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Original Article

Peer Bullying in the Preadolescent Stage: Frequency and Types of Bullying and the Affecting Factors

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ABSTRACT

Aim: This study was conducted to determine the types, frequencies and the affecting factors of peer bullying among 6th, 7th, and 8th grade students of secondary schools in a city center in Cappadocia.

Materials and Methods: A total of 3.059 students were attending secondary schools in a city center and this study sample consists of 1.288 students. Prior to the study, approval from the ethical council and institute, as well as written consent from students and their families were obtained. Data were collected via individual information forms and the Traditional Peer Bullying scale by the researcher through face-to-face interviews and the data obtained were evaluated by chi-square, single, and multiple logistic regression analysis.

Results: It was determined that the mean age of the students was 12.81±0.93 years, of them 51.7% were girls, 12.0% did bullying, 15.9% were exposed to bullying, 52.1% were exposed to verbal bullying, and 13.4% were exposed to physical bullying. Multiple logistic regression revealed that the most important factors affecting the bullying of other students were family structure, attitude towards school, and gender; those factors affecting exposure to bullying were attitude toward school, body mass index, and economical status. As the age of the students increased by one year, the likelihood of bullying increased by 1.2 times. Boys were bullied 1.5 times more than girls, and the students of separated parents were bullied 2.7 times more than those whose parents stayed together ($p<0.05$).

Conclusion: As bullying within schools is an important problem, it may be advisable to take into account the factors affecting bullying (age, gender, economic situation, family structure, attitude toward school, etc.) when conducting studies to prevent bullying in schools.

Keywords: Peer bullying, preadolescent stage, school nursing, school health

Introduction

Bullying, which is an important part of violence in school, is a common problem all over the world (1-6). School bullying is defined as the disruptive behavior of one or more students toward another student or other students with regularity and purpose and without any provocation (7). Bullying is classified into physical (hitting, pushing, spitting), verbal (swearing, assigning nicknames, insulting), relational/social aggression (e.g. social exclusion, rumour spreading, ostracizing and exclusion from games), and cyber bullying (bringing discomfort to others through the use of cell phones and the internet, humiliation) (8-10).

Studies conducted in various countries revealed a bullying prevalence of 8%-75% in schools (5,11-17). In a

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meta-analysis on bullying prevalence with an overall sample of 335.519 youth (12-18 years), the authors found a mean prevalence of 35% for traditional bullying (16). Of those students who reported being bullied, 13% were made fun of, called names, or insulted; 12% were the subject of rumors; 5% were pushed, shoved, tripped, or spat on; and 5% were excluded from activities on purpose (17). As the result of the studies in Turkey, it has been determined that the bullying prevalence was between 30-75% (18-23).

Bullying can affect the psycho-social health of school-aged children, and this effect may continue throughout the child's life (5,6,14,24-26). Children who are exposed to bullying report problems such as emotional trauma, a negative impact on school life, syndromes such as depression and anxiety, anxiety spectrum disorders such as social phobia and post-traumatic stress disorder, behaviors such as psychotic symptoms and somatic symptoms (e.g., stomach ache, headaches, dizziness, and back pain), sleep disorders, and physical damage in the short term (16,26-30).

When considering the adverse effects of bullying on the personality of students in the long term, low self-esteem, problems in interpersonal relations, and an increase in depression levels have been reported (24-27,31). Bullying exerts negative effects not only on those who are bullied but also on those who bully (5,31,32). The school performance of bullies and their success in their future lives has been determined to be low (6,32). The ability to establish and improve positive relationships with others in their adult years was negatively influenced by chronic bullying, and bullies tended to collect more criminal records than their non-bully counterparts (32,33).

Bullying is clearly an important problem based on a number of studies (1,2,5,11,13,14,16,25,34-36), and the need for preventive programs to be developed quickly has been emphasized (37-39). This problem, which is seen especially among early adolescents (34,36), is an issue that health professionals, such as school nurses, psychologists, psychology consultants, and physicians, and families should address (1,28,40). Besides collaborating with other disciplines, school nurses also play an important role in preventing bullying (1,4,6,41) through primary, secondary, and tertiary precautions (14). School nurses are health professionals who prevent the occurrence of bullying events and provide coordination of care in the process of occurrence, evaluate the effects of bullying on the victim and the bully and also plan and maintain their care (4,41).

It is important to know individual, familial and environmental risk factors related to bullying, to organize training programs on bullying and to ensure participation of students, families, teachers and school staff in these programs (6). Adolescents' tendency to violence; age, gender, socio-economic status, family structure and characteristics have an important role (4). Determining the characteristics of the bullying situation is essential in preventing it.

Therefore, this study was conducted to determine the types and frequencies of peer bullying, as well as the factors that affect bullying, among students in 6th, 7th, and 8th grade classes at secondary schools in a city center of Cappadocia.

Materials and Methods

This study was conducted in a cross-sectional design. Literature showed that bullying is mostly observed in 6th, 7th and 8th grade students of primary school (40,42). There were a total of 3.059 students in the 6th, 7th, and 8th grade classes of 11 secondary schools in a city center of Cappadocia. A required study sample of 1.200 was calculated by considering a frequency of 40% (18) with 95% probability (alpha=0.05) and 80% power; thus, 1.288 students were recruited to participate in this work. The students to be sampled were rated according to schools, grades and gender. According to this, a random batch was determined from the 6th, 7th and 8th grades of each school. According to the class list in the selected batch, the students were numbered by using a random numbers table. A questionnaire was applied to selected students in a class. The sample of students representing the school and the number of classes are given in Table I.

Ethics

The study was approved by the Ethics Committee of Nevşehir Hacı Bektaş Veli University (approval number: 2014/01.01). Written consent from the Provincial Directorate for National Education, and written and verbal consent from the students and their families were obtained. The researchers made necessary explanations before the study.

Data Collection

The researchers made all necessary explanations before the study. Data were collected using an individual information form, which includes the socio-demographic characteristics of the students and their families, and the Traditional Peer Bullying scale (TPBS) via face-to-face meetings. The duration of the survey application was determined as one lesson time (40 minimum) for each

class by the researchers. The students, teachers and school staff were provided with counselling on bullying.

Measures

Individual Information form

The individual information form was developed from literature sources and included 26 questions on the socio-demographic characteristics pertaining to the students such as school studied at, age, gender, grade, parental education status, socio-economic status, number of siblings, attitude toward school and their knowledge about bullying and exposure to bullying. In this study, students' attitude toward school was determined using the closed-ended question "Do you like school?". Income status of students was determined using the question "How do you see the economic situation of your family?".

Traditional Peer Bullying scale

The TPBS that was modified by Burnukara and Uçanok (19) is composed of two parallel forms that aim to determine the prevalence of both exposure to peer bullying and determining the kinds of bullying attitudes of adolescents in the school environment over the prior 6 months. This scale is composed of 31 items evaluated via a 4-point Likert scale. In each item, "a" measures the victim experience and "b" measures the bully experience of adolescents. The scale includes six sub-dimensions of verbal, relational, physical, attack with personal objects, social exclusion, and threats/intimidation.

In this study, students were divided in three groups, as bully, victim and bully-victim, according to their scores from the TPBS. Adolescents with scores above the standard deviation of mean peer bullying practice scores (scores received from the bully form) were bullies, those who incurred scores above the standard deviation of mean peer bullying exposure scores (scores from victim form) were victims, and those with scores above the standard deviation of means of both peer bullying practice and peer bullying exposure scores (scores received from both bully and victim forms) were bully/victims. In the study of Burnukara and Uçanok (19), Cronbach's alpha of victim form reached 0.90 but totalled 0.91 for the bully form in the TPBS.

In this study, Cronbach's alpha was found to be 0.92 for the victim form and 0.89 for the bully form.

Statistical Analysis

Independent variables of the study were as follows; age, gender, economic status, body mass index (BMI) of students and socio-demographic characteristics such as age, gender, occupation and education status of parents. The dependent variables of the study are as follows; the scores obtained from the TPBS. Chi-square, single, and multiple logistic regression analyses were applied, and $p<0.05$ was accepted to indicate a statistically significant difference.

In this study, BMI was calculated [body weight (kg)/height squared (m^2)] after researchers measured the weight and height of the adolescents. The growth curves developed by Neyzi et al. (43) for Turkish children were used in the assessment of BMI. BMI in the 5-14.9th percentile was evaluated as slim, BMI in the 15-84.9th percentile was considered as normal weight, the 85-94.9th percentile was

Table I. Number of students representing schools and classes

School Name	6th grade		7th grade		8th grade		Total
	Male	Female	Male	Female	Male	Female	
Toki 125. Yıl Ortaokulu	24	23	21	23	16	10	117
Mihriban Emin Günel Ortaokulu	23	26	23	26	26	25	149
75. Yıl Ortaokulu	27	40	30	30	35	23	185
Damat İbrahim Paşa Ortaokulu	38	47	35	39	28	28	215
23 Nisan Ortaokulu	11	10	11	12	10	16	70
Gazi Ortaokulu	10	4	3	9	7	9	42
H. Lütfü Pamukcu Ortaokulu	14	25	18	24	22	29	132
İstiklal Ortaokulu	23	22	23	23	28	23	142
M. Gülen Ortaokulu	7	11	6	16	10	13	63
Atatürk Ortaokulu	23	15	11	13	13	12	87
Cumhuriyet Ortaokulu	13	13	20	10	14	16	86
Total	213	236	201	225	208	204	1.288

accepted as overweight, and those with BMI over the 95th percentile were considered as obese.

Results

Among the participants, 34.9% were in the 6th grade class, 37.6% were 13 years old, 52.2% were underweight, and 57.5% had a high socio-economic status. About 92% of the students lived with their parents, 87.3% liked school, and 96.2% did not participate in absenteeism without reason (Table II).

Among the participants, 12% were bullies and 15.9% were exposed to bullying (victims). When they experienced bullying, 23.1% of the students stayed calm and ignored their bully, 16.9% warned their bully, 16.8% reported the incident to the school management and their teachers, and 12.1% responded in the same manner (Table III).

According to the subscales, 52.1% of the students had been bullied verbally while 13.4% had been bullied physically (Table III).

Boys, older students, and those who have parents living separately were more bullied than other students ($p<0.05$), and students who were overweight and had a low socio-economic status tended to be exposed to more bullying than their counterparts ($p<0.05$) (Table IV).

The most important factors affecting whether students bullied their peers were family structure [odds ratio (OR) 2.67, 95% GA 1.47-4.83), attitude toward school (OR 1.86, 95% GA 1.19-2.13), gender (OR 1.47, 95% GA 1.02-2.09), and age (OR 1.21, 95% GA 1.00-1.47); ($p<0.05$), and the differences observed were statistically significant. As the age of the students increased by one unit (year), the frequency of bullying situations increased by 1.2 times ($p=0.049$). Boys were bullied 1.5 times more than girls ($p=0.039$), and students who did not like school were bullied 1.9 times more than those who did ($p=0.007$). Students whose parents had separated were bullied 2.7 times more than those whose mothers and fathers were together ($p=0.001$) (Table V).

The most important factors affecting exposure to bullying were attitude toward school (OR 2.80, 95% GA 1.90-4.13), BMI (OR 2.29, 95% GA 1.27-4.16), economic status (OR 1.51, 95% GA 1.09-2.09), and age (OR -0.74, 95% GA 0.63-0.88) ($p<0.05$), and the differences observed were statistically significant. As the age of the students decreased by one unit (year), the risk of bullying increased by 0.7 times ($p<0.001$), and students who were overweight were exposed to bullying 2.3 times more than those who were not ($p=0.006$). Students who did not like school were exposed to bullying 2.8 times more than those who did ($p<0.001$), and students with a low socio-economic background were exposed to bullying 2.5 times more than those with a high socio-economic status ($p=0.004$) (Table V).

The threats/intimidation behaviors of students were mostly affected by gender (OR 2.71, 95% GA 1.79-4.09), and attitude toward school (OR 1.98, 95% GA 1.23-3.19) ($p<0.05$). Also, the most important factor affecting verbal

Table II. The introductive characteristics of the students (n=1.288)

Introductive Characteristics	n	%
Class level		
6th class	449	34.9
7th class	426	33.1
8th class	413	32.0
Gender		
Girl	667	51.8
Boy	621	48.2
Age		
11 years	100	7.8
12 years	379	29.4
13 years	484	37.6
14- 5 years	325	25.2
BMI		
Low	672	52.2
Normal weight	551	42.8
Overweight and obese	65	5.0
Economical level		
Well	741	57.5
Moderate	488	37.9
Low	59	4.6
Family situation		
Parents are together	1.186	92.0
Parents are separated	73	5.7
Mother or father died	29	2.3
Attitude toward school		
Like	1.125	87.3
Dislike	163	12.7
Absenteeism		
Occurs	49	3.8
Does not occur	1.239	96.2

BMI: Body mass index

bullying was attitude toward school (OR 1.64, 95% GA 1.17-2.30) (p<0.05). The most important factors affecting physical bullying were gender (OR 2.39, 95% GA 1.70-3.36) and attitude toward school (OR 2.01, 95% GA 1.33-3.04) (p<0.05). Absenteeism, which was the most important factor in relational bullying, was found to be statistically significant (OR -0.47, 95% GA 0.22-1.00) (p<0.05). The most important factors affecting attacks with personal objects were gender (OR 2.74, 95% GA 1.61-4.67) and absenteeism (OR -0.41, 95% GA 0.16-1.00) (p<0.05). Attitude toward school was found to be the most important factor influencing social exclusion [(OR 1.75, 95% GA 1.12-(-2.72)] (p<0.05) (Table VI).

Table III. Situations of students for bullying and exposure to bullying and their reactions when they experience bullying behaviours according to the scale points

TPBS means of students	**n**	**%**
Situation of bullying		
Bullies others	154	12.0
Does not bully others	1.134	88.0
Situation of exposure to bullying		
Exposed to bullying	205	15.9
Not exposed to bullying	1.083	84.1
Bullying sub-dimensions**		
Threats/Intimidation	118	9.2
Physical bullying	173	13.4
Verbal bullying	670	52.1
Relational bullying	128	9.9
Attacking with personal items	69	5.4
Social exclusion	153	11.9
Given Reactions*		
Staying calm, not minding, not caring	297	23.1
Telling to the teacher	217	16.8
Warning	218	16.9
Doing the same	156	12.1
Beating	92	7.1
Getting sad/crying	87	6.8
Being angry	26	2.0
Asking the reason	21	1.6
Other***	71	5.6
No answer	208	16.2

*More than one answer was taken. Percentage was calculated on the basis of 'n', **In bullying sub-dimensions; only the numbers and percentages of bullying are given, ***Other (Telling the family, break up, solacement, protecting the victim, finding the truth, laughing, apologizing, not looking at his/her face)
TPBS: Traditional Peer Bullying scale

Boys were exposed to threats/intimidation behaviors 2.7 times more, physical bullying behaviors 2.4 times more, and attacks with personal objects 2.7 times more than girls (p<0.001). Students who did not like going to school showed threats/intimidation behaviors 2 times more (p=0.005), verbal bullying 1.6 times more (p=0.004), physical bullying 2 times more (p=0.001), and social exclusion 1.8 more (p=0.013) than students who liked going to school (Table VI). In the victim form; girls were exposed to verbal bullying 0.7 times more, relational bullying 0.6 times more, and social exclusion 0.7 times more than boys; by contrast, boys were exposed to threats/intimidation 1.6 times more than girls (p<0.05). Students with a higher BMI were exposed to verbal bullying 2 times and social exclusion 2.5 times more than those with a lower BMI (p<0.05). Students who did not like school were exposed to threats/intimidation behaviors 2 times more, verbal bullying 1.9 times more, physical bullying 2 times more, relational bullying 3 times more, attacks with, personal objects 2.8 times more, and social exclusion 1.7 more than those who liked school (p<0.05) (Table VI).

Students with mothers who graduated from secondary or high school were exposed to intimidation and threatening behaviors about 0.6 times less than those whose mothers graduated from primary school only (p<0.05). Students with a low socio-economic status were exposed to threatening and intimidating behaviors 2.1 times more, verbal bullying 2.1 times more, and social exclusion 2.2 times more than those with a high socio-economic status (p<0.05) (Table VI).

Discussion

The findings of the study conducted in order to determine the types and frequencies of peer bullying, as well as the factors that affect bullying, among students in 6th, 7th, and 8th grade classes at secondary schools are discussed below.

Some studies have found bully rates of between 2% and 18%, victim rates between 4.8% and 26%, and bully-victim rates between 2% and 24% (7,18,19,35,44,45). In this study, 12% of the students bullied, 15.9% were exposed to bullying (victims), and 15.1% were bully/victims; thus, bullying in schools should be considered an important problem (Table III). Hesapçıoğlu et al. (20) found that 23.4% of students were victims of bullying, 28.5% were bullies and 13.4% were both bullies and victims.

According to subdimensions, it was found that students performed mostly verbal bullying, other studies

show that students are exposed to mostly verbal bullying (18,26,28,35,44,46,47). Students exposed to bullying behaviors reported trying to stay calm, ignoring their bully (23.1%), warning their bully (16.9%), talking to their school principal and teachers (16.8%), and bullying back (12.1%) in response to being bullied (Table III). In other studies, participants stated that when they were exposed to bullying, they reacted by thinking of this behavior as a

Table IV. The students' bullying and exposure to bullying according to their introductive characteristics

Introductive characteristics	Bully		Non-bully		Exposed to bullying		Not exposed to bullying	
	n	%	n	%	n	%	n	%
Gender								
Girl	60	9.0	607	91.0	111	16.6	556	83.4
Boy	81	13.0	540	87.0	87	14.0	534	86.0
	χ^2=5.405 p=0.020				χ^2=1.712 p=0.191			
Age								
11 years	8	8.0	92	92.0	19	19.0	81	81.0
12 years	41	10.8	338	89.2	77	20.3	302	79.7
13 years	46	9.5	438	90.5	65	13.4	419	86.6
14 years	37	12.2	266	87.8	62	10.6	271	89.4
15 years	9	40.9	13	59.1	5	22.7	17	77.3
	χ^2=22.687 p<0.001				χ^2=15.843 p=0.003			
BMI								
Low	66	9.8	606	90.2	104	15.5	568	84.5
Normal weight	66	12.0	485	88.0	75	13.6	476	86.4
Overweight	9	13.8	56	86.2	19	29.2	46	70.8
	χ^2= 2.035 p=0.362				χ^2=10.914 p=0.004			
Economical level								
Well	78	10.5	663	89.5	93	12.6	648	87.4
Moderate	56	11.5	432	88.5	88	18.0	400	82.0
Low	7	11.9	52	88.1	17	28.8	42	71.2
	χ^2=3.369 p=0.498				χ^2=15.384 p<0.001			
Attitude to school								
Like	112	10.0	1013	90.0	150	13.3	975	86.7
Dislike	29	17.8	134	82.2	48	29.4	115	70.6
	χ^2=8.967 p=0.003				χ^2=28.418 p<0.001			
Family situation								
Parents are together	122	10.3	1064	89.7	184	15.5	1002	84.5
Parents are seperated	19	18.6	83	81.4	14	13.7	88	86.3
	χ^2=6.702 p=0.010				χ^2=0.231 p=0.631			
Absenteeism								
Occurs	8	16.3	41	83.7	11	22.4	38	77.6
Does not occur	133	10.7	1106	89.3	187	15.1	1052	
	χ^2=1.512 p=0.219				χ^2=1.961 p=0.161			

BMI: Body mass index

joke, by not minding the mockings, by responding verbally or physically or by avoiding, by not going to school, by sharing this with their closest friends, families, teachers, and school management (46,47). Verbal bullying is very common in schools and society because verbal bullying is not typically considered a type of bullying which may cause serious results and sometimes is supported by individual's environment and family.

There are factors such as age and gender in bullying. These changes in bullying rates can be thought to be caused by differences in demographic and social risk factors (such as age, gender, income status, family structure, family attitude, societal values, ethos) (8). In one study, the most frequently reported reason for bullying was physical weakness, but also being fat and being poor were among the other causes (48). In this study, boys, older students, and those who have parents living separately were more bullied than other students ($p<0.05$), and students who were overweight and had a low socio-economic status tended to be exposed to more bullying than their counterparts ($p<0.05$) (Table IV). These findings are similar to other studies in the literature (18,19,22,23,32,34,37,39).

Table V. The students' bullying and exposure to bullying according to their introductive characteristics

Introductive characteristics	Multiple binary logistic regression analyses (model: backward wald)	
	Bullied	Exposed to bullying
	OR (95% CI)	OR (95% CI)
Age (years)	1.21 (1.00-1.47) p=0.049	-0.74 (0.63-0.88) p<0.001
Gender		
Girl	1	-
Boy	1.47 (1.02-2.09) p=0.039	-
BMI		
Weak 1	-	1
Normal	-	-0.94 (0.67-1.31) p= 0.713
Overweight	-	2.29 (1.27-4.16) p=0.006
Like to school		
Like	1	1
Not like	1.86 (1.19-2.13) p=0.007	2.80 (1.90-4.13) p<0.001
Economical level		
Well 1	-	1
Moderate	-	1.51 (1.09-2.09) p=0.013
Low	-	2.53 (1.35-4.75) p=0.004
Familial situation		
Parents are together 1	1	-
Parents are separated	2.67 (1.47-4.83) p=0.001	-

OR: Odds ratio, CI: Confidence interval, BMI: Body mass index

The present study found that boys were more likely to be victims of bullying than girls ($p<0.05$) (Table IV,V). In various studies on the relationship between bullying and gender, boys were observed to be bullied and exposed to bullying to a greater extent than girls (26,39,44).

