kg), 16800mg of irbesartan (280 mg/kg), and 700mg of hydrochlorothiazide (11,67mg/kg). Upon presentation to the PICU at the 6th hour of ingestion, she had hypotension with a blood pressure of 75/40 mmHg (MAP 51 mmHg). The heart rate was 138 beats/min, and the respiratory rate was 28 /min. Laboratory tests revealed elevated serum creatinine of 2.3 mg/dL and lactic acidosis (pH 7.24, lactic acid 8.4mmol/L).

A transthoracic echocardiograph showed normal biventricular function. Three liters of crystalloid were given, and she was started on high doses of norepinephrine (1.5 mcg/kg/min), epinephrine (1.2 mcg/kg/min), and terlipressin (25 mcg/kg/dose). She received a twice bolus of 20% lipid emulsion (1.5 mL/kg). Hyperinsulinemia/euglycemia therapy (HIET), calcium gluconate (1 mEq/kg/hour, target iCa^{++} level >1.5 mmol/L), and MB (1mg/kg/hour infusion after 2 mg/kg loading dose) were started. Shortly the patient was intubated for increased work of breathing and a decrease in Glasgow Coma Scale (GCS). Despite high-dose vasopressors, urine output and lactic acidosis were worsening, and we initiated VA-ECMO approximately eight hours after arrival. The patient was placed on VA-ECMO at the bedside, with a 21 Fr right femoral vein and a 19 Fr left femoral artery with a distal perfusion cannula. Heparin infusion started at 10 IU/kg/hour after a single 30 IU/kg bolus with a target ACT of 180-220 seconds. Following the initiation of VA-ECMO, we observed a gradual improvement in blood lactate concentration and metabolic acidosis, and we simplified our management approach by discontinuing hyperinsulinemia-euglycemia therapy, and lipid emulsion.

An acute ischemia developed at the arterial cannulation side (left foot) on the second ECLS day. Doppler ultrasonography showed arterial thrombosis, and the patient underwent a thrombectomy. The patient was decannulated on day three and extubated on day 4. His vasopressor requirement improved steadily after admission, and by day 6, she was weaned off all vasopressors. He was discharged to an acute rehab facility on day 18.

DISCUSSION

CCB and ARB overdose can be fatal due to refractory peripheral vasodilation, myocardial depression, acute renal failure, and deep hypokalemia. Initial stabilization consists of providing systemic management, including airway, respiratory, and circulatory control. A recent review about symptomatic CCB poisoning recommends fluid repletion, IV calcium, HIET, adrenergic agents according to the type of shock, and atropine for adult patients. In patients who are refractory to the first-line treatments, second-line therapies are incremental doses of HIET, IV lipid-emulsion therapy (ILE), and VA-ECMO in case of refractory shock.[4]

Calcium replacement is the most important step in CCB poisoning. Administration of 10% calcium gluconate 30–60 mL every 10 –20 minutes or an infusion at 0.6–1.2 mL/kg/hour is generally effective. CCB poisoning leads to insulin resistance, so insulin therapy is recommended with 0.5–2 U/kg/hour as an initial dose. Doses up to 10/U/kg/hour are supported only

by case series. It is supposed that ILE provides an energy source to myocytes and compartmentalizes xenobiotics into the lipid phase. A twice bolus of lipid emulsion 20% 1.5 mL/kg, then an infusion of 0.25 mL/kg/min for 30–60 minutes is suggested. MB resolves vasoplegia by reversing CCBs' effects, decreasing intracellular cyclic guanosine monophosphate (cGMP), scavenging nitric oxide (NO), and inhibiting NO synthesis. Currently, there is not enough evidence to recommend the routine administration of MB in vasodilatory shock.[4]

In studies conducted in our country with patients admitted to PICU due to drug poisoning, the frequency of CCB poisoning was reported as %1.2-1.7.[5,6] Among these patients, mortality was reported in one patient who presented with CCB and ARB combined overdose. Combined overdoses of dihydropyridines with ARBs/ACEIs caused more significant hypotension and required more hemodynamic support than overdoses of dihydropyridines alone.[7] In these scenarios, there is a notable increase in cardiac output due to the extensive drug-induced vasodilation and the requirement of massive doses of vasoactive medications to sustain adequate end-organ perfusion pressure.

Several centers have reported the use of ECLS to treat distributive shock following CCB overdose and a combined amlodipine, lisinopril, and hydrochlorothiazide overdose with good results.[8-10] ECMO has been shown to have reasonable outcomes for advanced CCB poisoning, mostly in the adult population. However, high-flow ECMO applications can be quite challenging, especially in pediatric patients, due to the small diameters of arteries and veins.

A systemic review that aimed to describe the mortality and the complications observed with ECMO use in patients with CCB overdose reported that 26 patients (11.4%) had extremity complications secondary to ischemia.[11] Sorabella et al. reported four pediatric CCB cases who underwent central ECMO cannulation.[12] These patients aged between 12 and 17 years had a rising lactate level and profoundly elevated VIS score at the time of ECMO cannulation. Similar to our cases, they initiated VA-ECMO within 8 hours of admission in three patients. In the pediatric population, providing high-flow ECMO support with peripheral cannulation is technically difficult because of the smaller vein diameter. They concluded that central ECMO support in cases of massive vasodilatory shock following CCB overdose is safe and effective. Both of our cases had leg ischemia due to peripheral cannulation. Although it did not cause morbidity in long-term follow-up, it caused early ECMO termination in one patient. In these patients, the choice of peripheral or central ECMO should be made by making a patient-specific benefit-loss calculation.

In conclusion, VA-ECMO can be a life-saving treatment modality for individuals experiencing severe cardiogenic and distributive shock resulting from substantial overdoses of CCBs and ARBs. Patients with CCB and ARB overdose should be referred to ECMO centers after first-line medical management. Although complications related to peripheral cannulation are frequently observed, it is possible to reduce the rate of undesirable outcomes with close monitoring and appropriate treatments.

Informed consent

Written informed consent was obtained from the patients for the publication of the case report.

Author contribution

Surgical and Medical Practices: GK, İE, KC, ONT; Concept: GK, PYÖ; Design: PYÖ, BK; Data Collection or Processing: GK, SÇ; Analysis or Interpretation: GK, PYÖ; Literature Search: GK, KC, SÇ ; Writing: GK,PYÖ. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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