In this study, boys tended to engage in threats/intimidation, physical bullying, and attacking with personal objects more often than girls. By comparison, girls were more exposed to verbal and relational bullying and social exclusion than boys (Table VI). Similar studies revealed that boys were physically bullied more than girls and that boys were at higher risk of bullying than girls (22,26,49). Verbal bullying through mocking, relational attacks, and social exclusion were observed more frequently among girls than boys (22,38,49). The results of this study are similar to those in the literature. Thus, in school, boys may be at higher risk of physical bullying than girls and the latter may be at higher risk of verbal bullying than the former.

In this study, age was determined as a factor affecting bullying and exposure to bullying (Table IV). As the age of students increased by one unit (year), the frequency of bullying situations increased (Table V). While one previous study demonstrated that negative behaviors related to bullying decreased with increasing age (22), two other studies revealed that bullying increased with age, similar to the results of the present work (24). Also, in a study investigating bullying among classes, it was found that the students who were in the 8th class bullied more than the other students in the 6th and 7th grade classes; by contrast, students in the 6th grade class were more exposed to bullying than students in the 7th and 8th grade classes (46). Therefore, teaching students efficient problem-solving methods and empathy prior to the age when the risk of bullying increases could contribute to decreasing future bullying behaviors.

Students who were overweight were more exposed to bullying than those who were not ($p=0.006$) (Table IV,V); these students reported verbal bullying and social exclusion ($p<0.05$) (Table VI). A previous study indicated

Table VI. The mean scores from subdimensions of bully and victim scales of the students according to their introductive characteristics

Introductive characteristics	Multiple binary logistic regression analyses (model: backward wald)					
	Threats/ intimidation	**Verbal bullying**	**Physical bullying**	**Relational bullying**	**Attack with personal objects**	**Social exclusion**
	OR (95% CI)	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
Bully form gender (1)						
Girl	1	-	1	-	1	-
Boy	2.71 (1.79-4.09) p<0.001	-	2.39 (1.70-3.36) p<0.001	-	2.74 (1.61-4.67) p<0.001	-
Absenteeism						
Occurs	-	-	-	-	-	-
Does not occur	-	-	-	1 -0.47 (0.22-1.00) p=0.049	1 -0.41 (0.16-1.00) p=0.049	-
Attitude to school (1)						
Like	1	1	1	-	-	1
Dislike	1.98 (1.23-3.19) p=0.005	1.64 (1.17-2.30) p=0.004	2.01 (1.33-3.04) p=0.001	-	-	1.75 (1.12-2.72) p=0.013
Victim form						
Variables	Threats/ intimidation	Verbal bullying	Physical bullying	Relational bullying	Attack with personal objects	Social exclusion
	OR (95% CI)	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
Age (years)	-	-	0.80 (0.69-0.94) p=0.007	-0.83 (0.72-0.97) p=0.018	-	-0.78 (0.67-0.92) p=0.003
Gender (1)						
Girl	1	1	-	1		1
Boy	1.60 (1.18-2.17) p=0.003	-0.72 (0.54-0.95) p=0.021		-0.58 (0.44-0.78) p<0.001	-	-0.68 (0.50-0.92) p=0.012
BMI (1)						
Low 1	-	1	-	-	-	1
Normal	-	1.40 (1.04-1.86) p=0.024	-	-	-	-0.98 (0.72-1.35) p=0.910
Overweight	-	2.10 (1.16-3.81) p=0.015	-	-	-	2.48 (1.40-4.40) p=0.002
Attitude towards school (1)						
Like	1	1	1	1	1	1
Dislike	2.00 (1.35-2.96) p=0.001	1.86 (1.28-2.71) p=0.001	1.98 (1.34-2.94) p=0.001	2.99 (2.08-4.31) p<0.001	2.77 (1.86-4.13) p<0.001	1.70 (1.13-2.53) p=0.011
Mother education (1)						
Primary school 1	1	-	-	-	-	-
Secondary-high school	-0.60(0.43-0.83) p=0.002	-	-	-	-	-
University	-0.85(0.48-1.51) p=0.570	-	-	-	-	-

Table VI. Continued

Introductive characteristics	Multiple binary logistic regression analyses (model: backward wald)					
	Threats/ intimidation	Verbal bullying	Physical bullying	Relational bullying	Attack with personal objects	Social exclusion
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Economical level (1)						
Well 1	1	1	-	-	1	1
Moderate	1.58 (1.15-2.19) p=0.005	1.40 (1.04-1.86) p=0.024	-	-	1.50 (1.06-2.11) p=0.021	1.63 (1.20-2.21) p=0.002
Low	2.12 (1.12-4.01) p=0.020	2.10 (1.16-3.81) p=0.015	-	-	1.78 (0.88-3.62) p=0.109	2.19 (1.17-4.11) p=0.014

OR: Odds ratio, CI: Confidence interval, BMI: Body mass index

that obese or overweight students were more exposed to bullying than those who were not overweight (p<0.05) (49-51).

In this study, students with a low economic status were more exposed to bullying than those with higher economic backgrounds (p=0.003) (Table IV,V). Students with a low economic status were mainly exposed to threats/intimidation, verbal bullying, and social exclusion (Table VI). In a previous study, a positive relationship between exposure to bullying situations and a low socio-economic status and a negative relationship between bullying and a high socio-economic status were found (52). Another study revealed that individuals with economic trouble in the family reported higher rates of bullying (p<0.01) and exposure to bullying (p<0.001) than those without (53). Thus, according to the results of several studies, children with a low socio-economic status are at higher risk of being bulled than those with a higher socio-economic status. The school counselor, school nurse, and teachers should consider this situation.

In this study, students who did not like school bullied more and were exposed to more bullying than those who liked school (Tables IV,V,VI). Similar to our results, those students who did not like the school bullied and were exposed to bullying (p<0.05) more than the others in Ergün's (53) work. A strong positive relationship between liking school and being a victim was observed, attendance to school among bully students was less and they had higher absenteeism mostly. Not liking school and high levels of absenteeism can thus be considered as risk factors of being bullied.

Besides personal reasons, some important reasons to explain violent events at school include a low socio-economic status and a separated family unit (32,49,54). In a systematic review, children without a traditional family structure were found to be at a higher risk of bullying compared with children with such a structure (55). In our study, similarly to the literature, students whose father and mother were separated were bullied more often than those whose parents were together (p=0.001) (Table IV,V). Yang et al. (56) found that children with a single parent were bullied more than others (p<0.001).

In this study, students whose mothers had graduated from secondary and high school were exposed to threats/intimidation to a lesser extent than those whose mothers had graduated only from primary school (p<0.05) (Table VI). In another study, students whose mothers had a high level of education were at less risk of being bullied than those with a low level of education (57).

Study Limitations

One limitation of this study is that the research was done with students in only one city in Turkey where the data were collected. Therefore, the results obtained without research can be generalized to students in this research group.

Conclusions

Bullying behaviors among school-aged children occurred more frequently among boys, students who did not like school, those who lived with single parents, and those who were exposed to bullying. Exposure to bullying was affected by being overweight, not liking one's school, and a poor economic status. It could be suggested that these students and their families should be regularly followed up concerning bullying, and programs to prevent bullying should be developed and disseminated among students, teachers, and parents.

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Ethics

Ethics Committee Approval: The study was approved by the Ethics Committe of Nevşehir Hacı Bektaş Veli University (approval number: 2014/01.01).

Informed Consent: Written and verbal consent from the students and their families were obtained.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

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Original Article

Risk Factors of Bloodstream Infections Caused by Carbapenem-resistant Gram-negative Pathogens in Pediatric Critical Care Settings

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ABSTRACT

Aim: Infections and sepsis are the leading causes of death in non-cardiac intensive care units (ICUs) and account for 40 percent of all ICU expenditures. Data regarding bloodstream infections (BSIs) due to a carbapenem-resistant gram negative (CRGN) microorganisms in pediatric ICUs still remain limited.

Materials and Methods: This study was conducted retrospectively in patients who were admitted to two pediatric critical care units between January 2011 and December 2017. Patients were assigned to two groups. Patients with BSI caused by a CRGN microorganism and infections were assigned to the BSI group and those other than BSI were assigned to the non-BSI group.

Results: This study included 89 critically ill children with a mean age of 52.1 (±65.1) months. The requirements for invasive procedures including tracheostomy, Foley catheter and central venous catheter were not statistically different among the groups, p values were 0.159, 0.291 and 0.803, respectively. The majority of the patients admitted to pediatric intensive care unit were due to sepsis/septic shock in the BSI group (n=18, 58%) and in the non-BSI group, this figure was 37.9% (n=24). Prior third/fourth generation cephalosporin exposure was significantly more common in the BSI group (51.6% vs 15.5%, p<0.001), carbapenem exposure was not significantly different among the groups (35.5% vs 56.9%, p=0.054). Neutropenia (<500/mm^3) and thrombocytopenia (150x103/mm^3) were significantly more common in the BSI group (p=0.011 and p=0.010) and the C-reactive protein level was significantly higher (p=0.018). Crude and attributable mortality did not show any significance between the groups, p values were 0.578 and 0.955, respectively.

Conclusion: CRGN infections are still a major cause of morbidity, mortality and healthcare associated infections. In this study, we evaluated patients with BSI due to a CRGN microorganism and compared them with other infection types. The risk factors and outcomes were similar except for prior cephalosporin exposure. As a conclusion, we have to enhance infection control programs and prevent patients from redundant antibiotic exposure.

Keywords: Carbapenem-resistant gram-negative microorganism, bloodstream infection, pediatric critical care unit

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Introduction

Antibiotic resistance across Gram-negative bacteria has progressively disseminated to countries worldwide, presenting a serious public health concern. Although intensive care units (ICUs) account for fewer than 10 percent of total beds in most hospitals, the majority of all healthcare associated infections occur in ICU departments of hospitals (1,2). Infections and sepsis are the leading causes of death in non-cardiac ICUs and account for 40 percent of all ICU expenditures (3). A recent review which evaluated carbapenem-resistant *Enterobacteriaceae* (CRE) infections reported that the majority of children (53%) acquired carbapenem-resistant gram negative (CRGN) infections during their ICU stay (4). Vincent et al. (3) concluded that infections are common in patients in contemporary ICUs, and a longer duration hospital stay correlated with the risk of infection. Infections due to CRE in adult populations have been associated with poor clinical outcomes, including mortality rates as high as 40-65% while mortality can reach up to 90% in children (4,5). Data regarding bloodstream infections (BSIs) due to a CRGN pathogen in pediatric ICUs still remain limited (6,7). Therefore, we evaluated the clinical and laboratory features of BSIs caused by a CRGN pathogen and compared them with other types of infections including urinary tract infections (UTI), ventilator-associated pneumonia (VAP) and meningitis.

Materials and Methods

This study was conducted retrospectively in patients who were admitted to two pediatric critical care units between January 2011 and January 2017. The demographic characteristics, medical history, comorbidity, pathogens isolated and antimicrobial susceptibility of isolated pathogens, treatment administered, administration of other nephrotoxic agents, duration of pediatric intensive care unit (PICU) stay before the isolation of resistant microorganisms, presence of medical devices, such as ventriculo-peritoneal devices, central catheters, urinary catheters, and endotracheal or tracheostomy tubes were recorded retrospectively from the medical records.

Ethics

This study was granted permission by the Ethical Board of İzmir Katip Çelebi University (approval number: 58/March 24,2016). Informed parental consent was not obtained due to retrospective design of this study.

Microbiologic Testing

Presumptive identification of Gram-negative pathogens was identified by Vitek-Mass Spectrometry (MS) (bioMérieux, France). Vitek-MS using Matrix assisted laser desorption ionization time of flight MS technology, which is a new technology for species identification based on the protein composition of microbial cells, was used. The isolate was tested for antibiotic sensitivity on Muller Hinton agar by the Kirby Bauer disc diffusion technique using standard methods. Susceptibilities to amikacin, ceftriaxone, ceftazidime, piperacillin-tazobactam, cefoperazone-sulbactam, imipenem, meropenem, colistin and tigecycline were determined according to the Clinical and Laboratory Standards Institutes guidelines. The isolate was tested for antibiotic sensitivity on Muller Hinton agar by Kirby Bauer disc diffusion technique using standard methods. For susceptibilitytests, *E. col*i ATCC 25922, *P. aeruginosa* ATCC 27853, and *E.coli* NCTC 13846 were used as quality control strains (8).

Definitions

We reviewed the medical records of the enrolled patients and collected their case information. A standard form was used to collect the epidemiologic data including age, sex, underlying diseases (pulmonary disease, malignancy, cardiovascular disease, hematologic/solid organ transplantation, metabolic disease, genetic syndrome, prematurity, renal disease, liver disease), medication or intervention (presence of tracheal cannula, central venous catheter, presence of a Foley catheter, mechanical ventilation, immunosuppressive therapy and steroid, treatment by antibiotics). The diagnosis of infection was based on clinical features and the isolation of bacteria from a normally sterile site. Those patients with CRGN BSI were defined as the BSI group and those patients with other infection types such as VAP, UTI and meningitis were included in the non-BSI group. Standard definitions for nosocomial infections and VAP were used according to the Center for Disease Control and Prevention definitions (9) and diagnosis of sepsis was made according to the International Pediatric Sepsis Consensus (10).

Crude mortality was defined if the patient died within 1 month of the infection and attributable mortality was defined if the patient died directly related to the breakthrough infection.

Statistical Analysis

Statistical analyses were performed using SPSS for Windows (version 22.0; SPSS, Inc., Chicago, IL, USA). Numerical data were expressed as medians (interquartile range). Mann-Whitney U and Wilcoxon tests were used for inter-variable analysis. Categorical variables were evaluated

with the chi-square test or the two-tailed Fisher exact test and presented as percentages in acquiring CRGN infections. Comparisons were referred to as statistically significant if the p values were <0.05.

Ethics

This study was granted permission by the Ethical Board of İzmir Katip Çelebi University (approval number: 58/March 24,2016).

Results

This study included 89 critically ill children with a mean age of 52.1 (±65.1) months between January 2011 and December 2017. The most common type of infection was VAP (59 cases, 66.2%), followed by BSI (31 cases, 39.6%), UTI (10 cases, 11.2%), meningitis (3 cases, 3.3%). Both bloodstream infection and VAP occurred in 7 (7.8%) patients, BSI and UTI occurred in 3 (3.3%) patients and VAP and UTI occurred in 3

Table I. Risk factors and outcomes of Carbapenem-resistant gram-negative bloodstream infections (BSIs) and comparison with non-BSI group

	BSI (n=31)	**Non-BSI (n=58)**	**p value**
Age, months, mean ± SD	32.8 (±37.04)	66.7 (±72.9)	0.022
Hospital stay prior to BSI (median, ±SD) (day)	17 (9.5-128.1)	10 (11.6-21.8)	0.803
Total hospital stay (median, ±SD) (day)	27 (2.89-168.65)	34 (34.2-56.9)	0.384
Underlying diseases (n, %)	-	-	0.029
- Previously healthy	1 (3.2)	12 (20.7)	
- Chronic neurological/neuromuscular disorder	9 (29)	18 (31)	
- Hematologic/solid malignancy	1 (3.2)	3 (5.2)	
- Chronic liver diseases	1 (3.2)	4 (6.9)	
- Chronic lung disease	2 (6.5)	9 (15.5)	
- Congenital heart disease	4 (12.9)	6 (10.3)	
- Bone marrow/solid organ transplantation	7 (22.6)	2 (3.4)	
- Primary immune deficiency	3 (9.7)	3 (5.2)	
Others	3 (9.7)	1 (1.7)	
Cause of PICU admission (n, %)			
- Sepsis/Septic shock	18 (58.1)	24 (41.4)	0.165
- Respiratory failure	10 (32.3)	22 (37.9)	
- Trauma	1 (3.2)	9 (15.5)	
- Status epilepticus	0	2 (3.4)	
- Cardiopulmonary arrest	2 (6.5)	1 (1.7)	
Tracheostomy (n, %)	10 (32.3)	11 (19)	0.159
Foley catheter (n, %)	24 (77.4)	50 (86.2)	0.291
Central venous catheter (n, %)	29 (93.5)	55 (94.8)	0.803
Thrombocytopenia (<150x10^3/mm^3) (%)	13 (50)	13 (22.4)	0.031
Neutropenia (<500/mm^3) (%)	4 (13.8)	0 (0)	0.011
WBC (mm^3)	13100 (7677-16018)	12600 (12058-16438)	0.207
ANC (mm^3)	7250 (5040-12477)	9140 (8528-12564)	0.105
PLT (x103/mm^3)	212 (140153-298944)	315 (285627-399193)	0.010
CRP (mg/dL)	9.65 (7.47-12.5482)	7.3 (5.43-82051)	0.018
Attributable mortality (n, %)	5 (16.1)	11 (19)	0.740
Crude mortality (n, %)	5 (16.1)	18 (%31)	0.126

BSI: Bloodstream infection, SD: Standard deviation, PICU: Pediatric intensive care unit, WBC: White blood cell, ANC: Absolute neutrophil count, PLT: Platelet, CRP: C-reactive protein

(3.3%) patients. The most common underlying disease was chronic neurological disorder in the BSI group (n=9, 29%) and also in the non-BSI group (n=18, 31%) and this was followed by bone marrow/solid organ transplantation (n=7, 22.5%) while chronic lung diseases was seen in 15.5% (n=9) in the non-BSI group (Table I). The majority of the patients were admitted to PICU due to sepsis/septic shock in the BSI group (n=18, 58%) and in the non-BSI group, this figure was 37.9% (n=24). The requirement of invasive procedures including tracheostomy, Foley catheter and central venous catheter were not statistically different among the groups, p values were 0.159, 0.291 and 0.803, respectively. The mean age of the patients was significantly younger in the BSI group than the non-BSI group (12 months vs 32 months, p=0.022). Total and prior hospital stay did not show any significant difference, p levels were 0.384 and 0.803, respectively. Prior third/fourth generation cephalosporin exposure was significantly more common in the BSI group (51.6% vs 15.5%, p<0.001), carbapenem exposure was not significantly different among the groups (35.5% vs 56.9%, p=0.054). Crude and attributable mortality did not show any significance between the groups, p values were 0.578 and 0.955, respectively. Neutropenia (<500/mm^3) and thrombocytopenia (150x10^3/mm^3) were significantly more common in the BSI group (p=0.011 and p=0.010) and the C-reactive protein level was significantly higher (p=0.018). White blood cell, absolute neutrophil count and hemoglobin level did not show any statistical significance between the groups, p levels were 0.271, 0.121 and 0.822, respectively (Table I), isolated microorganisms have been shown in Table II.

Discussion

In this study, a retrospective case-control study was conducted to evaluate the risk factors for the acquisition of BSI caused by CRGN microorganisms and to compare with infection types other than BSI in those patients admitted to PICUs of two teaching hospitals. We found BSIs occurred in younger patients and thrombocytopenia and neutropenia were significantly more common in the BSI group. The crude and attributable mortality rate did not show statistical significance between the groups. Over recent years, CRGN infections have been attributed as being a significant cause of healthcare associated infections, significant mortality and morbidity. Previous adult studies suggested that elderly patients are more vulnerable to CRE infections. On the other hand, a recent study from the UK evaluating CRE infections demonstrated the majority of patients (6/9; 66.6%) were under 1 year of age (8). Similarly, we found that patients with BSI were younger than those patients with other types of infection.

A recent study evaluated the risk factors and clinical outcomes of patients with CR *Acinetobacter baumannii* bacteremia and found that the independent risk factors were hematological malignancy, previous cefepim exposure and the use of total parenteral nutrition (11,12). Routsi et al. (13) suggested prior exposure to carbapenems were independent risk factors for the acquisition of CR-GN bacilli. Previous administration of carbapenems was the only factor related with the development of CR-GNB if the source of infection was other than VAP. Patients with bacteremia were more likely to have additional devices and a longer hospital stay. In the present study, the carbapenem exposure rate was similar among the groups while prior cephalosporin was 3-fold more common in the BSI group when compared with the non-BSI group (p<0.001).

A recent meta-analysis evaluating 9 studies reported that death rates were higher in patients who had bacteremia caused by a CRGN pathogen when compared with a CSGN pathogen. However, they suggested no difference between the groups; bacteremia and other infections (14). We compared patients with BSI caused by a CRGN pathogen and other types of infection due to a CRGN pathogen and did not

Table II. Isolated microorganisms and isolation sites

Isolated microorganisms	Blood (n=31)	Endotracheal lavage (n=59)	Urine (n=10)	Cerebrospinal Fluid (n=3)
Pseudomonas aeruginosa	6	18	2	1
Acinetobacter baumannii	16	35	5	1
Klebsiella pneumoniae	7	3	2	1
Escherichia coli	1	-	1	-
Serratia marcescens	1	-	-	-
Acinetobacter baumannii+ Pseudomonas aeruginosa	-	2	-	-
Acinetobacter baumannii+ Klebsiella pneumoniae	-	1	-	-

find a significant difference. A case control study was used to identify risk factors and compare outcomes (15). Previous studies demonstrated 3-6 times higher mortality among CRE-infected patients when compared with Carbapenem-sensitive *Enterobacteriaceae* infected patients (16-18). We did not find a significant difference among our groups.

Acquired risk factors for CRE infection in children include underlying chronic medical conditions, invasive medical devices, frequent or prolonged hospitalizations, prior antibiotic exposure, age, and travel from endemic regions (16). Among the BSI and non-BSI groups, prior and total hospital stay duration did not show any difference.

Thrombocytopenia is a common finding in patients with bacterial sepsis as a result of marrow suppression, consumption due to Disseminated intravascular coagulation (DIC) and inflammatory response, being either drug-induced or not. A recent study compared methicillin-resistant and methicillin-sensitive *Staphylococcus aureus* infected patients and found no significant difference for thrombocytopenia (19). A recent multicenter observational study demonstrated that thrombocytopenia within the first 24 hours of septic shock onset to be a prognostic marker of survival at day 28 in a large cohort of ICU patients (20). We found that patients in the BSI group were significantly more likely to develop thrombocytopenia in line with previous reports.

There are several advantages of this study. The main advantages are that this is the largest series in pediatric critical care settings, it is the first study that evaluates the impact of having BSI due to a CRGN pathogen and it has a multicenter design. The main limitations of this study were its retrospective design and the lack of any molecular characterization of the microorganisms which can affect the outcomes of these infections. We additionally defined CRGN as an organism demonstrating resistance to at least one carbapenem antibiotic and therefore could not assess the risk factors particularly for carbapenemase-producing CRGN, which may be distinct from those of non-carbapenemase-producing CRGN.

CRGN infections are still a major cause of morbidity, mortality and healthcare associated infections. In this study, we evaluated patients with BSI due to a CRGN microorganism and compared them with other infection types. The risk factors and outcomes were similar except for prior cephalosporin exposure.

Conclusion

We have to enhance infection control programs and prevent patients from redundant antibiotic exposure. Our current knowledge is based on adult studies due to lack of prospective and case-control design studies. Therefore, further larger and prospective design studies are needed.

Ethics

Ethics Committee Approval: This study was granted permission by the Ethical Board of İzmir Katip Çelebi University (approval number: 58/03, 24,2016).

Informed Consent: Informed parental consent was not obtained due to retrospective design of this study.

Peer-review: Externally peer-reviewed

Authorship Contributions

Concept: Z.Ş.B., Design: Z.Ş.B., Supervision: A.B.A., B.K., Resource: F.K., M.D., P.Y., Materials: F.K., M.D., P.Y., Data Collection and/or Processing: F.K., Z.Ş.B., Analysis and/or Interpretation: Z.S.B., F.K., M.D., P.Y., F.Ç., N.Y.Ö., Literature Search: Z.Ş.B., D.Y.Ç., Writing: Z.S.B., Critical Reviews: Z.Ş.B., A.B.A., B.K.

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Original Article

Factors Affecting Physical Growth in Children with Primary Vesicoureteral Reflux: A Single Center Experience

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ABSTRACT

Aim: Primary Vesicoureteral reflux (VUR) is defined as retrograde urine flow from the bladder to the upper urinary system due to an insufficient valvular mechanism in the ureterovesical junction. We aimed to clarify factors affecting physical growth in children with primary VUR.

Materials and Methods: The study was performed retrospectively in 260 primary VUR patients without chronic renal disease. Height and weight z-scores were calculated by anthropometric references in Turkish children and compared between patients grouped according to clinical properties.

Results: Mean age of diagnosis was 43±4 months and mean duration of follow-up was 4.2±1.4 years. Mean height and weight z-scores of the 260 children were 0.22±0.96 and -0.11±1.0 at diagnosis; 0.14±0.97 and 0.01±1.3 at last visit respectively. Age at diagnosis, gender, grade, laterality and persistency of VUR had no impact on height and weight parameters. Although initial and final height z-scores were similar, we showed a higher height z-score improvement in patients with renal scarring and similarly in patients with surgery performed at least 6 months after the diagnosis. Mean final height and weight z-scores and weight z-score improvement were significantly lower in patients with urinary tract infections (UTIs) than in those without UTIs at follow-up. Further analysis concerning UTIs showed that final height z-scores were significantly lower in patients with afebrile UTIs at follow up, while it was similar between patients with and without febrile UTIs.

Conclusion: The presence of renal scarring and UTIs at follow-up may lead to growth alterations in patients with primary VUR. Therefore, physicians and parents should be aware of UTI symptoms, even in the absence of fever, in pediatric VUR, thus preventing renal scarring and alterations in growth.

Keywords: Child, growth, urinary tract infection, vesicoureteral reflux

Introduction

Vesicoureteral reflux (VUR) is a common urological abnormality with a prevalence of 1-2% of the pediatric population and defined as retrograde urine flow from the bladder to the upper urinary system due to an insufficient valvular mechanism in the ureterovesical junction (1). Although most cases with particularly low-grade VUR resolve spontaneously, its persistence accounts for 7-17 % of end-stage renal disease (2,3). Diagnosis is usually made upon investigating a urinary tract infection (UTI), antenatal hydronephrosis or sibling screening. However, flank pain, proteinuria, hypertension, enuresis and voiding dysfunction may occasionally lead to diagnosis. Voiding

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cystourethrogram (VCUG) is the reference standard test in VUR diagnosis and follow-up (4). The aim of treatment is to prevent UTIs and renal damage (5,6).

Renal damage and persistent VUR have been reported to alter physical growth in former studies, however, recent data revealed no relevance between renal damage, UTIs, VUR grade and growth (7-9). With this study, we aimed to clarify factors affecting physical growth in children with primary VUR in a larger population.

Materials and Methods

Patients

The study included 260 primary VUR patients, 155 females (59.6%) and 105 males (40.4%), followed up between August 2003-August 2012 at our department. Patients with chronic renal disease, malabsorption or systemic diseases were excluded from the study. Age at diagnosis, symptoms prior to diagnosis, comorbid urinary abnormalities, gender, VUR grade and laterality, renal scarring, treatment procedure, time of surgery, duration of antibiotic prophylaxis, frequency of UTI (febrile or afebrile) at follow-up, VUR persistency, resolving time of VUR and growth parameters were retrospectively recorded from the medical records of the patients. In our clinical practice, height and weight had been recorded every 6 months in patients younger than 3 years of age and annually in patients older than 3 years.

Height and weight z-scores were calculated by anthropometric references in Turkish children and mean z-scores were compared within the different groups of patients (10).

VUR was diagnosed by VCUG and graded from 1 to 5 according to the criteria of the International Reflux Study Committee (11). Grade 4 and 5 VUR were classified as high-grade VUR in our study. We defined early diagnosed VUR as VUR diagnosed in the first 3 months of life. Patients are surgically treated by an endoscopic subureteric injection of polytetrafluoroethylene (Polytef) paste or Cohen's ureteroneocystostomy when necessary. Resolution was defined as an absence of VUR in VUG three months after endoscopic surgery or 6 months after open surgery (12).

Cortical scarring was defined as a defect in the normal reniform outline on dimercaptosuccinic acid scanning. A photon deficient area was defined as a focal or diffuse area of reduced uptake of the radionuclide with preservation of the normal reniform outline (13).

UTI is described as significant bacteriuria in a urine culture test taken appropriately. Significant bacteriuria is defined as ± standard deviation >1.000 colony forming unit (cfu) with suprapubic, >10.000 cfu with catheterization technique and >100.000 cfu with midstream urine analysis (14-16).

The Ethics Committee of Dr. Behçet Uz Children's Training and Research Hospital approved the study (approval number: B-10-4-ISM-4-35-65-72, date: 27/09/2012). All patients and parents gave their informed consent prior to their inclusion in the study.

Statistical Analysis

The distribution of data was evaluated with the Kolmogornov-Smirnov test. If appropriate, numeric variables were analyzed with the Student t-test and ANOVA tests. If not appropriate, numeric variables were compared by the Mann-Whitney U and Kruskall-Wallis tests. Pearson correlation analysis was performed between two numeric variables. Categorical variables were analyzed with chi-square and if possible, Fisher's exact chi-square tests. Odds ratio with 95% confidence intervals were used to quantify the risk. Analysis was performed with the (version 16.0; SPSS) statistical significance was considered at $p<0.05$.

Results

The mean age at diagnosis was 43±4 months (range: 1 to 174 months). Twenty-nine patients (11.2%) were diagnosed as early diagnosed VUR as defined above. Mean duration of follow-up was 4.2±1.4 years (range: 3-9 years). Symptoms prior to diagnosis, urinary comorbidities and disease characteristics in patients are shown in Table I.

VCUG revealed mild VUR (< grade 4) in 178 (68.5%) and severe VUR (≥ grade 4) in 82 (31.5%) patients. Mean resolution time was 22±13 months (range: 2-82 months) in patients with spontaneous resolution. Antibiotic prophylaxis was given to 248 patients (95%) with a mean duration of 25±1 months. Cohen's ureteroneocystostomy was performed in 59 patients with a recovery rate of 96.6% (n=57), whereas VUR resolved in 48 (77.4%) of 62 patients for whom endoscopic Polytef was injected.

Mean height and weight z-scores of the 260 children were 0.22±0.96 and -0.11±1.0 at diagnosis; 0.14±0.97 and 0.01±1.3 at their last visit respectively. Initial and last height and weight z-scores and changes during follow-up were compared in patients according to gender, age at diagnosis, the presence of renal scarring, VUR grade, VUR laterality, VUR persistency, spontaneous resolution, resolution with surgery and surgery timing at follow up. This data is shown in Table II. Although initial and final height z-scores

were found statistically similar between patients grouped according to the presence of renal scarring and surgery timing, annual height z-score improvement was found to be higher in patients with renal scarring and similarly in patients on whom a surgery was performed at least 6 months after the diagnosis. Growth parameters among the patients according to the presence of UTIs during follow-up are shown in Table III.

Table I. Clinical characteristics of patients with primary vesicoureteral reflux

Parameters		**n**	**%**
VUR grade	Grade 1	26	10
	Grade 2	62	23.8
	Grade 3	90	34.6
	Grade 4	47	18.1
	Grade 5	35	13.5
Bilateral VUR		123	47.3
Renal scarring		110	42.3
Symptoms prior to diagnosis	Afebrile UTI	106	40.7
	Febrile UTI	61	23.5
	Antenatal hydronephrosis	30	11.5
	Enuresis	18	7
	Sibling VUR	2	0.8
	Asymptomatic	43	16.5
Urinary comorbidities (n=59, 22.7%)	Duplicated collecting system	20	7.7
	Nephrolithiasis	13	5
	Paraurethral diverticulosis	9	3.5
	Horseshoe kidney	4	1.5
	Renal ectopia	3	1.2
	Hypospadias	3	1.2
	Renal agenesis	3	1.2
	UPJ obstruction	4	1.6
VUR outcome	Persistent	106	40.8
	Spontaneous	49	18.9
	Surgical	105	40.3
Patients with height z-score <-2 at Diagnosis/Last visit		4/5	1.5/1.9
Patients with Weight z-score <-2 at Diagnosis/Last Visit		5/3	1.9/1.1
Total number of patients		260	100

VUR: Vesicoureteral reflux, UTI: Urinary tract infection, UPJ: Ureteropelvic junction

Discussion

Primary VUR is an isolated abnormality, characterized by retrograde urine flow from the bladder. Whereas secondary VUR develops from an underlying urinary system anomaly such as neurogenic bladder, obstructive uropathy or posterior urethral valve (3). Treatment modalities are observational follow-up, continuous antibiotic prophylaxis and open or laparoscopic surgery (5). Controversy exists regarding the use of continuous antibiotic prophylaxis vs observation, but a recently published meta-analysis showed a significantly reduced risk of febrile and symptomatic UTIs with continuous antibiotic prophylaxis (6).

The best indicators of physical growth and development are weight and height gain in children. Growth monitoring according to standardized charts at regular intervals and early recognition of growth alteration are necessary for the well-being in children with chronic diseases.

In the literature, it was formerly suggested that VUR affects physical growth in children and also surgical treatment may lead to an improvement in growth parameters (17,18). Wingen et al. (19) prospectively evaluated the growth in 236 children with VUR and found no relevance between renal scarring, VUR degree and laterality, UTI frequency and growth indices. Conversely, Polito et al. (20) recently reported that the initial height z-score was found to be significantly lower in children with bilateral VUR and renal scarring, and the same group showed the highest height z-score improvement at follow up (21). Although initial and final height z-scores were similar, our study showed significantly higher height z-score improvements in patients with renal scarring. This finding may be due to the effects of other clinical parameters on growth such as age at diagnosis, additional urinary malformations or UTIs. We speculate that patients with renal scarring had a better catch up in growth with optimal management.

Another study found that the patients who were diagnosed after their first month of life had higher height improvement than patients diagnosed before one month of age (22). We also investigated the age at diagnosis based on a cut-off value of 3 months. Weight and height z-scores at diagnosis and follow-up were found to be similar between those patients whose diagnosis was made before 3 months of age and those who were diagnosed after 3 months of age.

Moreover, two independent studies showed lower height z-score changes in patients with persistent VUR

than surgical or spontaneous resolved VUR (7-9). In another recent study from our country, high-grade VUR was linked with growth alteration among 97 children. Additionally, bone age was found to be significantly lower in participants with renal scars compared to those without renal scars (23).

However, weight and height z-scores and their changes did not differ between those patients with persistent VUR, spontaneous resolution or surgical repair in our study. However, we found higher height z-score improvement in patients with a surgical procedure performed at least 6 months after the diagnosis. This data suggesting a better catch up in growth in children with delayed surgery, led us to think that it might be preferably to wait for spontaneous recovery for 6 months in selected cases.

UTI is the most relevant health problem in children with VUR. Malaki et al. (8) investigated growth parameters in children with UTIs and indicated that the presence, laterality and grade of VUR had no impact on growth parameters. Contrarily, striking evidence about the growth-altering effects of UTIs were present in our study. Final height and weight z-scores and weight z-score improvement were significantly lower in those patients with UTIs than those without UTIs at follow-up. This finding suggests that UTIs may cause growth retardation in patients with VUR.

Table II. Growth parameters and their changes at follow-up of patients with primary vesicoureteral reflux according to clinical characteristics

Parameters		**n**	**Initial height z-score ± SD**	**Final height z-score ± SD**	**Total height z-score change ± SD**	**Annual height z-score change ± SD**	**Initial weight z-score ± SD**	**Final weight z-score ± SD**	**Total weight z-score change ± SD**	**Annual weight z-score change ± SD**
Gender	Female	155	0.26±0.91	0.11±0.99	-0.14±0.87	0.04±0.22	-0.51±1.1	0.14±1.3	0.20±0.98	0.06±0.25
	Male	105	0.17±1.02	0.08±0.95	0.09±0.94	-0.03±0.22	-0.01±0.98	0.26±1.2	0.28±1.2	0.06±0.28
	p		0.497	0.815	0.637	0.688	0.8	0.384	0.606	0.791
Age at diagnosis	≤ 3 months	29	0.14±0.82	0.22±0.96	0.07±1.29	-0.01±0.27	0.08±0.91	0.75±1.72	0.67±1.9	0.14±0.44
	> 3 months	231	0.23±0.97	0.09±0.97	-0.15±0.83	-0.04±0.21	-0.05±1.0	0.12±1.24	0.18±0.92	0.49±0.24
	p		0.641	0.493	0.379	0.343	0.103	0.103	0.388	0.462
VUR grade	Grade 1-3	178	0.28±1.00	0.28±0.88	-0.14±0.90	-0.04±0.23	-0.03±1.10	0.18±1.31	0.21±1.01	0.06±0.27
	Grade 4-5	82	0.11±0.84	0.14±1.10	-0.08±0.89	-0.02±0.18	-0.05±0.98	0.22±1.41	0.27±1.21	0.06±0.27
	p		0.173	0.390	0.959	0.603	0.896	0.959	0.684	0.530
VUR laterality	Unilateral	137	0.17±0.97	0.05±1.04	-0.12±0.92	-0.04±0.23	-0.08±1.05	0.14±1.37	0.23±1.09	0.05±0.26
	Bilateral	123	0.28±0.95	0.16±0.89	-0.11±0.88	-0.02±0.21	0.02±1.07	0.25±1.24	0.23±1.10	0.06±0.27
	p		0.389	0.337	0.909	0.413	0.425	0.505	0.932	0.732
Renal scarring	Present	110	0.16±0.92	-0.01±0.83	-0.01±0.83	0.01±0.16	-0.03±1.07	0.23±1.22	0.25±1.09	0.06±0.29
	Absent	150	0.27±0.98	0.06±0.96	-0.21±0.93	-0.06±0.25	-0.06±1.06	0.15±0.42	0.21±1.10	0.05±0.23
	p		0.371	0.391	0.055	**0.019**	0.812	0.651	0.747	0.607
VUR recovery	Persistent	106	0.30±1.01	0.11±1.0	-0.19±0.85	-0.06±0.24	0.11±1.08	0.28±1.2	0.16±0.90	0.03±0.24
	Spontaneous	49	0.29±0.09	0.13±1.0	-0.16±1.11	-0.04±0.26	-0.14±1.13	0.19±1.3	0.33±1.42	0.09±0.34
	Surgical	105	0.09±0.85	0.09±0.88	-0.01±0.78	-0.01±0.16	-0.14±0.98	0.11±1.39	0.26±1.05	0.06±0.23
	p		0.267	0.962	0.331	0.172	0.150	0.311	0.829	0.682
Surgery time	In the first 6 months	50	0.23±0.76	0.09±0.90	-0.14±0.74	-0.02±0.16	-0.13±0.99	0.19±1.36	0.33±0.91	0.09±0.21
	>6 months after diagnosis	59	-0.07±0.97	0.12±1.02	0.20±0.78	0.04±0.16	-0.18±1.02	0.02±1.45	0.19±1.09	0.04±0.23
	p		0.065	0.894	0.024	0.042	0.777	0.483	0.478	0.296

Significant p values are in bold
SD: Standard deviation, VUR: Vesicoureteral reflux

Table III. Growth parameters of patients with primary vesicoureteral reflux according to presence of urinary tract infections at follow-up

Parameters	UTI			Febrile UTI at follow-up			Afebrile UTI at follow-up		
	Yes (n=83)	No (n=177)	p	Yes (n=17)	No (n=243)	p	Yes (n=73)	No (n=187)	p
Initial height z-score ± SD	0.07±0.90	0.30±0.98	>0.05	0.20±1.05	0.23±0.95	>0.05	0.07±0.91	0.29±0.97	>0.05
Final height z-score ± SD	-0.12±0.93	0.21±0.98	0.008	-0.31±0.96	0.11±0.97	>0.05	-0.16±0.95	0.20±0.97	**0.007**
Total height z-score change ± SD	-0.05±0.20	-0.02±0.23	>0.05	-0.23±0.68	-0.11±0.91	>0.05	-0.23±0.90	-0.08±0.90	>0.05
Annual height z-score change ± SD	-0.19±0.87	-0.08±0.91	>0.05	-0.06±0.15	-0.03±0.23	>0.05	-0.06±0.20	-0.02±0.22	>0.05
Initial weight z-score ± SD	-0.22±0.97	0.05±1.10	>0.05	-0.18±1.23	-0.03±1.05	>0.05	-0.20±0.94	0.03±1.10	>0.05
Final weight z-score ± SD	-0.20±1.07	0.38±1.37	0.001	-0.43±1.11	0.24±1.30	0.039	-0.12±1.10	0.32±1.38	**0.035**
Total weight z-score change ± SD	0.01±0.21	0.08±0.28	0.034	-0.43±1.10	0.24±1.31	>0.05	0.09±0.92	0.29±1.10	>0.05
Annual weight z-score change ± SD	0.02±0.92	0.33±1.15	0.031	-0.26±0.76	0.26±1.12	>0.05	0.02±0.21	0.07±0.29	>0.05

UTI: Urinary tract infections, SD: Standard deviation
Significant p values are in bold

Further analysis concerning UTIs showed that final height z-scores were significantly lower in patients with afebrile UTIs at follow up, while it was similar between patients with and without febrile UTIs. We thought this might be due to the small number of patients with febrile UTIs or the inadequate treatment of afebrile UTIs. Thus, we speculate that the symptoms of afebrile UTIs could be more often underestimated in clinical assessment.

Study Limitations

The limitations of our study were the absence of a prospective design and the lack of information about the nutrition status of participants.

Conclusion

Our study highlighted that the presence of renal scarring and UTIs at follow-up may lead to growth alterations in patients with primary VUR. We speculate that the presence of overall normal growth parameters may be due to a high antibiotic prophylaxis rate, which could prevent UTIs in our study group. The most striking insight in the present study was particularly the negative impact of afebrile UTIs on growth in patients with primary VUR. Therefore, physicians and parents should be aware of UTI symptoms even in the absence of fever in pediatric VUR.

Ethics

Ethics Committee Approval: The Ethics Committee of Dr. Behçet Uz Children's Training and Research Hospital approved the study (approval number: B-10-4-ISM-4-35-65-72, date: 27/09/2012).

Informed Consent: All patients and parents gave their informed consent prior to their inclusion in the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: R.M.K.E., E.S., Design: R.M.K.E., E.S., Data Collection or Processing: R.M.K.E., Analysis or Interpretation: R.M.K.E., E.S., Literature Search: R.M.K.E., Writing: R.M.K.E., E.S.

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Original Article

A Retrospective Evaluation of Mean Platelet Volume and the Neutrophil-to-lymphocyte Ratio in Children with Chronic Urticaria

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ABSTRACT

Aim: Recently, it has been reported that the mean platelet volume (MPV) and neutrophil-to-lymphocyte ratio (NLR) can be used as indicators of inflammation in various inflammatory diseases such as psoriasis, ankylosing spondylitis and ulcerative colitis. In this study, we aimed to assess MPV levels and NLR in children with chronic urticaria (CU) and to compare them with healthy controls.

Materials and Methods: The cases of 46 children with CU [11 with inducible urticaria (IU) and 35 with chronic spontaneous urticaria (CSU)] admitted to our outpatient clinics, and 30 healthy children were evaluated retrospectively.

Results: No statistically significant differences among the CU, CSU, and IU and the control groups were found in terms of NLR and MPV levels ($p>0.05$). The platelet counts in the CU, CSU, and IU and control groups were not statistically significantly different ($p>0.05$).

Conclusion: We found that MPV levels and NLR were not different in children with CU, CSU, and IU and in healthy children. It seems that the MPV and NLR cannot be used as inflammatory markers of CU in children. We believe that further studies are required in this field.

Keywords: Chronic urticaria, mean platelet volume, neutrophil-to-lymphocyte ratio

Introduction

Chronic urticaria (CU) is an inflammatory disease, characterized by a daily or near daily occurrence of urticarial symptoms, occurring over a period of more than 6 weeks. CU in children is less common than in adults, affecting 0.1-3.0% of children (1,2). CU is divided into 2 sub-types, known as chronic spontaneous urticaria (CSU) and inducible urticaria (IU). Unlike CSU, in IU, the appearance of clinical manifestations is evoked by physical-environmental stimuli and not spontaneously. The two subtypes of CU can coexist within the same child (3).

The pathogenesis of CU is complex and not yet fully understood. However, mast cells are the key elements in CU pathogenesis (4,5). CU is characterized by predominantly non necrotizing infiltrate CD4+ lymphocytes, with variable numbers of monocytes, neutrophils, eosinophils, and basophils as an inflammatory disease of skin (6,7). Platelets play a crucial role in inflammation and their role in CU has been investigated (8). Platelet size indices, neutrophil-to-lymphocyte ratio (NLR) and C-reactive protein (CRP) have been reported as an inflammatory index in various inflammatory diseases such as urticaria, psoriasis and

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Familial Mediterranean fever (FMF) (7-10). Studies assessing the association of CU and mean platelet volume (MPV) in children, however, are limited (8,11). To our knowledge, NLR has not so far been evaluated in patients with urticaria. In this study, we aimed to assess MPV levels and NLR in children with CU and to compare them with those of healthy children.

Materials and Methods

The cases of 46 children with CU who were 18 years of age or less (11 with IU and 35 with CSU) admitted to our outpatient clinics between April 2013 and August 2015 were evaluated retrospectively. Because of the retrospective nature of this study, Haseki Training and Research Hospital Local Ethics Committee rejected to our application. An informed consent form was obtained from the patients' parents.

Those children with CSU with active lesions were included in the study. Those children who had a history of diseases such as hypertension, hyperlipidemia, obesity, diabetes mellitus (DM) that affect MPV levels and those who had a history of any corticosteroids use within one month and antihistamines use within one week prior to admission were excluded from the study (12). Age and sex-matched healthy children who visited the outpatient clinics for regular check-ups were enrolled into the control group. The control group included 30 healthy children who were 18 years of age or less, with no history of any dermatological and systemic diseases, and had no history of any drug use within 6 months prior to the study. NLR was obtained by dividing the neutrophil count by the lymphocyte count. The age, age at onset, duration of disease, gender, presence of any concomitant disease, leukocyte, neutrophil, lymphocyte, platelet, MPV, NLR, and CRP levels of the children with CU were examined. In addition, routinely requested tests for diseases that may accompany or may trigger CU (complete blood count, liver and kidney function tests, urine analysis, thyroid function tests and antibodies, total immunoglobulin E, throat and urine cultures, stool parasite exam, anti-streptolysin O, hepatitis markers (hepatitis B surface antigen (HBsAg), anti-HBs, anti-hepatitis C virus), *Helicobacter pylori (H. pylori)* stool direct antigen, anti-nuclear antibodies, rheumatoid factor, lung and sinus X-ray) were examined. In the control group, the age, gender, leukocyte, neutrophil, lymphocyte, platelet, MPV, and NLR levels were examined and compared with those of the children with CU.

Statistical Analysis

SPSS 15.0 for Windows was used for the statistical analysis. For descriptive statistics; numbers and percentages for categorical variables, and the mean and standard deviation, and the median for quantitative variables were given. Comparisons between two independent groups were carried out using the Student's t-test for quantitative variables with normal distribution, and the Mann-Whitney U test was used for quantitative variables which did not exhibit normal distribution. For comparisons of more than 2 groups, the one-way ANOVA test was used when the normal distribution condition was present, and the Kruskal-Wallis test was used when the parametric test condition was not present. The rates of categorical variables between groups were tested by chi-square analysis. When the relationship between the numerical variables provided parametric test conditions, the Pearson correlation analysis was applied, when it did not provide results, the Spearman correlation analysis was used. Statistical significance was accepted as $p<0.05$.

Results

Of the 46 children with CU, 18 (39.1%) were girls and 28 (60.9%) were boys; of the 30 healthy children, 10 (33.3%) were girls and 20 (66.7%) were boys. The mean age of the children with CU was 12.59±4.55 years (3-18 years), and of the control group, 11.5±3.1 years (5-15 years). The two groups were matched in terms of mean age and gender ($p>0.05$). The mean age at disease onset was 11.35±5.20 years (1-18 years). The duration of the disease was 18.67±27.68 months (1.5-144 months).

Thirty-two children had CSU, 8 had symptomatic dermographism, 2 had cold urticaria, 2 had CSU + cholinergic urticaria, 1 had CSU+cold urticaria, and 1 had symptomatic dermographism + cold urticaria in the CU patient group. Three children with both CSU and IU were included in the CSU group. According to this, 11 (23.9%) of children had IU, and 35 (76.1%) had CSU.

Four children with CU were concomitant as follows: one of the children had psoriasis, 1 had vitiligo, 1 had FMF, and 1 had chronic sinusitis. The results of *H. pylori* stool direct antigen of 25 children with CU were obtained. Eleven of twenty-five children with CU were positive for *H. pylori* stool direct antigen. According to these findings, concomitant and other chronic inflammatory conditions (accompanying other chronic inflammatory disease and *H. pylori* stool direct antigen positivity) related to CU were present in a total of 13 children.

No statistically significant difference was detected between the CSU, IU and control groups in terms of leukocyte, hemoglobin (Hg), neutrophil, lymphocyte,

platelet counts, NLR and MPV mean values (p>0.05). No statistically significant difference was detected between the CU group and the control group's leukocyte, Hg, neutrophil, lymphocyte, platelet counts, NLR, and MPV mean values (p>0.05) (Table I).

No statistically significant difference was found in CRP levels between the children with IU and CSU (p>0.05).

In the CU and control groups, the platelet counts were negatively correlated with MPV levels (r=-0.345, p=0.002; r=-0.474, p=0.008).

There was not any statistically significant difference between CRP levels, platelet counts, MPV levels and NLR of children with CU with *H. pylori* positive and the children with CU with *H. pylori* negative (n=25, p>0.05). No statistically significant difference in platelet counts, MPV levels and NLR were found between the children with CU with *H. pylori* positive and the control group (p>0.05).

There was statistically no significant difference between CRP levels, platelet counts, MPV levels and NLR of the children with CU with other concomitant chronic inflammatory conditions and those children with only CU (n=27, p>0.05). No statistically significant difference was found in platelet counts, MPV levels and NLR between the children with CU with concomitant and other chronic inflammatory conditions and the control group (p>0.05).

Discussion

Many etiologic factors have been associated with the origin of CU, but most cases are idiopathic (1,2). Physical factors play a major role in CU (1). Of our children with CU, IU made up 23.9% and CSU accounted for 76.1%.

Table I. The laboratory values of the chronic urticaria and control groups

	Chronic urticaria, n=46	**Control group, n=30**	**p value**
	Mean ± SD	**Mean ± SD**	
Leukocyte, (10^3/uL)	7.3±2.1	7.8±1.9	0.254
Hemoglobin, (g/dL)	13.3±1.1	13.1±1.3	0.375
Neutrophil, (10^3/uL)	3.9±1.6	4.3±1.6	0.186
Lymphocyte, (10^3/uL)	2.6±0.8	2.6±0.7	0.973
NLR	1.6±0.8	1.9±1.1	0.135
Platelet, (10^3/uL)	285.9±70.2	316.3±93.0	0.109
MPV, (fL)	8.9±1.4	9.2±1.2	0.427

SD: Standard deviation, NLR: Neutrophil-to-lymphocyte ratio, MPV: Mean platelet volume

The pathogenetic mechanism of CU is not yet well understood; however, the activation of skin mast cells play a key role in inflammation associated with the disease. Mast cell activation and the release of mediators, particularly histamine, can impact cutaneous inflammatory processes and the accumulation and activation of other cells (4,13,14). The activation and degranulation of mast cells can be triggered by a number of mechanisms such as autoimmunity, complement components, and coagulation cascade (4,6). In recent years, platelets have been found to play a dominant role in the immune/inflammatory processes (15). The role of platelets in inflammatory skin diseases such as atopic dermatitis, psoriasis, and urticaria has been evaluated (15,16). It is considered that activated platelets might have an impact on mast cells, probably through the activation of the coagulation cascade (8,16). It has also been reported that platelet activation products such as platelet factor 4 and beta-thromboglobulin levels are elevated in pressure and cold urticaria which are subtypes of IU (17,18).

CRP is a sensitive systemic marker of inflammation, responding to interleukin-6 (IL-6) (7). In recent years, some systemic inflammatory diseases have been shown to be positively associated with CRP (19-22). In our study, there was no difference in CRP levels between the CSU and IU groups. Since the CRP could not be examined in the healthy children in our study, we are unable to make any further comment.

MPV shows platelet size and it is used to show platelet function and activation. While the count of platelets increases during inflammation, their volume tends to decrease or increase (23). MPV increases in type 2 DM, smoking, hypertension, hypercholesterolemia, obesity, coronary heart diseases and metabolic syndrome (12). In our study, only one patient (2.2%) had an increased MPV (MPV >12.0 fL). No additional pathology was found to affect MPV levels in the children with CU. In our study, MPV levels and platelet counts showed no difference between the CSU, IU, and control groups. In Kasperska-Zając et al. (22) study, no difference was found in the platelet counts and MPV levels between CSU and healthy control subjects. When the platelet counts were evaluated according to disease severity, in the severe group, it was found to be significantly higher than the less severe group and the control group. While Isiksacan et al. (24) found low MPV, Confino-Cohen et al. (25) found high MPV in CU. Akelma et al. (11), though, found the MPV value to be lower in the CSU group than the control group, and the platelet counts to be higher, and they reported that the decline in MPV may be used as an inflammatory marker in pediatric patients with CSU.

For CSU patients resistant to histamine, no difference was found in their platelet counts compared to control and non-histamine resistant CSU, while the MPV values were determined as higher (20). Additionally, higher MPV levels were determined in patients with CU using the positive autologous serum skin test (26-28). In the literature, these different results suggested to us that more studies need to be performed with a larger volume of patients. Different results may be associated with patients being in different age groups [only Akelma et al. (11) study population is based on a children's group, the other studies are focused on adult age groups (20,22,24-28)] and also the patients being grouped in different ways may cause results to differ. In addition, because our patient group was mainly made up of the childhood age group, the severity of the disease, and the correlation between the severity of the disease and the inflammation parameters could not be evaluated.

NLR is a cost-effective method, and high levels of NLR are considered as an inflammatory marker (29). We have not encountered any studies in our literature review that investigated NLR being used as an inflammatory marker in urticaria yet. In our study, no difference was found in NLR levels among children with CU and healthy children, and the CSU group and the IU group. In studies of psoriasis and FMF, high NLR was found and it was reported that NLR is a marker of inflammation in patients with psoriasis and FMF (9,10,30,31).

We did not find any differences in the terms of MPV levels and NLR among children with CU with *H. pylori* positive, children with CU with *H. pylori* negative and the control group. Additionally we also did not find any differences in the terms of MPV levels and NLR among children with CU with concomitant and other chronic inflammatory conditions, only children with CU and control group. These findings show us that MPV and NLR do not change in chronic inflammation. Also, according to these findings, we did not think concomitant and other inflammatory conditions led to a bias.

Study Limitations

The greatest limitation of our study was that it was a retrospectively designed study so there was an inability to show CRP in healthy children, to show disease severity, and there was an inability to get the results of *H. pylori* for all children with CU.

Conclusion

In our study, we detected that the platelet count, MPV levels, and the NLR did not differ in children with CU, CSU, and IU and the control group. It seems that the simple tests like MPV and NLR cannot be used as inflammatory markers of CU in children. We believe that more studies need to be performed pertaining to this topic.

Ethics

Ethics Committee Approval: Retrospective study.

Informed Consent: An informed consent form was obtained from the patients' parents.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: M.A.D., H.D., H.N.S.D., Design: M.A.D., H.D., Data Collection or Proces-sing: M.A.D., H.D., İ.O.T., Analysis or Interpretation: M.A.D., H.D., Literature Search: M.A.D., H.D., İ.O.T., H.N.S.D., Writing: M.A.D., H.D.

Conflict of Interest: None of the authors had conflict of interest.

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Original Article

Results of Vincristine, Cyclophosphamide and Topotecan Protocol in Refractory/Relapsed Pediatric Solid Tumors: A Single-center Experience

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ABSTRACT

Aim: Despite dramatic progress in the treatment of pediatric solid tumors in the last 3 decades, confronting a relapsed or refractory patient is still challenging. We report our experience of refractory/relapsed pediatric solid tumor patients treated with vincristin + topotecan + cyclophosphamide (VTC) as a salvage therapy.

Materials and Methods: Eleven refractory/relapsed patients (5 neuroblastoma, 4 Ewing's sarcoma, 1 rhabdomyosarcoma and 1 osteosarcoma) who were given VTC as a salvage therapy were evaluated. All of them were metastatic at diagnosis and received appropriate initial chemotherapy. VTC consisted of vincristin (1.5 mg/m^2 on day 1), cyclophosphamide (600 mg/m^2/day with mesna, on days 1 and 2) and topotecan (1 mg/m^2/day on days 1, 2 and 3).

Results: Eleven patients received a total of 53 courses of VTC with a median of 4 (range: 2-14). Median age at diagnosis was 12 years. One patient achieved complete response, 6 patients had stable disease, and 4 patients had progressive disease after 2 courses of VTC. The median survival duration was 28 months after diagnosis while it was 16 months after relapse. The median survival duration after first VTC was 5 months (2-21 months). Myelosuppression was the primary dose limiting toxicity.

Conclusion: We concluded that VTC has a clinically tolerable but non-satisfactory effect on relapsed/refractory solid tumors in children.

Keywords: Refractory solid tumors, salvage chemotherapy, VTC treatment

Introduction

Despite dramatic progress in the treatment of pediatric solid tumors in the last 3 decades, confronting a relapsed or refractory patient is still challenging. These children, almost invariably, receive multimodal therapy that consists of radiation, chemotherapy (CHEMO) and surgery making them "heavily pre-treated patients". As a result, further therapies become intolerable. At the same time, current salvage chemotherapies do not provide satisfying results yet. Thus, novel chemotherapy regimens are needed.

Topotecan (TOPO), a camptothecin analogue, produces DNA strand breaks by forming a ternary complex with DNA and topoisomerase 1 (1). After its first approval for use in the treatment of recurrent ovarian cancer in 1996, clinical trials assessing camptothecins against various types of cancer have gained speed (2). The role of camptothecins in combination CHEMO has been another debate topic since then. *In vitro* synergism of topotecan with alkylating agents was shown in various studies (3,4). Consequently, clinical studies evaluating a combination of TOPO with

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other antineoplastic agents [including cyclophosphamide (CYC)] against solid tumors has been in favor (5,6). The Children's Oncology Group conducted a phase 2, randomized comparison study of TOPO plus CYC versus TOPO alone in recurrent/refractory neuroblastoma (NBL) patients revealing significantly better progression free survival but not overall survival (7). Other recent studies, despite the considerably low toxicity profile of this combination, pointed to modest activity of TOPO+CYC and the need for better combinations (8-10).

Another chemotherapeutic agent, vincristine, is thought to have a synergistic effect when combined with other anticancer drugs (11). It is suggested for use with topotecan as well (12). Kebudi et al. (13) recently published their results of a vincristine, TOPO and CYC CHEMO protocol vincristin + topotecan + cyclophosphamide (VTC) in recurrent/progressive Ewing sarcoma (ES) patients.

In the light of this data, we opted to apply VTC as a salvage treatment protocol in refractory/relapsed pediatric solid tumor patients after 2008. Here, we report our experience of refractory/relapsed pediatric solid tumor patients treated with VTC as a salvage therapy.

Materials and Methods

Clinical and laboratory data of all refractory/relapsed pediatric solid tumor patients who had received VTC CHEMO protocol at Kocaeli University Clinic of Pediatric Oncology after 2008 were collected from the patients' database with the approval of the Local Ethics Committee. Eleven refractory/relapsed patients (5 NBL, 4 ES, 1 rhabdomyosarcoma and 1 osteosarcoma) who were given VTC as a salvage therapy were retrospectively evaluated. Informed consent for VTC treatment was obtained from all the patients/parents. VTC consisted of vincristin (1.5 mg/m^2 on day 1), CYC (600 mg/m^2/day with mesna, on days 1 and 2) and TOPO (1 mg/m^2/day on days 1, 2 and 3). VTC was given over a 2-night stay in hospital and the patients were discharged on the 3rd day of hospitalization. The courses were repeated every 21 days with adequate hematological values (absolute neutrophil count >1.000 mm^3, platelet count >100.000/mm^3). None of the patients received any other anti-cancer or investigational drugs during their VTC cycles. Physical examination and laboratory evaluation were both performed just before each cycle and also when it was required (during febrile neutropenia or before transfusion).

We recorded the patients' ages, genders, diagnoses, initial site and stage of tumor, other chemotherapies that were given prior/after VTC, data on the surgery and radiotherapy if there was any, time of relapse, presence of metastasis, status of the disease during the initiation of VTC (progression vs relapse), response after 2nd, 4th and 6th-10th VTC therapy course if available and the last status of the disease (remission/alive with disease/died of disease). The response to VTC was assessed via standard radiologic evaluations (computerized tomography, magnetic resonance imaging and ^{18}F-FDG PET/CT where available), and the following criteria were used: [complete response (CR), no evidence of disease for 4 or more weeks; partial response (PR), at least 50% decrease in all measurable lesions for 4 or more weeks; progressive disease (PD), at least 20% increase in the size of any lesions; stable disease (SD), absence of CR, PR or PD].

We provided supportive care whenever needed and also hydration, antiemetics (granisetron) and granulocyte colony stimulating factors (beginning 24 hours after the end of VTC, lenograstim) as standard treatment. We also recorded the number of febrile neutropenic attacks, days of extra hospitalization caused by febrile neutropenic attacks and demand for blood products (packed red blood cells and thrombocyte suspensions) from the beginning of the first VTC cycle to 1 month after the last VTC was given. Blood product transfusions were performed in our outpatient clinic.

Statistical Analysis

All signs and findings of toxicities were searched for and recorded from the database regarding the Common Terminology Criteria for Adverse Events v4.0 provided by the National Institute of Health.

No specific statistical analysis was used in the study as we only observed the response rate after VTC treatment. All data of the study were analyzed with Microsoft Excel, 2007.

Results

We detected 11 relapsed/refractory solid tumor patients treated with VTC at our institution between January 2008 and November 2014. The patient characteristics are shown in Table I. The median age at diagnosis was 12 years (range: 3.5-18 y). All eleven of the patients were metastatic at diagnosis and received appropriate initial CHEMO. All patients had surgical intervention but none had a complete tumor resection during the initial treatment. Ten of the patients received radiotherapy, the exception was the osteosarcoma patient (#7). All but 3 relapsed and these 3 patients (#4, #7 and #8) still had progressive disease despite ≥3rd line therapy given after diagnosis. Median time from first remission to relapse was 14 months (range: 5-36

Table I. Patient Characteristics

Patient	Age at diagnosis (years)	Gender	Diagnosis	Localization of primary disease	Metastasis	Initial CHEMO*	Primary site XRT	Time to relapse after first remission	Localisation of relapse	Relapse treatment before VTC
#1	5	M	Neuroblastoma	Right adrenal	Bone	TPOG	25 Gy	14 mon	Metastatic (Brain)	Ifosfamide+Carboplatin+Etoposide (ICE)
#2	14	M	Ewing sarcoma	Right iliac bone	Lungs	EVAIA	50.4 Gy	17 mon	Primary site	ICE
#3	12	F	Ewing sarcoma	Cervical vertebrae	Brain	EVAIA	48.6 Gy	17 mon	Metastatic (Brain)	Ifosfamide
#4	4.5	M	Neuroblastoma	Right adrenal	Lungs, bone, bone marrow	TPOG	25 Gy	no remission	N/A	ICE, Irinotecan + temozolamide
#5	3.5	F	Neuroblastoma	Left adrenal	Bone marrow	TPOG	25 Gy	8.5 mon	Primary site + Metastatic (lungs, bone)	none
#6	6	F	Neuroblastoma	Right adrenal	Bone, bone marrow	TPOG	25 Gy	10.5 mon	Primary site + Metastatic (bone marrow)	ICE
#7	18	M	Osteosarcoma	Left femur	Lungs	COG	none	no remission	N/A	Ifosfamide, Gemcitabine + docetaxel
#8	15.5	M	Ewing sarcoma	Left iliac bone	Lungs	EVAIA	45 Gy	no remission	N/A	ICE, Irinotecan + temozolamide, Gemcitabine+Docetaxel
#9	7	M	Neuroblastoma	Right adrenal	Bone, bone marrow	TPOG	25 Gy	36 mon	Metastatic (Bone, bone marrow)	ICE, Irinotecan+temozolamide
#10	14	F	Ewing sarcoma	6th right rib	Bone	EVAIA	54 Gy	12 mon	Primary site + Metastatic (lungs)	ICE
#11	14	M	Rhabdomyosarcoma	Left leg	Iliac lymph nodes	EVAIA	45 Gy	15 mon	Metastatic (lungs, bone)	none

CHEMO: Chemotherapy, XRT: Radiation therapy, ICE: Ice, compression, elevation, VTC: Vincristin + topotecan + cyclophosphamide, M: Male, F: Female, TPOG: Turkish Pediatric Oncology Group, EVAIA: IECESS Treatment Protocol, COG: Children Oncology Group Treatment Protocol, N/A: Not available

months). Only one patient (#2) had a relapse at the primary tumor site, the other 10 patients had either primary and metastatic tumors or only metastatic tumors.

The eleven patients received a total of 53 courses of VTC with a median of 4 (range: 2-14). One patient achieved CR, 6 patients had SD, and 4 patients had PD after 2 courses of VTC (Table II). None of the patients showed PR. One patient (#1) is alive and in CR while the other 10 patients died of either relapsed or progressive disease. The median survival duration was 28 months (range: 10-67 months) after diagnosis while it was 16 months (range: 2-49 months) after relapse. The median survival duration after the first VTC was 5 months (2-21 months). The patient (#1) with brain metastasis did not have surgery for metastasis but received whole brain radiotherapy (30 Gy in 10 fractions). Three NBL patients had undergone autologous stem cell transplantation with a high dose CHEMO (ASCT + HD) (#1 alive, #6 and #9 died of disease), but the other two NBL patients (#4 and #5) did not receive ASCT+HD as their parents refused. Also, one patient (#4) had 131-I-MIBG therapy. Four patients (#2, #8, #10 and #11) received palliative radiotherapy at local inoperable sites aiming to relieve pain. None of the patients had therapeutic surgery during their VTC cycles.

VTC was well tolerated. We observed hematologic toxicity to be frequent. Myelosuppression was the primary dose limiting toxicity. All patients developed grade 3-4 anemia in a total of 15 courses. There were 9 grade 3-4 thrombocytopenia episodes in 9 patients. There were 4 febrile neutropenic episodes in 3 patients, 2 of them were bacteremia, and all were managed by intravenous antibiotics administered in hospital. These episodes resulted in a total of 30 additional inpatient days. We did not encounter a non-hematological toxicity of 3 grade or over. There were no significant toxicities or deaths related to VTC. We did not need to reduce the VTC dose for any patient.

Discussion

There are many studies drawing attention to the relatively superior effect of the TOPO+CYC combination for the treatment of various types of recurrent/refractory pediatric solid tumors. Most of these studies have focused on NBL and ES patients (6-9). The Pediatric Oncology Group (POG) studied TOPO + CYC treatment in a heterogeneous group of recurrent/refractory pediatric solid tumors and demonstrated a better objective response rate (>10%) in rhabdomyosarcoma, NBL and ES patients in phase studies (5,14). Currently, we need to achieve better results and combining vincristine with TOPO + CYC appears to be a smart move as it is an M-phase specific chemotherapeutic and this leads to an expectation of an additional anti-cancer effect.

Our patient group consisted of mostly NBL and ES patients. Only 1 patient (#1) had CR and none had PR. The objective response rate (CR + PR) was 9% overall and it was 20% among the NBL group. Patient #1's relapse occurred in the brain and the other NBL patients had metastases in various places; in the lungs, bones, bone marrow and a recurrence of the tumor at the primary site. A recent report (15), assessing 8.369 pediatric NBL patients,

Table II. Study group response to VTC treatment

#	Number of VTC cycles	Response after 2nd VTC	Response after 4th VTC	Response after 6th-10th VTC	Follow-up time after first VTC	Overall follow-up time after diagnosis	Last status of patient
1	14	CR2	CR2	CR2	12 mon	29 mon	Alive
2	4	SD	PD	N/A	5 mon	38 mon	DOD
3	8	SD	SD	PD	9 mon	66 mon	DOD
4	2	PD	N/A	N/A	2 mon	10 mon	DOD
5	2	PD	N/A	N/A	2 mon	10.5 mon	DOD
6	2	PD	N/A	N/A	4 mon	13.5 mon	DOD
7	2	PD	N/A	N/A	3 mon	20 mon	DOD
8	4	SD	PD	N/A	14 mon	26 mon	DOD
9	4	SD	PD	N/A	3 mon	67 mon	DOD
10	6	SD	SD	PD	11 mon	28 mon	DOD
11	5	SD	PD	N/A	21mon	36 mon	DOD

VTC: Vincristin + topotecan + cyclophosphamide, CR: Complete response, PD: Progressive disease, SD: Stable disease, N/A: Not available, DOD: Died of disease

has shown important clinical and biological differences. We earlier speculated in another report (16) that the differentiation of NBL cells varies individually during disease progression causing differences in the response to treatment and clinical outcome. This divergence could also affect radiological and other laboratory results, as well. We believe the discrete clinical features of patient #1 are associated with his better response to VTC. Furthermore, topotecan is known to penetrate well into the central nervous system (17). In our study, overall objective response rates, both among all patients and only in the NBL group, are lower than POG's TOPO + CYC study group (5), stated as 67% in rhabdomyosarcoma, 46% in NBL, 35% in ES patients and 42% overall.

All ES patients had SD after 2 VTC cycles. We observed 2 of 4 ES patients (the other 2 progressed) to sustain SD for the first 4 VTC cycles but their disease also progressed after 6-8 cycles of VTC. Kebudi et al. (13) reported an objective response of 50% (2 patients CR, 5 patients PR) in their relapsed/progressive ES patient series (14 episodes in 13 patients) treated with VTC. In another study (8) of TOPO + CYC performed in 14 relapsed/progressive (3 metastatic at diagnosis) ES patients, 3 patients (2 with local relapse) showed PR (23%) while none had CR. Hunold et al. (6) reported "time to relapse" and "local therapy" as significant prognostic factors in their ES series (including both pediatric and adult patients) treated with TOPO + CYC.

All the studies mentioned above seem to have better response rates than ours. We do not deny the objective effects of both TOPO + CYC and VTC therapies, however, the relative low number of high stage patients in their cohorts may have resulted with inevitably biased response rates. Our patients mostly had early relapses (8 of 9 relapsed patients) and all were metastatic with high stage tumors. All these factors could be responsible for our patients' low objective response.

Study Limitations

The small sample size, heterogeneity of the diagnoses and retrospective design are the major limitations in our study.

Conclusion

We concluded that VTC has a clinically tolerable but non-satisfactory effect on refractory/relapsed solid tumors in children.

Ethics

Ethics Committee Approval: Retrospective study.

Informed Consent: Informed consent for VTC treatment was obtained from all the patients/parents.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: U.D., F.Ç., M.K., Design: U.D., F.Ç., M.K., Data Collection or Processing: U.D., F.Ç., M.K., Analysis or Interpretation: U.D., F.Ç., M.K., Literature Search: U.D., F.Ç., M.K., Writing: U.D., F.Ç., M.K.

Conflict of Interest: None of the authors had conflict of interest.

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Original Article

The Role of Cardiac Magnetic Resonance Imaging in the Determination of Cardiovascular Anomalies in Children and Young Adults with Turner Syndrome

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ABSTRACT

Aim: Congenital cardiovascular (CV) anomalies and aortic dilatation are common in patients with Turner syndrome. The aim of this study was to compare echocardiography (ECHO) findings with CV anomalies and aortic dilatation identified using magnetic resonance imaging (MRI) in children and young adults with Turner syndrome.

Materials and Methods: Twenty-six girls with Turner syndrome aged 11-20 years were recruited through tertiary centers. CV anomalies and aortic diameter were evaluated using CV-MRI. Auxological measurements, karyotype analyses, medical therapies (growth hormone, estrogen, and thyroid replacement therapy) and transthoracic ECHO findings were recorded for all participants.

Results: Normal cardiac anatomy was identified in 16 (61.5%) of our 26 cases, with no cardiac pathology being identified via either CV-MRI or ECHO. CV anomalies were identified in 5 of the 26 (19.2%) patients via CV-MRI. Aortic dilatation was determined in four patients (one with descending and ascending aorta, one with ascending aorta, and two with descending aorta). Aortic size index was <2 cm/m^2 in all patients. ECHO was normal for the three patients with malformations detected via CV-MRI.

Conclusion: CV-MRI identifies significant cardiac lesions missed by ECHO in pediatric patients with Turner syndrome, especially aortic dilatation and other vascular anomalies.

Keywords: Turner syndrome, cardiac magnetic resonance imaging, cardiovascular anomalies

Introduction

Turner syndrome, or monosomy X, is caused by a complete or partial absence of one of the two normal X-chromosomes (1). It affects one in 2000 live-born females. The most serious clinical aspect of the syndrome is due to congenital and/or acquired cardiovascular diseases (CVD). CV morbidity has been estimated to affect approximately 50% of patients with Turner syndrome. CV anomalies include bicuspid aortic valve (BAV), persistent left superior vena cava, anomalous pulmonary venous return, elongation of the transverse aorta, coarctation of the aorta, aortic dissection, and dilatation and pseudocoarctation of the aorta (2-4). However, the syndrome has also been associated with other arterial and venous anomalies. The incidence of

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CV lesions ranges from 23% to 45% (3,5). Mortality rates are three times higher in women with Turner syndrome than in the normal female population (1). Shortened lifespan is often due to CV complications, such as aortic dilatation and dissection (6). Transthoracic echocardiography (ECHO) and CV-magnetic resonance imaging (MRI) are the principal methods used for the diagnosis and surveillance of these conditions (7). A high prevalence of structural anomalies in patients with Turner syndrome that are not revealed via ECHO have been detected using CV-MRI. Although ECHO is a standard method for evaluating cardiac anatomy in Turner syndrome patients, its usefulness in the evaluation of vascular anomalies is limited. CV-MRI is recommended for the management of patients with Turner syndrome (7-9). The aim of this study was to compare ECHO findings with CV anomalies and aortic dilatation identified using MRI in children and young adults with Turner syndrome.

Materials and Methods

Twenty-six girls and women with Turner syndrome aged 11-20 years were enrolled in this study. Subjects able to tolerate CV-MRI without sedation were included, and patients less than 11 years were therefore excluded. Relevant clinical data, including auxological measurements (weight, weight standard deviation score (SDS), height, height SDS, body mass index (BMI), and BMI-SDS), karyotype analyses, and medical therapies (growth hormone, estrogen, and thyroid replacement therapy) were recorded. Body surface area (BSA) was calculated based on the formula described by Du Bois and Du Bois (10). ECHO findings were recorded retrospectively.

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation (Ege University) and with the Helsinki Declaration of 1975, as revised in 2008, and have been approved by the institutional committees of Ege University (approval number: 18-7.1/31). Informed consent was obtained.

Magnetic Resonance Imaging

All patients underwent imaging on a 3 Tesla MR scanner (Verio, Siemens Medical Systems) using a body coil and included axial T2 weighted (W) HASTE sequences. MR angiography was conducted with flash 3D coronal images and 0.2 mmol/kg of Gadolinium-chelate contrast media administered through an antecubital vein with a MR compatible injector (Ulrich, Germany). Post gadolinium axial T1-W-VIBE images also were performed. The diameters of the ascending and descending aorta were measured on axial T1-W images at the level of the right pulmonary artery, perpendicular to the long axis of the ascending aorta in a blinded fashion.

All participants tolerated CV-MRI without sedation or complications. Measurements were recorded for ascending and descending aortic diameter and pulmonary conus diameter, and aortic size index (ASI) (ascending aorta/BSA). Measurements were standardized by BSA to determine z-scores. The aorta and pulmonary conus were considered dilated in cases of a z-score greater than 2. ASI values were also calculated (cm/m^2). Aortic coarctation, transverse arch, bovine arch, left vertebral artery anomaly, aberrant right subclavian artery, persistent left superior vena cava and partial pulmonary venous return anomaly were recorded.

Statistical Analyses

Descriptive statistics were used for data analysis. Continuous data were expressed as mean values with ranges. z-scores were calculated for weight, height, and BMI, and represented as mean values [±standard deviation (SD)]. The frequencies of vascular anomalies and cardiac lesions were analyzed, and any disparity between ECHO and CV-MRI findings was noted.

Results

Twenty-six girls with Turner syndrome, aged 11-20 years of age, were included in the study. Mean age at investigation was 16.6±2.8 years. The patients' clinical characteristics are shown in Table I. Karyotype analysis revealed 57.7% (n=15) 45,X monosomy, 30.8% (n=8) mosaicism, and 11.5% (n=3) isochromosome. In terms of treatment, 84.4% (n=23) of the patients received growth hormone therapy. CV anomalies were identified in five of the 26 (19.2%) patients via CV-MRI. Of these, 45,X monosomy karyotypes were identified in four and 46,X,i(Xq) in one. CV-MRI revealed pseudocoarctation in two patients, aberrant right subclavian artery in two, and azygos lobe fissure variations in one. An appearance compatible with bicuspid aorta was identified via ECHO in one case in which pseudocoarctation was detected via CV-MRI and in one patient with right aberrant subclavian artery detected via CV-MRI. ECHO was normal for the other three patients with a malformation detected via CV-MRI. CV-MRI was normal in two cases in which ASD secundum was detected via ECHO (Table II).

Mean ± SD of ascending aortic diameter 2.16±0.29 cm and z-score 0.08±1.4, descending aortic diameter 1.63±0.30 cm and z-score -0.07±1.34, and pulmonary conus diameter

1.91±0.47 cm and z-score -0.94±1.59 were detected. The mean ± SDASI was 1.44±0.24 cm/m^2 (Table III). Aortic dilatation was determined in four patients (15.3%) in our study (one with descending and ascending aorta, one with ascending aorta, and two with descending aorta). ASI was <2 cm/m^2 in all patients.

Discussion

CV-MRI is the gold standard method for the diagnosis and follow-up of thoracic aorta morphological anomalies in patients with Turner syndrome (7). Transthoracic ECHO may be of limited use in assessing the anatomy in an abnormally shaped chest, and can underestimate the size of both the ascending and descending aorta in patients with Turner syndrome. Although CV-MRI is clearly recommended in the guidelines, the optimal timing of the first imaging is not well established. CV-MRI is used in older girls and adults who are able to tolerate the procedure without sedation. Subsequent routine imaging is recommended every 5-10 years (11). Patients over 10 years of age and evaluated with MRI without the need for sedation were included in our study group.

Growth hormone deficiency is associated with increased CV risk (12). Growth hormone and the 45,X monosomy karyotype correlate with a dilated proximal aorta (13). Donadille et al. (14) emphasized that patients with monosomy X in a cohort study should be monitored more closely in CV terms. Karyotype analysis revealed 45,X monosomy in four of the five patients with cardiac anomaly detected via CV-MRI and in all four patients with enlarged aortic diameter. Except for one patient in whom an aberrant right subclavian artery anomaly was detected, all cases were treated with growth hormone.

Pseudocoarctation of the aortic arch is a rare congenital anomaly which resembles true coarctation and is caused by the presence of a narrowing in the descending thoracic aorta immediately distal to the origin of the left subclavian artery (15). In our study, pseudocoarctation was detected in two cases via cardiac MRI, but this finding was not detected using ECHO in one case.

Ho et al. (2) estimated a prevalence of aberrant right subclavian artery frequency in Turner syndrome of 8%, compared to 0.4-2% in the normal population (16). In our study, an aberrant right subclavian artery anomaly was detected with CV-MRI in two cases. BAV is also common in Turner syndrome (17). In their comparison of CV-MRI and ECHO, Ostberg et al. (8) demonstrated an 18% prevalence of BAV based on ECHO findings (CV-MRI data were not shown). BAV has been determined in 1.5-17.5% of children and adults with Turner syndrome using CV-MRI and ECHO (3,4). Bicuspid aorta was determined in three patients via ECHO in our study. None of these patients exhibited valve pathology via CV-MRI.

Table I. Clinical characteristics of study participants with Turner syndrome

Age at investigation (year)	16.6±2.8
Weight SDS	-0.06±1.33*
Height SDS	-1.96±1.14*
BMI-SDS	1.24±0.99*
BSA (m^2)	1.48 (1.30-1.58)*
45,X monosomy	15/26 (57.7%)**
Mosaicism	8/26 (30.8%)
Isochromosome	3/26 (11.5%)
Growth hormone therapy	23/26 (88.4%)**
Estrogen-replacement therapy	22/26 (84.6%)**
Thyroid-replacement therapy	4/26 (15.3%)**

*Variables are represented as means±standard deviation, **Categorical variables are represented as frequencies (%)
SDS: Standard deviation score, BMI: Body mass index, BSA: Body surface area

Table II. Comparison of CV-MRI findings with echocardiography

CV-MRI		**Echocardiography**	
Findings	**n**	**Findings**	**n**
Aberran right subclavian artery	2	Bicuspid aorta	1
		Normal	1
Pseudocoarctation	2	Bicuspid aorta	1
		Normal	1
Azygos lobe fissure variation	1	Normal	1
Aortic dilatation	4	Bicuspid aorta	1
		Normal	3
Normal	17	Secundum ASD	2

CV-MRI: Cardiovascular-magnetic resonance imaging, ASD: Atrial septal defect

Table III. CV-MRI measurement data of study group

	Mean ± standard deviation	**z-score**
Ascending aortic diameter (cm)	2.16±0.29	0.08±1.4
Descending aortic diameter (cm)	1.63±0.30	-0.07±1.34
Pulmonary conus diameter (cm)	1.91±0.47	-0.94±1.59
Aortic size index (cm/m^2)	1.44±0.24	-

CV-MRI: Cardiovascular-magnetic resonance imaging

A greater incidence of interrupted inferior vena cava with azygos continuation has also been reported in patients with Turner syndrome (3,4). A variation of azygos lobe fissure was detected in one patient via MRI in our study.

It is generally agreed that patients with Turner syndrome have a significantly elevated risk of aortic dissection. The few risk factors described include hypertension, the presence of BAV or coarctation, and dilatation of the aorta (8,18). Dilatation of the aorta in certain anatomical locations has been associated with an increased risk of dissection. Castro et al. (19) CV-MRI study of children and young adults with Turner syndrome reported aortic dilatation in 26.7% of patients. Another pediatric study reported an incidence of aortic dilatation of 37% in Turner syndrome patients (13). In a study of children and young adults with Turner syndrome by Yiğit et al. (20), CV-MRI and 3D contrast-enhanced MRI angiography revealed incidences of BAV of 19.6%, coarctation of 6.5%, ascending aorta dilatation of 28.3% and descending aorta dilatation of 15.2%. BAV was identified as an important risk factor for aortic dilatation. In another study, possession of the 45,X karyotype and BAV predicted dilatation of the ascending aorta, but dilatation of the descending aorta was only observed in patients with coarctation (21). In our study, one patient with a dilated aortic diameter had a bicuspid aortic appearance via ECHO. Karyotype analysis was 45,X monosomy in all cases in which we detected aortic dilatation. ASI is a method used to evaluate the degree of aortic disease. A ratio of 2 cm/m^2 requires close follow-up, while values >2.5 cm/m^2 require transfer to an experienced center. ASI >2 cm/m^2 is considered to represent an absolute contraindication for pregnancy (22,23). ASI values were <2 cm/m^2 in all our patients.

Study Limitations

One of the limitations of our study was the small sample size. Further research with a larger patient series, especially in the pediatric age group, is now needed. The second limitation is that breathing and cardiac artefacts may have prevented the correct viewing of the CV-MRI.

Conclusion

CV-MRI should be performed on patients with Turner syndrome even if ECHO reveals a normal cardiac anatomy. CV-MRI can identify significant cardiac lesions missed by ECHO in pediatric patients with Turner syndrome, especially aortic dilatation and other vascular anomalies. Early diagnosis and an early institution of preventative and medical measures are critical for preserving the quality of life and increasing the lifespan in Turner syndrome patients.

Ethics

Ethics Committee Approval: The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation (Ege University) and with the Helsinki Declaration of 1975, as revised in 2008, and have been approved by the institutional committees of Ege University (approval number: 18-7.1/31).

Informed Consent: Informed consent was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ş.D., D.G., R.S., E.L., Concept: S.Ö., Ö.K., Design: S.Ö., Ö.K., Ş.D., Data Collecting or Processing: Ö.K., İ.M., Analysis or Interpretation: R.S., S.Ö., Ö.K., Literature Search: Ö.K., Writing: Ö.K., R.S.

Conflict of Interest: No conflict of interest was declared by the authors.

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Original Article

Determination of Variables Influencing the Quality of Life in Children with Liver Transplantation

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ABSTRACT

Aim: This clinical study examined various dimensions of the Quality of Life (QoL) in children who had undergone liver transplantation.

Materials and Methods: The patient group (n=50) of the study consisted of children and their families where the child had received a liver transplant (possibly from their mother) in Ege University Organ Transplant Research Center. The control group (n=50) consisted of children and their families who did not undergo any organ transplants, did not have any health issues and were of similar age, gender and socio-economic status with the members of the study group. The children in the study were examined with a QoL questionnaire named KINDer Lebensqualitätsfragebogen (Children's Quality of Life Questionnaire).

Results: The overall QoL and the QoL in the physical, emotional, self-esteem, family, friend, and school sub-categories as reported by the children themselves in the study group, in both the 8-12 and 13-16 year age groups were determined to be higher ($p<0.05$) when compared to those children in the control group. Similarly, the QoL for the children in the study group, as reported by their families were determined to be higher ($p<0.05$) when compared to the control group.

Conclusion: Liver transplantation has effects on the QoL of both the children and their families.

Keywords: Liver transplantation, quality of life, children, KINDL

Introduction

Solid organ transplantation is one of the methods used for the treatment of end-stage organ failures (1). However, the greatest barrier for organ transplantation is insufficiency of cadaver-derived organs both in our country and abroad. This is why patients on the waiting list for transplantation and their families are under psychological stress facing great fear of loss of life. Especially, if the patient is a child, this situation causes great changes in the family and the imaginary world of the child since he/she cannot comprehend the events properly.

The term "quality of life (QoL)" was first used in United States in 1950s, and later it was widely used to measure a sense of well-being both in health and society (2). Health-Related QoL is a versatile notion including the physical, emotional and social well-being of the patient, and is

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defined as the patient's perception of the influences of the disease and its treatment (3,4). There are a few generic QoL instruments developed for children and adolescents. The Children's Quality of Life Questionnaire (KINDL) measure is used in children with various chronic diseases and developmental problems, in order to determine which dimension of their lives are affected due to these diseases or their therapies (5,6). KINDL is a QoL measure for children developed in Germany by Ravens-Sieberer and Bullinger (7) in 1998. It is a validated and highly reliable generic QoL measure used for the assessment of physical, mental and social conditions. KINDL was lately validated in a number of languages (8-10). Eser et al. (8) validated its Turkish version in 2004, and it was shown to be valid and reliable in the Turkish language.

The aim of this study was a multidimensional assessment of the QoL in children with liver transplantation, and to determine the factors that affect the QoL of these children.

Materials and Methods

The study group consisted of 50 children between the ages of 7-16 years who had undergone liver transplantation in our center more than 1 year previously, and were admitted to our Organ Transplantation Polyclinic for routine follow up and their families. All children and their families agreed to participate in the study. The control group consisted of healthy age-, sex-, and socio-economic status- matched controls and their families (n=50) who agreed to participate in the study.

A pediatric gastroenterologist examined the files of the children in the study group. The participants in the control group were randomly chosen from different neighboring provinces and localities of İzmir. The age and gender of the participating child, as well as the age, educational status etc. of the participating parent were recorded in the socio-demographic data form in the control group, and all participants filled in the same forms used by the study group.

Ege University Nursing Faculty Ethics Committee (approval number: 2008-55). Informed parental consent was obtained for all infants. A Patient Data Form was used to record data regarding the illness and the social status of the child and their family. The children who had received transplants completed KINDL.

Children's Quality of Life Questionnaire

The tests were applied according to the age groups of the children by dividing them into three age groups: 4-7 years age group, 8-12 years age group and 13-16 years age group. This scale consists of a total of 30 items. Six subscales, respectively, examine the functionality in physical well-being (4 items), emotional well-being (4 items), self-esteem (4 items), family (4 items), friends (4 items), school (4 items) and chronic disease (6 items) subgroups. The degree of the problem specified in the item answered was asked to the parents and children. The scale is graded on a 5-point Likert scale. Including the parents' forms, all forms consist of the same items, and they differ only for the items regarding the developmental stage of the child and the sentences including third person pronouns to make the child's understanding easier. The higher the score reported, the better the QoL experienced.

Statistical Analysis

All data were transferred into the computer using (SPSS) version 10.0 (SPSS Inc. Chicago IL, USA). Frequency and chi-square tests were used for the analysis of demographic data, and Mann-Whitney U test and Wilcoxon tests were used to analyze the QoL and the effects of the variables on the QoL. The concordance between the points of the children and their parents was analyzed using Pearson's correlation analysis.

Results

The most common reason for the liver transplantation was biliary atresia (n=12, 24%). Other causes were progressive familial intrahepatic cholestasis (n=8, 16%), tyrosinemia (n=5, 10%), fulminant hepatitis (n=7, 14%), glycogen storage disease (n=4, 8%), autoimmune hepatitis (n=3, 6%), Wilson's disease (n=2, 4%), cryptogenic cirrhosis (n=3, 6%) and miscellaneous (n=6, 12%). The distribution of the patients (study and control groups) is shown in Table I. The ages of the children were similar in the study and the control groups ($p>0.05$).

Study group in 8-12 years of age had higher scores in physical well-being, family and school subgroups compared to the control group ($p<0.05$). KINDL evaluation in 8-12 years age group is shown in Table II.

Gender's effect on the sum score was significant in the 13-16 years age group control and study groups ($p<0.05$). Thirteen-16 years age boys in the study group had self-esteem, friends, chronic disease subgroups and sum scores higher compared to the girls. The girls in this age group had higher scores in the physical and emotional well-being subgroups than the boys. There was no significant difference in the sum score between 13 and 16 years in both groups ($p>0.05$). However, its impacts on the physical well-being and friend subgroups were found to be significant

(p<0.05). KINDL evaluation in the 13-16 years age group is shown in Table III.

Rejection of the transplant was shown to affect the sum score in both age groups (p<0.05). In order to determine which dependent variable caused the basic effect on the variable, a further analysis was carried out and details are shown in Table IV and V. The variable of being educated had a significant effect on the sum score in both age groups (p<0.05).

In this study, further analysis was done to determine the difference between parent-reported physical well-being, emotional well-being, social and school subgroups for the study and the control groups. The group effect was not found significant on the sum score (p>0.05). The analysis of the emotional well-being, self-esteem and school subgroups were significantly higher in the study group compared to the control group (p<0.05). KINDL evaluation for the family is shown in Table VI.

Table I. The distribution of the study and control groups

Variable	Study group		Control group		p value
Age	**n**	**%**	**n**	**%**	
8-12 year age group	32	64.00	29	58.00	0.380
13-16 year age group	18	36.00	21	42.00	
Gender					
Male	52% (n=24)	-	60% (n=30)	-	-
Female	48% (n=24)	-	40% (n=30)	-	-

Table II. Children's Quality of Life Questionnaire* evaluation in 8-12 year age group

KINDL	The mean scores of the study group	The mean scores of the control group	p value
Sum score	74.88±13.85	66.47±10.97	0.018
Physical well-being	75.07±22.84	65.75±19.01	0.013
Emotional well-being	73.66±19.93	65.00±20.96	0.130
Self-esteem	74.18±18.72	68.25±20.56	0.277
Family	74.56±19.61	61.08±19.01	0.014
Friends	78.26±15.84	78.26±15.84	0.108
School	73.28±18.58	66.25±17.02	0.015
Chronic disease	63.91±15.36	00+00	-

KINDL: Children's Quality of Life Questionnaire

Discussion

The QoL significantly improves in liver-transplant children. This improvement is more prominent in patients with inherited metabolic diseases under 5 years of age (11,12). Avitzur et al. (12) reported high QoL in 32 liver-transplant pediatric patients 10 years after the transplantation despite chronic extrahepatic morbidity. In our study, children who had a critical operation such as a liver transplantation had a high QoL perception similar to previous reports, even in some subgroups, transplant patients had higher scores than the healthy control group. Perception of high physical well-being in the study group may be related to their previous disease experiences. Those children, who endured serious health problems before, could now tolerate milder diseases in this period of their lives. In a similar study performed

Table III. Children's Quality of Life Questionnaire* evaluation in 13-16 year age group

KINDL	The mean scores of the study group	The mean scores of the control group	p value
Sum score	64.71±19.74	64.47±10.78	1.000
Physical well-being	71.88±22.40	61.31±23.52	0.013
Emotional well-being	63.54±26.88	64.88±20.20	0.966
Self esteem	65.19±26.04	67.26±19.45	0.813
Family	57.63±26.73	59.72±19.50	0.909
Friends	66.66±17.67	74.40±12.00	0.046
School	57.29±22.30	58.63±15.62	0.820
Chronic disease	68.51±14.91	00+00	-

*KINDL: Children's Quality of Life Questionnaire

Table IV. Children's Quality of Life Questionnaire evaluation according to postoperative education status of the study group (8-12 years age group)

8-12 years age group children KINDL	Educated	Not educated	p value
Sum score	79.09±8.75	70.76±9.20	0.027
Physical well-being	76.62±18.46	58.98±22.47	0.008
Emotional well-being	73.75±19.96	74.27±15.54	0.977
Self esteem	86.25±12.80	74.53±16.79	0.213
Family	73.75±6.84	78.24±15.63	0.414
Friends	86.25±2.79	78.55±17.29	0.221
School	81.54±13.76	62.87±13.71	0.003
Chronic disease	69.99±10.37	57.90±11.99	0.023

KINDL: Children's Quality of Life Questionnaire

by Tarter et al. (13), the liver transplant patients were first evaluated when they were on the waiting list, and then 2 years after transplantation, and it was found that their total QoL scores after transplantation were better than the control group, however their psychological scores were lower (14). In our study, 32 children in the 8-12 years of age study group reported that their total QoL scores were higher than the control group. However, 18 children in the 13-16 years of age study group had sum scores of QoL similar to control group. The scores for physical well-being were higher and the friend scores were lower than the control group. In the friend subgroup, if expressions such as "I felt different from other children" are taken into consideration, although a generalization is difficult, we can talk about the effect of the social environment on this age group. In a similar study, the statement of one child without any health problem as "the worst years of my life are my years in school, because the teachers say do what you can, even if you can't, this is not important" is the best example for this (15). As Bucuvalas and Ryckman (15) reported on the long-term results of liver transplant children, one of the most important problems for these patients is the long term and regular use of drugs. Attending school and school trips complicate the regular use of drugs. Informing teachers and other school workers on this issue is very important. In our study, the parents were aware of this situation and most of the families reported that they had informed the school management and teachers verbally.

Table V. Children's Quality of Life Questionnaire evaluation according to postoperative education status of the study group (13-16 years age group)

13-16 years age group children KINDL domains	Educated	Not educated	p value
Sum score	78.63±20.90	63.20±19.94	0.029
Physical well-being	79.00±31.74	74.52±18.65	0.036
Emotional well-being	60.00±32.05	64.90±25.96	0.582
Self esteem	74.16±10.68	61.45±29.89	0.038
Family	67.50±33.48	53.84±24.14	0.027
Friends	72.50±15.05	64.42±18.64	0.290
School	72.50±8.38	51.44±23.40	0.010
Chronic disease	70.41±18.88	67.78±13.93	0.046

KINDL: Children's Quality of Life Questionnaire

Table VI. Children's Quality of Life Questionnaire evaluation of parents

KINDL domains	The mean scores of the study group	The mean scores of the control group	p value
Sum score	72.88±13.85	68.47±17.97	0.618
Physical well-being	70.07±12.84	66.75±16.01	0.113
Emotional well-being	70.66±10.93	77.00±10.94	0.017
Self esteem	72.28±26.12	68.95±6.46	0.027
Family	64.56±19.61	69.08±17.01	0.319
Friends	68.26±11.54	68.26±15.84	0.408
School	63.28±28.98	56.25±17.02	0.031
Chronic disease	63.36±16.36	00+00	-

KINDL: Children's Quality of Life Questionnaire

Balaska et al. (16) determined that there was increasing general health, physical function and emotional function one year after the transplantation. A number of other studies reported that, as the duration after transplantation increases, the functional status scores also increase (16,18). In our study, we determined that as the years passed by after transplantation, the QoL increased in a number of subgroups.

The most important problem for children who have had a transplant is the rejection of the organ. Despite all new developments, the risk of organ rejection persists all life-long in transplant patients, and every new rejection attack traumatizes the child and the family. In this study, we determined lower sum scores in children who had experienced rejection attacks.

The importance of education before and after transplantation both for the patient and parents in the transplantation process is known. In Sweden, a study performed on 18 children aged between 4-18 years noted that education of the families/children for their new lives after transplantation was important for their QoL (15). In our study, the patients' and parents' sum scores were higher in both age groups in the educated group. It was seen that the basic effect of education was particularly linked to physical well-being and its effect.

For children, most studies refer to the evaluations of the family, teacher or the hospital staff. In fact, these evaluations are considered if the child is unable to answer the questions because of his/her illness or that he/she is too young. The correlation among the scores is affected by factors such as age, gender and the disease. In addition, it has been reported that a higher concordance is seen in the domains in which behaviors can be observed such as physical functionality when compared to emotional or social functionality (19). The studies performed in different

disease groups showed different concordances in different subgroups (20,21). Varni et al. (21) found that the scores obtained in the sick children group were higher than the parent-reported scores in all subgroups. In our study, we used a scale which enabled parent evaluation, and compared the patient and the parent scores, and found the highest concordance between the parent and the child evaluations in the school subgroup in the transplant group.

Conclusion

Regular education programs must be constituted for children who have undergone transplants and their families before and after transplantation. They must follow a prepared template and at the same time answer the determined needs of the patients/families. In this way, the QoL of the recipients will be better and their post-transplantation course will be more comfortable.

Ethics

Ethics Committee Approval: Ege University Nursing Faculty Ethics Committee (approval number: 2008-55).

Informed Consent: Informed parental consent was obtained for all infants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: N.A., S.A., B.B., Concept: S.A., M.K., Ç.O.E., Design: B.B., Data Collection or Processing: N.A., M.K., E.K.T., Analysis or Interpretation: Ç.O.E., S.A., B.B., Literature Search: S.A., N,A., M.K., E.K.T. Writing: N.A., C.E., M.K., E.K.T.

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Original Article

Six Clinical Predictors for Intractable Childhood Epilepsy

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ABSTRACT

Aim: This study aimed to determine the significance of six clinical predictors associated with medically intractable childhood epilepsy.

Materials and Methods: A retrospective cohort study was conducted. A total of 241 children with diagnosed epilepsy were recruited and divided into two groups: 61 patients with intractable epilepsy, and the other 180 patients who responded well to antiepileptic drugs. We investigated seizure semiology, etiology of epileptic encephalopathy, EEG abnormalities and defined the odds ratios (ORs) of predictor factors for intractable childhood epilepsy; age of seizure onset, asphyxia, neonatal intensive care unit (NICU) history, consanguineous marriage, abnormal neuro-imaging, neuropathologic exam, prematurity, parents' seizure history.

Results: According to logistic regression analysis, the major risk factors for intractable childhood epilepsy are (1) neuropathologic examination p=0.000, OR= 58.28 CI= 23.95-141.63; (2) abnormal neuro-imaging p=0.000, OR= 37.55 CI= 16.41-85.94 (3) age of seizure onset p=0.001, OR= 9.43 confidence interval (CI): 3.66-24.3 (4) asphyxia p=0.001 OR= 4.16 CI= 1.75-9.87 (5) consanguineous marriage p=0.001 OR= 3.02 CI= 1.53-5.97 (6) NICU history p=0.003 OR= 2.59 CI= 1.38-4.87 (95% CI).

Conclusion: The presented six predictors can be used to determine the medical intractability in children with epilepsy in order to provide early alternative treatment protocols for better seizure control.

Keywords: Childhood epilepsy, intractability, epileptic encephalopathy, predictor factors

Introduction

Epilepsy is a heterogeneous group of neurological diseases characterized by recurrent non-triggered seizures (1). Although the condition often responds well to single drug therapy, in some cases, seizure control cannot be achieved by two or more drugs. This group is defined as resistant epilepsy, which accounts for 30%-35% of all epilepsies. The concept of resistant epilepsy was defined by the International League Against Epilepsy (ILAE) in 2010 as the failure to achieve seizure freedom in a period of three months and having on average one seizure per month, despite adequate trials of two or more tolerated, appropriately chosen and used anti-epileptic drugs (whether as mono-therapies or in combination) with effective serum levels (2).

Early detection of resistant epileptic patients may be possible with the identification of predisposing factors. Anatomical and functional connections in developing brains are different from mature brains, assynaptic structuring and modification continue and plasticity is seen in a higher

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ratio (3). Seizure control via early treatment in childhood epilepsies has significant importance for the prevention of neuronal damage due to recurrent seizures, attaining normal development, minimizing drug side effects and increasing quality of life (4). The aim of this study was to determine the leading factors for resistant epilepsy in epileptic patients presenting at Manisa Celal Bayar University Faculty of Medicine, Department of Pediatric Neurology.

Materials and Methods

This retrospective study was conducted as a case control type at Celal Bayar University Medical Faculty Pediatric Neurology Clinic between 01/01/2011-31/12/2015. The charts of 2.200 patients who presented due to seizures were examined. Patients having two or more non-triggered seizures on different days were diagnosed with epilepsy. The patient group consisted of 61 intractable epilepsy patients who were followed regularly for at least two years. Power analysis was performed according to sample size and determined as 90% when d=0.60, α=0.05 was accepted (5).

The control group consisted of 180 cases selected by a simple random sampling method among epileptic patients who responded well to antiepileptic drugs, matched with age and gender. Age and gender, first seizure age, seizure features, asphyxia, premature birth, hospitalization in neonatal intensive care unit, consanguineous marriage, parents' seizure history and neurological examination findings were recorded from both group charts.

The first electroencephalographic (EEG) findings of the patients were reviewed by the same pediatric neurologist. These were divided into two groups: normal and abnormal EEG. Abnormal EEG findings were listed as focal/multifocal pattern, organizational impairment/slow pattern, generalized disorders and specific disorders (burst suppression, hypsarrhythmia etc.). Likewise, initial magnetic resonance imaging (MRI) results were classified as normal and abnormal [the findings revealed acquired conditions (trauma, stroke, infection), structural and congenital anomalies, neurometabolic and neurodegenerative disease].

The study was approved by the Celal Bayar University Medical Faculty Local Ethics Committee (approval number: 20478486-296, date: 19,08,2015). Consent form was filled out by all participants.

Inclusion and Exclusion Criteria

Selection of the Patient Group: Epileptic patients without a seizure-free period of three months and having on average one seizure per month despite adequate trials of two or more tolerated, appropriately chosen and used antiepileptic drugs (whether as mono-therapies or in combination) with effective serum levels were considered as resistant epileptic patients. Among these intractable epileptic patients, 61 were included in this study. Medications used at the time of seizure in the emergency room and during epileptic status, medications discontinued without effect or due to side effects were not included in the used drug list of cases.

Selection of the control group: The control group consisted of 180 patients who responded well to anti-epileptic drugs alone or two in combination.

Definitions

The classification and terminology of the ILAE was used for this study. Classification of seizure type was made according to revised International Classification of Epileptic Seizure. Videos of the first seizure recorded in hospital (if available) were used to classify the seizures. Otherwise, the classification was made based mainly on information received from family members who saw the seizure.

Asphyxia was defined as having an Apgar score below 3 in the first minute, below 5 in the fifth minute, an interventional birth, difficult (traumatic) birth, late crying and late onset of respiration or the need for resuscitation at birth. Patients whose records were unclear concerning these data were not included in this study. The reason for the neonatal hospital admission (difficult birth, premature birth, newborn infection, jaundice) was investigated. Motor mental retardation was evaluated in consideration with the delay in the developmental stages and/or developmental tests (Denver or WISCR-R) made according to age groups. Presence of decreased muscle strength, tonus changes, deep tendon reflexes, pathological reflexes, involuntary movements, disturbance in walking and posture, defect in balance and sense examination were considered in pathologic neurological examination. Neurocutaneous diseases, diagnosed or suspected by physical examination revealing signs such as café au lait spots, hypopigmented skin findings, were noted. The pathologies identified in electroencephalography were classified as generalized sharp and/or spike waves, focal-multifocal sharp waves, ground rhythm disturbances (deficiency in backward maturation, asymmetry etc.) and specific disorders (burst suppression, hypsarrhythmia etc.). Cranial imaging findings were divided into either with pathology or without pathology.

Statistical Analysis

The SPSS 15.0 programme was used for the statistical analysis of the study. Chi-square tests were used to compare differences between categorical variable frequencies and Student's t-tests were used to compare continuous variables in two independent groups. Risk analysis of the independent variables was also performed in the case and control group. Estimated relative risks were presented as the OR and 95% CI. The level of statistical significance was set at $p<0.05$.

Results

General Features

A total of 241 patients consisting of intractable epilepsy (61) and drug-responsive epilepsy (180) were included in the study. There were 111 females (46.1%) and 130 males (53.9%). Among the 61 intractable cases, 35 were male (57.4%) and 26 were female (42.6%). Ninety-five males (52.8%) and 85 females (47.2%) were in the drug-responsive epileptic group. There was no statistically significant difference between the groups in terms of gender (p=0.318). The mean age of the intractable epilepsy group was 7.00±4.36 years and the mean age of the control group was 7.18±4.51 years (p=0.795). There was no statistically significant difference between the groups. It was seen that the age of first seizure was mostly in the 0-1 age range (65.6%) in the intractable epilepsy group, whereas the range was found mostly in the 1-5 years (45.0%) in the drug-responsive epilepsy group. This showed that as the age increased, the frequency of intractable epilepsy decreased and this relationship was significant (p=0.001).

When the risk factors for intractable epilepsy were evaluated in both groups, the presence of neuropathologic examination, asphyxia history, consanguineous marriage, neonatal intensive care unit (NICU) history and abnormal neuro-imaging findings and age of seizure onset being less than 1 year were statistically significant. The presence of pathological examination findings was the most important risk factor of the intractable childhood epilepsy (p=0.000; OR= 58.26; 95% CI= 23.97-141.63). Abnormal imaging, the asphyxia history, consanguineous marriage and NICU admission were significantly higher in the intractable epilepsy group. However, the parents' history for epilepsy (p=0.057; OR= 1.71; 95% CI= 0.93-3.12) and prematurity (p=0.353; OR= 1.24; 95% CI= 0.57-2.69) were not significant risk factors (Table I).

The most common type of seizures was partial type (42.6%), generalized tonic-clonic (24.6%) and myoclonic seizures (14.8%) in the intractable epilepsy group. Epileptic spasms were seen only in the intractable epilepsy group, at a rate of 8.2%. In the drug-responsive epilepsy group, the most common type of seizures was generalized tonic-clonic (31.6%), partial type (23.8%) and generalized tonic (17.8%) (Table II).

While the first-line EEG findings were pathologic in all intractable epilepsy cases, the pathologic EEG results were 54.3% in the drug-responsive epilepsy group. In a separate evaluation of the results of patients having pathologic EEG, the most common EEG pathology in both groups was a focal/multifocal epileptiform pattern. The second most common pathology was the generalized epileptiform pattern. A statistically significant difference was found between the case and control groups in terms of EEG pathologies (Table III).

Classification of Epileptic Encephalopathy

Of the 61 patients in the intractable epilepsy group, 28 (45.9%) were found to have epileptic encephalopathy. West syndrome in 12 (42.8%) cases was the most common among these cases with epileptic encephalopathy. The second most common type was electrical status epilepticus of sleep syndrome in 5 (17.8%) patients. The number of cases with Lennox-Gestaut syndrome was 4 (14.2%), cases with Dravet syndrome were 3 (10.8%), cases with Landau-Kleffner syndrome were 2 (7.2%) and there were 2 (7.2%) cases with Doose syndrome.

Discussion

Approximately 30%-35% of childhood epilepsies are intractable epilepsies (2). Various medical problems including aspiration, cardiac arrhythmia or refractory status epilepticus are frequently observed in patients with intractable epilepsy. In particular, children are more susceptible to drug toxicity due to multiple drug use and behavioral and academic problems are more likely to develop.

Factors that may lead to resistance development in childhood are not clear and are thought to be multifactorial. One of the notable risk factors is age at onset of seizures. In many studies based on age at onset of the first seizure, the ratios of seizure in the first year of life ranged from 50% to 60% in intractable epilepsy patients and from 10% to 20% in drug-responsive epilepsy patients, and this was reported as a risk factor (6-8). It is known that the onset of seizures within the first year of life facilitates the epileptogenic tendency during the development of the immature brain (9). In this study, we found that the 65.6% of patients with intractable epilepsy had their first seizure at under one year of age, in line with other studies (p=0.001).

It is known that having neonatal seizures in premature infants and abnormal brain MRI results are associated with poor prognosis in terms of neurological development (10). Pathologic cranial MRI has been found in all premature infants who had seizures due to various reasons during the neonatal period and progressed to resistant epilepsy (11,12). In this study, although the presence of prematurity was not significant in terms of risk of resistant epilepsy (p=0.353), cranial MRI findings were pathologic in all four patients with resistant epilepsy and premature birth.

It has been reported that epilepsy seen in neonatal intensive care units due to various reasons was a risk factor for intractability and an important etiological cause. Gururaj et al. (13) showed that 18% of patients in a neonatal intensive care unit had their first seizure and a significant relationship was found between them in terms of resistance development. Hypoxic or asphyxic events, seen especially in the perinatal period, facilitate epileptogenesis in the future and are important in the development of resistance by leading epileptic foci (14). Hypoxic ischaemic encephalopathy (HIE) is one of the most important causes of mortality and morbidity in the neonatal period. In a study conducted in our country, it was reported that HIE is associated with a mortality rate of 10%-50% and morbidity rate of 21%-55% in the advanced stage (15). In another study, Gürbüz et al. (16) found

Table I. The predictor risk factors for intractable childhood epilepsy according to logistic regression analysis

Variables	Intractable epilepsy		Drug responsive epilepsy		p value	OR (95 CI%)
	Number	%	Number	%		
Age of seizure onset						
0-1	40	65.6	41	22.8	0.001	9.43 (3.66-24.30)
1-4	15	24.6	81	45.0		1.79 (0.65-4.89)
5 years and above (ref)	6	9.8	58	32.3		1.04 (0.11-9.91)
Prematurity						
Yes	11	18	27	15	0.353	1.24 (0.57-2.69)
No (ref)	50	82	153	85		
Asphyxia						
Yes	13	21	11	6.1	0.01	4.16 (1.75-9.87)
No (ref)	48	78	169	93.9		
NICU history						
Yes	24	39.7	36	20	0.003	2.59 (1.38-4.87)
No (ref)	37	60.3	144	80		
Parents seizure history						
Yes	25	41	52	28.9	0.057	1.71 (0.93-3.12)
No (ref)	36	60.7	128	71.1		
Consanguineous marriage						
Yes	20	32.8	25	13,9	0.001	3.02 (1.53-5.97)
No (ref)	41	67.2	155	86.1		
Abnormal imaging						
Yes	38	85.2	11	13.3	0.000	37.55 (16.41-85.94)
No (ref)	23	14.8	169	86.7		
Neuropathologic exam						
Yes	46	75.4	9	5	0.000	58.26 (23.95-141.63
No (ref)	15	24.6	171	95		
Totally	61	100	180	100.0	-	-

OR: Odds ratio, CI: Confidence interval, NICU: Neonatal intensive care unit

that risk factors that have influence on the prognosis of patients with neonatal seizures are etiological diagnosis, seizure type, birth weight, abnormal EEG activity and status epilepticus. In our study, the presence of neonatal intensive care admission history increased the risk of intractable epilepsy by 2.59 (95% CI= 1.38-4.87) times and increased the intractability development rate by 4.16 (95% CI= 1.75-9.87) times, especially if admitted due to asphyxiated delivery.

Another criterion that has been the subject of many studies as a risk factor for the development of intractability in epileptic patients is the first seizure type. Gururaj et al. (13) and Chawla et al. (14) found the generalized tonic seizure was the most common type in the intractable epilepsy group in their case control studies. On the other hand, Ohtsuka et al. (17) reported myoclonic as the most common, while Kwong et al. (18) reported that partial seizure was seen most. In our study, the most common seizure type was partial seizure in the intractable epilepsy group. The cause of the variation of seizure type frequencies reported so widely in different studies is directly related to observation of the seizure moment for the first time by the mother and other relatives and unclear definition or limited experience of the first-seen or referred to physician.

The presence of various pathologies in the neurological examination in epileptic patients is thought to be associated with the development of intractable epilepsy. In a few studies from Chawla et al. (14) and Seker Yilmaz et al. (19), the pathologic-neurological examination was found to be significant and high in intractable epilepsy cases. In accordance with the literature, in our study, the presence of pathologic findings on neurological examination was found to be 58 times more in intractable epilepsy and has been shown as the most important risk factor (p=0.000; OR= 58.26; 95% CI= 23.95-141.63). This possibly reflects the severity of brain damage.

In our study, positive family seizure history did not seem to pose a risk for the development of intractable epilepsy. Similarly, in one study, there was no significant correlation found between family history and intractable epilepsy (20).

Table II. Distribution of both groups according to seizure semiology

	Intractable epilepsy		**Drug responsive epilepsy**		**Total**		**p value**
	Number	**%**	**Number**	**%**	**Number**	**%**	
Generalized tonic	4	6.6	32	17.8	36	14.8	0.000
Generalized tonic clonic	15	24.6	57	31.6	72	29.8	
Myoclonic	9	14.8	12	6.6	21	8.6	
Atonic	1	1.6	24	13.4	25	10.4	
Epileptic spasm	5	8.2	0	0	5	2.2	
Partial seizure	26	42.6	43	23.8	69	28.6	
Absence	1	1.6	12	6.6	13	5.4	
Total	61	100	180	100	241	100	

Table III. Distribution of both groups according to electroencephalographic findings

	Intractable epilepsy		**Drug responsive epilepsy**		**Total**		**p value**
	Number	**%**	**Number**	**%**	**Number**	**%**	
Focal / multifocal pattern	23	37.7	47	26.1	70	29.0	0.000
Organization disorders /slow pattern	12	19.7	16	8.9	28	11.6	
Generalized disorders	17	27.9	33	18.3	50	20.7	
Burst suppression	1	1.6	0	0	1	0.4	
Hipsarrhytmia	8	13.1	0	0	8	3.3	
Normal	0	0	84	46.7	84	34.9	
Total	61	100	180	100	241	100	

In the intractable epilepsy group, 32.8% of the children's parents had consanguineous marriage. The consanguineous marriages were significantly higher in the intractable epilepsy group when the two groups were compared. We consider that genetic etiologies are crucial predictors for intractability. Both genetic research and family screening programs as well as future genetic studies will guide resistance development, prognosis and treatment methods.

Evaluation of the EEG findings, detection of pathological findings and classification of these findings that led to the development of more intractable epilepsy types has been another researched subject. In a study conducted by Gururaj et al. (13), there was no difference between pathological EEG results of resistance epilepsy cases and drug-responsive cases, and this was not considered as a risk factor. However, in this study, about half of the first EEG results of drug-responsive epilepsy patients were pathologic, whereas in the intractable epilepsy patient group, all of the first EEG results were found to be pathological. Berg et al. (21) reported that the focal epileptiform pattern was found to be the most common EEG abnormality in the development of refractory epilepsy. On the other hand, Ohtsuka et al. (6) found that the detection of generalized abnormalities in EEG was seen as an important factor in the development of intractable epilepsy. In our study, the focal/multifocal epileptiform pattern was the most common pathologic EEG finding in both groups and it did not lead to a prediction of the development of intractable epilepsy. However, the findings of burst suppression and hypsarrhythmia patterns, which can be seen in patients with specific epileptic encephalopathy, were found only in patients with intractable epilepsy.

When cranial MRI findings were examined, pathology was found in 62% of patients with intractable epilepsy, whereas it was only found in 18% of patients in the drug-responsive group. This demonstrates that the presence of pathologic MRI findings increases the likelihood of developing intractable epilepsy. In a study conducted by Chawla et al. (22), a strong correlation was found between the results of cranial MRI and the development of intractable epilepsy. In addition, the pattern of the pathological finding of MRI was also considered a risk factor for the development of intractable epilepsy. Russo et al. (23) conducted a study for this purpose and found structural and heterogeneous brain malformations more frequently. In our study, structural and congenital anomalies (34.6%) were the most common pathologies found in the intractable epilepsy group.

According to the data obtained in our study, the most important predictive risk factors for intractable epilepsy in childhood epilepsies were found as onset of seizures before one year of age, asphyxia history, neonatal intensive care hospitalization and consanguineous marriage. Early factors affecting the central nervous system appear to play an important role in the development of intractability. Acceptable treatment and follow-up are especially crucial for newborns with early onset seizures and perinatal asphyxic history. When the first seizure is of the partial type, the presence of pathologic findings in cranial MRI, the presence of pathology in neurological examination and the presence of pathologic findings in EEG were found to be other risk factors.

This case control study aimed to determine the risk factors for the development of intractable epilepsy and therefore the research design in relation to the cause and potential bias sources should be considered. Prospectively conducted cohort studies and multi-center case control studies are necessary in the investigation of causality. These are the limiting aspects of our study. However, this research was designed as a case control type in a rare health problem and the 90% sampling power is a powerful aspect of this study.

Conclusion

In long-term prognosis, it is important to switch dynamically to polytherapy in the early period of treatment and to apply non-pharmacological treatment, if necessary, in those patients with predictive factors for intractable epilepsy. The present study determined the risk ratios for intractable epilepsy in a Turkish population. During follow-up, it should be carefully questioned whether these six predictor factors are met; if so, the follow-up should be more intense, caregiver and parental support should be increased and different treatment options should be considered.

Ethics

Ethics Committee Approval: The study was approved by the Celal Bayar University Medical Faculty Local Ethics Committee (approval number: 20478486-296, date: 19.08.2015).

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.A., R.D.O., Concept: M.P, Design: M.P., Data Collection or Processing: S.A., R.D.O.,

Analysis or Interpretation: S.A., P.E.D., M.P., Literature Search: S.A., R.D.O., P.E.D., Writing: S.A.

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Original Article

Knowledge, Practice and Beliefs of Pediatric Nurses about Pain

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ABSTRACT

Aim: Pediatric nurses play a crucial role in the assessment and management of a child's pain. The main purpose of nursing care is to eliminate pain and improve the quality of life. The aim of this study was to evaluate the knowledge, practice and beliefs of pediatric nurses about pain.

Materials and Methods: The current study using a descriptive research design included 102 pediatric nurses working at Akdeniz University Hospital who agreed to participate in the study. Data were collected using a questionnaire developed by the researchers via a face to face interview method also by the researchers.

Results: Approximately half of these pediatric nurses (40.2%) are in the 20-29 age group, 51% are married and 80.4% are bachelor's degree holders. In this study, 56.9% of the nurses stated that they did not receive any education about pain and 51% stated that they had insufficient knowledge about the evaluation of pain. Although 67.6% of these nurses state that they have a pain scale in their clinics, 65.6% of the nurses in our study group do not know the name of the scale. Although pain is subjective, only 68.6% of the nurses believed that the child/mother had expressed the pain and 22.5% stated that the cause of the pain was always an illness. In the study, 88.2% of nurses stated that analgesia should not be given before the onset of pain.

Conclusion: It is very important to make in-service training programs for pain which is considered as a vital finding. It is recommended that nurses increase their level of knowledge to counter false beliefs/practices about pain. It is hoped that the results of this study will be a reference for the development and updating of nursing education, curricula and clinical training.

Keywords: Belief, knowledge, pain, pediatric nurse, practice

Introduction

Pain is one of the most common experiences, especially in children due to trauma, disease or various medical interventions (1). The International Association for the Study of Pain defines pain as an unpleasant sensory and emotional experience from actual or potential tissue damage or described in terms of such damage (2). It is stated in the literature that children are exposed to many painful interventions such as bleeding from the heifer from the newborn period, vaccination, arterial and venous interventions and so on (3-9). Unmanaged pain can have long-term physiological and psychological consequences, such as increased susceptibility to depression, lower quality of life, reduced independence, and decreased functioning in the activities of daily living (10-14). What a child remembers about previous painful events plays a vital role in his or her anticipation of, and response to, future pain (15). Pain relief and pain management are important to a child's normal

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growth and development. Nurses in particular have a very important place among other health professionals in the evaluation and management of pain (10,16). Nurses play a crucial role in the assessment and management of a child's pain, because they are the health care professional spending the most direct time with the child (17,18). Moreover, children have an ethical right to pain relief (19). Nevertheless, pain is not effectively managed by nurses due to insufficient information about pain, a demanding workload, a lack of a team approach, and communication problems (20,21). The American Academy of Pediatrics and American Pain Society attribute the lack of effective pain management to myths and insufficient knowledge of caregivers and an inadequate application of knowledge (22). Nurses' professional knowledge about pain and pain management is often described in terms of an absence or a lack of knowledge (23,24).

Inadequate pain assessment can lead to underestimation and undertreatment of pain in the pediatric population (25). In one study, it was determined that pediatric surgical nurses did not have enough knowledge about infants' pain assessment (26). Eti Aslan and Badır (27) have determined that nurses do not have sufficient knowledge about the nature, mechanism, evaluation and management of pain, and that they have false beliefs and misconceptions. In another study, a large proportion (96%) of nurses stated that they did not always believe the patient who told them about their pain and about half (47%) of these nurses stated that they did not follow up the behavior of the patients who could not express their pain (28). In another study, 95% of nurses stated that they did not know about any scale used to assess pain (29). Akin and Durna (30) stated that there was poor agreement between the symptoms indicated by the patients and the nurses. As a result of these studies, it is thought that nurses do not have adequate knowledge, experience and equipment concerning pain. Effective pain management includes pain screening, assessment (ongoing assessment and reassessment), diagnosis, documentation (timely and appropriate), treatment (pharmacological and non-pharmacological interventions), and continuous evaluation of care (31). Additionally, current recommendations for pain assessment in infants/children include the use of reliable, valid, sensitive, and developmentally appropriate tools that include both physiologic and behavioral indicators of pain (26). It is very important that pediatric nurses determine the cause, type, and severity of the child's pain, factors that reduce and increase pain, and do not have the wrong beliefs and thoughts about the pain. Therefore, the aim of this study was to evaluate the levels of knowledge, practices and beliefs regarding pain of nurses working at pediatric clinics and policlinics.

Research Questions

- What are the knowledge levels of pediatric nurses towards pain?
- What are the applications of pediatric nurses towards pain?
- What are the pediatric nurses' beliefs towards pain?

Materials and Methods

This was a descriptive study conducted in the pediatric clinics and polyclinics of Akdeniz University Hospital in Antalya, Turkey from February to April 2018. A total of 136 pediatric nurses were working in the pediatric clinics and polyclinics in Akdeniz University Hospital in 2018. Akdeniz University Hospital is the biggest and the most developed education hospital in the Mediterranean region in the southern part of Turkey. The hospital offers high quality and specialized treatment/care services to neonates, infants and children throughout the region as well as being a teaching hospital. Since the hospital has a large staff/patient capacity and a training center, this hospital was chosen for this research. Five hundred and twenty-nine physicians and 785 nurses were working in Akdeniz University Hospital in 2018. A total of 136 pediatric nurses were working in the pediatric clinics and polyclinics in Akdeniz University Hospital in 2018. Of the 136 pediatric nurses working in the pediatric clinics and polyclinics of the hospital, 34 did not answer the questionnaire because they were on vacation or on sick leave, or because they did not wish to, while 102 answered it, corresponding to 75% of the entire team.

In this study, two measures were used: 1) the Participant Demographic form which consisted of 14 questions about the nurses' age, sex, years of experience, educational background, publications followed related to their profession, and knowledge about pain assessment in clinics; and 2) the Pediatric Nurses' knowledge levels, practices and beliefs regarding pain which was developed by the researchers in accordance with the literature (13,14,16,26-29,32).

The questionnaire was tested on 15 pediatric nurses including the supervisor nurses in a pilot study before administration. These 15 pediatric nurses were asked about the comprehensibility of the questionnaire questions, the ease of answering and the ability of the questions to represent such a topic. The questionnaire was replicated

separately for each individual and they were asked to review the questionnaire and note their opinions in writing. The opinions and suggestions of the 15 nurses who were piloted were taken. In this way, it was attempted to obtain the reliability and the content validity of the questionnaire. The results of the pilot study were evaluated by the researchers. The participants found the questionnaire quite competent and understandable. In this pilot study, it was determined that the questions could be understood, and no changes were made. The nurses included in the pilot study were included in the study because there was no question which was not understandable after the feedback from the nurses.

The pediatric nurses were informed about the objectives and content of the study. The data of the research were collected by the researchers using a face-to-face interview method. The questionnaire took approximately 20 to 30 minutes to complete.

Ethical Considerations

After obtaining permission to conduct the study from the Akdeniz University Hospital administration, we obtained ethical approval from the Ethics Committee of Akdeniz University Non-invasive Clinical Trials (approval number: 70904504/81, date: 26.02.2018). Oral and written consent of the pediatric nurses was obtained after reading an informed consent document.

Statistical Analysis

Data were analyzed using SPSS (20.0) for Windows software. Statistical significance was established at an alpha level of 0.05. Descriptive statistics (frequency and percentage, standard deviation, mean) for the variables are given in Table I. Data were analyzed statistically by the chi-square test and/or the Fisher exact test to calculate the differences between proportions. Bonferroni Correction test was performed in binary comparisons and α=0.017 was taken.

Results

Sample Characteristics

The study demonstrated that 97.1% of the pediatric nurses are women, 40.2% are in the age range of 20-29 years, 51% are married and have children. 80.4% of the nurses have bachelor's degrees and only 7.8% have a post-graduate degree. 37.3% of nurses have a total working period of 0-5 years. More than half (74.5%) of the nurses follow scientific publications related to nursing and attend congress/seminar activities (81.4%). 56.9% of the nurses stated that they did not receive any education about pain, and 51% stated that their knowledge about the evaluation of pain was insufficient. Although 67.6% of the nurses say that they have a pain scale in their clinics, 65.6% of the nurses did not know the name of the scale (Table I).

Pediatric Nurses' Pain Assessment

When the pain assessment methods of pediatric nurses were examined, 21.6% of the nurses stated that they were evaluating the patients' behavior and 2.9% of the

Table I. Socio-demographic characteristics of pediatric nurses

Characteristics		**n**	**%**
Gender	Female	99	97.1
	Male	3	2.9
Age	20-29	41	40.2
	30-39	36	35.3
	40-49	22	21.6
	50-59	3	2.9
	>60	0	0.0
Marital status	Married	52	51.0
	Single	50	49.0
Has at least one child	Yes	52	51.0
	No	50	49.0
Educational status	Vocational school of health	7	6.9
	Associate degree	5	4.9
	Bachelor's degree	82	80.4
	Post-graduate	8	7.8
Experience as a nurse in years	0-5	38	37.3
	6-10	23	22.5
	11-15	16	15.7
	16-20	10	9.8
	>21	15	14.7
Nursing congress/Seminar participation	Yes	83	81.4
	No	19	18.6
Training on pain	Yes	44	43.1
	No	58	56.9
Is she/he competent about pain?	Yes	50	49.0
	No	52	51.0
Does the clinic have a pain scale?	Yes	69	67.6
	No	33	32.4

nurses evaluated the pain from the verbal expressions of the patients. In addition, a large majority (75.5%) of the nurses stated that they considered all the features (verbal expression, behaviors, verbal expression of the parents, doctor notes) when assessing pain. Table II shows the two-and-three comparison of the pain assessment methods of pediatric nurses.

Pediatric Nurses' Knowledge and Beliefs about Pain

Although pain is subjective, only 68.6% of the nurses believed that the child/mother had expressed the pain and 22.5% stated that the cause of the pain was always an illness (Table III). In this study, it was determined that nurses who were married (x^2=5.145, p=0.023), who were educated about pain (x^2=6.253, p=0.017) and who had a higher level of education (x^2=7.036, p=0.047), answered more "true" to the statement that "if the child/mother says there is pain, then there is pain". In addition, it was determined that nurses who participated in scientific congresses responded more "wrong" to the statement that "the cause of baby's/child's pain is always a disease" in this research (x^2=6.798, p=0.004).

Nearly half (49%) of the nurses said that "preterm infants are not more susceptible to pain than term infants" (Table III). In this study, it was determined that nurses who participated in scientific congresses (x^2=6.261, p=0.041) and who received education about pain (x^2=7.067, p=0.032) answered more frequently "true" to the statement that "preterm infants are more sensitive to pain than term infants". In addition, it was determined that nurses who had a working time of 0-5 years (x^2=13.861, p=0.045) and who had a higher level of education (x^2=21.667, p=0.000), responded more "wrong" to the statement that "preterm infants did not develop pain perception".

In this study, 47.1% of the nurses stated that "if the child is asleep, there is no pain". In this study, 37.3% of the nurses stated that "the unconscious child's pain cannot be assessed" (Table III). It is determined that nurses who are in the 20-29 age range (x^2=13.311, p=0.020), who are married (x^2=7.567, p=0.020), who have a higher level of education (x^2=13.223, p=0.017) and who received education about pain (x^2=6.831, p=0.032), answered more frequently "true" to the statement that "assessing the muscle tone of the child gives information about the pain". It was determined that nurses who have a working period of 0 to 5 years responded more correctly to "true" than those who worked for 6 to 10 years in the phrase "pain is a vital finding" (x^2=17.996, p=0.005).

Discussion

The management of pain depends mainly on the implementation of the nursing process through assessment planning, intervention, and evaluation (33). However, in one study, it was determined that nurses lack knowledge about pain and pain control in children. Additionally, it was determined that the nurses did not use any pain assessment scale and that they did not know about the scales used in the evaluation of pain (29). Asadi-Noghabi et al. (14) carried out a study entitled "Neonate pain management: what do nurses really know?". It was found that the nurses had poor performance regarding the assessment, measurement, and relief of pain. In this study, a low level of knowledge about pain management was observed, implying an inadequacy in nursing practice in the assessment and management of pain. Nurses should acknowledge the significance of pain and should improve their professional attitudes and knowledge in order to gain control over pain through a multidisciplinary approach and to prove the crucial and inevitable role of nurses in such a team (27). To accomplish this, pediatric nurses need to expand their knowledge, use appropriate assessment tools and techniques, anticipate painful experiences and intervene accordingly, use a multimodal approach to pain management, use a multidisciplinary approach when possible, involve families, and advocate for the use of effective pain management in children (22). It is very important to improve the knowledge and awareness of nurses on pain and pain management. Therefore, in this study, the knowledge levels, practices and beliefs of the pediatric nurses towards pain were evaluated.

According to the results of the research, a large majority of pediatric nurses are females. The population studied

Table II. Pain assessment of pediatric nurses

Pain assessment methods of nurses	n	%	x^2	p value
a. Verbal expression	3	2.9	Binary comparison* - a-b=x^2: 14.44 p<0.001 - a-c=x^2: 68.45 p<0.001 - b-c=x^2: 30.556 p<0.001 Triple comparison (x^2: 86.88, p<0.001)	
b. Behaviors	22	21.6		
c. All (verbal expression, behaviors, verbal expression of parents, physician's notes)	77	75.5		

*Bonferroni Correction was done and α=0.017 was used for bilateral comparisons

here consisted exclusively of women, as explained by the fact that the nursing profession still is almost exclusively a female profession, as also is reported by others (34,35). When analyzing time of service, we noted that 37.3% of the nurses had been working in the pediatric clinics for less than 5 years. In addition, the vast majority of nurses (80.4%) have a bachelor's degree with while only 7.8% have a post-graduate degree. Pediatric nurses need to be highly educated and experienced in pediatrics to provide higher quality care. Nurses play a key role as advocates for children in decisions about their health, and their competence is of particular interest in pediatric care. A nurse who is not sufficiently informed about pain will also have insufficient experience in assessing and managing the pain of their patient. In this study, 56.9% of the nurses did not receive any education about pain and 51% stated that their knowledge about the evaluation of pain was insufficient. In several studies, the main findings have been that nurses lack knowledge and that their education in pain management must improve (24,26,32,36-38). In one study, it was determined that only 56.2% of the nurses understood physiologic pain symptoms and 58.8% understood behavioral pain symptoms in newborns (36). Related to education, nurses lacked clinical education in pain assessment. Lack of pain education can affect pain management in children. Ekim and Ocakcı (38) found that pediatric nurses in Turkey need more education about pain management. Education programs for pediatric pain management should include the assessment of pain according to the child's developmental level and the approach to the child and their family when the child is in pain.

According to the results of this study, only 68.6% of the nurses stated that they believed the pain expression of the child/mother. Additionally, it was determined that nurses who are married, who receive education about pain and who have a high level of education believe more about the pain of their patients than the other nurses. Self-report is the most important indicator of the existence and intensity of pain for child patients (22,15). It is essential to master the specific knowledge required to assess, plan, implement and evaluate nursing interventions as well as cooperate with the child and his or her parents (39,40). Nurses sometimes communicate with the children, but at other times with their parents instead. Poor communication with

Table III. Pediatric nurses' knowledge and beliefs on pain

Knowledge and beliefs about pain	True	False	I do not know
The age and developmental level of the child should be considered in the evaluation of pain.	95.1	4.9	0
Pain is a vital finding.	70.6	25.5	3.9
If the child/mother says there is pain, then there is pain.	68.6	31.4	0
Babies/children feel pain less than adults.	15.7	82.4	2.0
Preterm infants did not develop pain perception.	27.5	71.6	1.0
Preterm infants are more susceptible to pain than term babies.	43.1	49	7.8
The cause of the baby's/child's pain is always a disease.	22.5	77.5	0
Assessing the muscle tone of the child gives information about pain.	70.6	23.5	5.9
The response to pain varies according to the age of the child.	93.1	6.9	0
Restlessness is an indication of pain.	86.3	12.7	1.0
Pain can be assessed at any age using scales.	90.2	9.8	0
There is no pain if the child is sleeping.	47.1	50	2.9
Pain affects the feeding of the baby/child.	97.1	2.9	0
Pain does not affect the vital signs of the baby/child.	11.8	88.2	0
Pain increases the child's heart rate.	99	1.0	0
Pain reduces the rate of the children's respiration.	19.6	80.4	0
Children who are unconscious can also be evaluated for pain.	51	37.3	11.8
Pain assessment should be performed with the patient.	95.1	4.9	0
Analgesics should be given before the onset of pain.	8.8	88.2	2.9
Some children can sleep because of excessive pain.	49	50	1.0

parents and knowledge deficits regarding children's pain management on a nurse's part can create obstacles in their ability to perform effective pain management (41,42). The nurses' communication skills need to be further developed. Nurses do not communicate adequately with children and their families due to busy working hours. Additionally, nurses do not take the time to evaluate vital signs such as pain. According to our results, 22.5% of the nurses stated that the cause of the pain was always a disease. According to this finding, when the doctor diagnosed the disease and determined the pain, the nurses evaluated the pain. Bergman (43) and Wang and Tsai (44) relate similar findings; in both studies, nurses reported that reliance on physicians' orders for pain care was a major barrier. In Wang and Tsai's (44) study, nurses said that they should be able to design a pain care regimen for patients based on immediate postoperative assessments instead of having to wait for the physicians' assessments and orders. For these reasons, it is thought that nurses are only interested in the orders of doctors without worrying about the evaluation and management of pain. Additionally, in our study, nurses who participated more in scientific congresses stated that the cause of pain was not only related to a disease. Therefore, it is very important for nurses to have the necessary knowledge and skill level in the evaluation of pain and to use their caregiver role independently from the doctor.

Nurses might fail to assess children's pain accurately, and assess pain mainly by observing a child's behavior and changes in his or her physiology (45). In this study, 37.3% of the nurses stated that pain cannot be evaluated in children who are unconscious. Rose et al. (46) found that nurses were significantly less likely to use behavioral assessment tools with non-verbal patients, thereby missing critical pain cues and experiences. Pain measurement scales are rarely used, and when they are used, nurses sometimes do not know how to interpret them and thus intervene inappropriately, leading to inadequate pain relief. In this study, 67.6% of nurses stated that they had a pain scale in their clinics, but 65.6% of nurses did not know the name of the scale. In one study, it was determined that one-half of the nurses did not have knowledge about pain scales (26). Although it is emphasized that pain assessment tools are important, these scales are not given importance in practice (47). The absence of standard pain assessment tools and the inability of nurses to use these scales constitute the two most important obstacles in the management of pain. In a study by Van Niekerk and Martin (48), nurses rated the information they received about pain management during workplace programs as poor, feeling that they required significantly more in-depth information during their initial education. For this reason, nurses are required to receive in-service training on pain and pain assessment scales. The results of our research have revealed that education about pain is necessary. According to the results of this study, it was determined that those nurses who were married, educated and educated about pain in the 20-29 age group were more concerned about muscle tone in order to evaluate the pain of the children compared to the others.

Although it is important for pediatric nurses to learn about pain, the content and continuity of education is also very important as pediatric nurses' false beliefs about pain cannot be corrected with a single educational session. Additionally, some studies (49,50) suggested that pediatric nurses are not using their theoretical knowledge in practice. The evaluation and management of pain should be continuous in school education programs and clinical training. Nevertheless, pain is a neglected topic in the educational programs of both nurses and physicians (51). In this study, approximately half of the nurses (49%) stated that "preterm infants are not more sensitive to pain than term infants". According to the results of this study, it was determined that those nurses who have a higher level of education, who received training about pain and who participated in scientific congresses had fewer false beliefs about pain. Therefore, in order to change these false beliefs, it is very important to make in-service trainings and to update the information continuously in clinical settings. We also think that ongoing education programs developed by official institutions may improve the knowledge level about pain management in nursing.

Study Limitations

We consider that this study is limited by the inclusion of a small number of nurses. This could be seen as a bias, perhaps, selection bias or analysis bias or measurement bias; however, we do not believe that this invalidates the findings.

Conclusion

It is considered that the results of this study will be a reference for the development and updating of nursing education, curricula and clinical training. Moreover, the low level of knowledge of nurses about pain scales indicates that nurses need education regarding this issue. It can be said that this situation is a reason for future training activities. Finally, pediatric nurses who advocate for improved pain management in children need stronger and more persistent information about pain.

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Ethics

Ethics Committee Approval: We obtained ethical approval from the Ethics Committee of Akdeniz University Non-invasive Clinical Trials (approval number: 70904504/81, date: 26.02.2018).

Informed Consent: Oral and written consent of the pediatric nurses was obtained after reading an informed consent document.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: V.A.C., Ş.Ç., E.E., Design: V.A.C., Ş.Ç., E.E., Data Collection or Processing: V.A.C., Analysis or Interpretation: V.A.C., Literature Search: V.A.C., Ş.Ç., E.E., Writing: V.A.C., Ş.Ç., E.E.

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Original Article

Evaluation of the Frequency of Obesity and Associated Factors in Children of Obese and Overweight Mothers

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ABSTRACT

Aim: The mother is an important determinant of the nutrition of her children. The aim of this study is to evaluate the relationship between obese or overweight mothers, their socio-demographic status and appetite on the anthropometric measurements of their children, and to evaluate the relationship between breastfeeding duration, initiation time of a complementary diet and children's body mass index (BMI) classification.

Materials and Methods: Children whose ages were between 2 and 5 years old, with no additional chronic disease, were included. The socio-demographic data, anthropometric measurements and appetites of the children and their mothers were determined. Obese or overweight mothers and mothers with normal BMI were studied as two separate groups. The duration of breastfeeding and initiation time of a complementary diet for the children was classified as <4 months, 4-6 months and >6 months.

Results: A total of 182 children (109 with obese and overweight mothers and 73 with mothers with normal BMI) were included. The ratio of overweight and obese children among the group of obese and overweight mothers was higher. When the weight, weight percentile and weight standard deviation score values of the obese or overweight mothers were compared with their children, a moderately statistically significant positive correlation was found. The ratio of overweight and obese children among the group of employed mothers, and the ratio of underweight children among the group of unemployed mothers, was high. A significant relationship was found between maternal appetite and the BMI classification of their children. No statistically significant difference was found between breastfeeding duration, initiation time of a complementary diet and children's BMI classification.

Conclusion: It was determined that the mother's characteristics of having a BMI classification of overweight or obese, excessive appetite and being employed may be risk factors in the development of overweight and obese children.

Keywords: Obesity, mother, child, overweight

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Introduction

The increase in obese and overweight children is an important health problem all over the world. In Turkey, especially in recent years, the prevalence of obesity has increased in children and adolescents. It is reported that 14.2-16.1% of children are overweight, and 8.3-10% are obese in Turkey (1,2). Parental obesity is thought to be a risk factor for childhood obesity (3). Sharing the same genetic burden and environmental conditions are influencing factors for parents and children (4).

Parental weight change is an independent predictor of child weight change (5). However, positive weight change in the mother had a more dominant influence than did a father's positive weight change (5). The mother is generally the principle responsible parent for the care of the child, and her knowledge and practices surrounding nutrition can be an influential factor in her child's development, as well as her own body composition (5,6). The sociocultural status of the mother, her level of knowledge and practices around nutrition, her employment status and how she acts as a role-model for her child regarding nutrition can shape the nutritional characteristics of the child and, ultimately, the child's body composition (7). In a systematic review, it is reported that breastfeeding has a small but consistent protective effect against obesity in children (8). However, some studies have reported an inverse relationship between breastfeeding and obesity (8). Additionally, it has been reported that complementary feeding, when initiated earlier than 4 months, increased the risk of being overweight and obese during childhood (9). For these reasons, the aim of this study is to evaluate the effect of having an obese or overweight mother, socio-demographic status and the appetite of the mother, on the anthropometric measurements of the child. The second aim is to evaluate the relationship between breastfeeding duration, initiation time of a complementary diet and children's BMI classification.

Materials and Methods

Children who were admitted to the pediatric gastroenterology and general pediatric outpatient clinic between August and November 2018 who were between the ages of 2 and 5 years and had no additional chronic disease were included in the study. The socio-demographic data of the children and their mothers were determined. The mothers' education level, employment status, appetite, level of knowledge about child nutrition, breastfeeding duration, initiation time of complementary feeding and family income were evaluated. The monthly income levels were grouped as ≤1600 Turkish Lira (TL), 1600-2500 TL, 2500-5000 TL and >5000 TL, based on the minimum wage. Appetite was classified and recorded as: very low (0 points), low (1 point), normal (3 points), strong (4 points), very strong (5 points). The appetite of the mother and the child were determined according to the score given by the mother.

The height and weight of the children and their mothers were measured by the same team using the same equipment. The weight, weight percentile, weight standard deviation score (SDS) and body mass index (BMI) of the children and their mothers were determined. The BMI of mothers and children were calculated by weight (kg)/height squared (m^2). The BMI of the children was rated as follows; >95 percentile=obese, 85-95 percentile=overweight, 5-85 percentile=normal, <5 percentile=underweight (10,11). The BMI of the mothers was classified as follows: >30=obese, 25-29.99=overweight, 18.5-24.99=normal and <18.5=underweight (http://www.who.int/mediacentre/factsheets/fs311/en). Children whose mothers were underweight were not included in the study. Children whose mothers were considered obese or overweight and children whose mothers' BMI was within the normal range were studied as two separate groups. The duration of breastfeeding and initiation time of a complementary diet for the children was classified as <4 months, 4-6 months and >6 months. The anthropometric measurements, parents' socio-demographic data, duration of breastfeeding and initiation time of a complementary diet and appetite were compared between the two groups. The relationship between the anthropometric measurements of the mothers and their children was also evaluated. Informed consent was obtained from all mothers participating in the study. Ethics committee approval was obtained from the Ethics Committee of İzmir University of Health Sciences, Tepecik Training and Research Hospital (approval number: 2019/7-25).

Statistical Analysis

All statistical analyses were performed using the IBM SPSS Statistics 25 package program (IBM Corp., Armonk, New York, USA). Data are presented as count (n), percent (%), mean, SD ($\overline{X}$±SD) and median 25%-75% quartiles [M (Q_1-Q_3)]. Shapiro-Wilk's test was used and a histogram and Q-Q plot were examined to assess the data normality. Mann-Whitney U test was used to compare the differences between the two groups for the children's age and BMI (percentile). The relationship between variables was

evaluated by Spearman correlation analysis. The relationship between categorical variables that have two categories or more than two categories were analysed using Pearson chi-square test and Continuity Correction test. A boxplot graph was used to show the shape of the distribution of breastfeeding duration (months) according to groups based on the children's BMI classification. A bar graph was used to visually compare data among categories concerning breastfeeding duration (3 categories), mother's appetite (5 categories) and initiation time of a complementary diet (3 categories).

Results

A total of 182 children with 109 obese or overweight mothers and 73 mothers who had normal BMI were included in the study. The socio-demographic and anthropometric findings of the children and mothers are shown in Table I. There were statistically significant differences, in terms of the BMI percentiles of the children, between the group of children with obese or overweight mothers and the group with mothers with normal BMI (p=0.011) (Table I). According to the children's BMI classifications, there is no significant relationship between the children of obese or overweight mothers and the children of mothers with normal BMI (p=0.170). However, the ratio of overweight and obese children among the group of obese and overweight mothers was higher than among the group with normal BMI mothers (Table II). A statistically significant difference was found between the BMI classification of the children with employed versus unemployed mothers (p=0.015). The distribution of overweight and obese children among the group of employed mothers and the distribution of underweight children among the group of unemployed mothers was high (Table II). When the weight, weight percentile and weight SDS values of the obese or overweight mothers were compared with their children, a moderately statistically significant positive correlation was found (r_s=0.215, p=0.025; r_s=0.319, p=0.001; r_s=0.319, p=0.001). A significant relationship was found between maternal appetite and the BMI classification of the child (p=0.005). Among the children of mothers with very good appetites, 18.5% were overweight and 20.4% were obese (Table II).

No statistically significant difference was found between the breastfeeding duration and the children's BMI classification (p=0.687) (Figure 1, Table II). However, the ratio of overweight and obese children among the group of children breastfed for less than 4 months was higher than the group of children breastfed for more than 6 months (Table II). When the children were evaluated according to the initiation time of a complementary diet, no significant difference was found (p=0.375) (Table II).

Table I. Socio-demographic and anthropometric findings of the children in the groups

	Groups		
	Obese or overweight mother (n=109)	**Mother with normal BMI (n=73)**	
Children			
	$\overline{X}$ ± SD	**$\overline{X}$ ± SD**	
	M (Q_1-Q_3)	**M (Q_1-Q_3)**	**p value**
Age	3.53±1.02	3.59±1.05	0.679+
	3.50 (2.83-4.50)	3.50 (2.75-4.50)	
BMI percentile	50.63±36.63	37.25±33.90	0.011+
	56.36 (13.00-89.03)	28.10 (4.36-69.89)	
	(n, %)	(n, %)	
Gender			
Girls	60 (55.0)	34 (46.6)	0.262†
Boys	49 (45.0)	39 (53.4)	
Mother			
	$\overline{X}$ ± SD	$\overline{X}$ ± SD	
	M (Q_1-Q_3)	M (Q_1-Q_3)	
Age	31.81±5.40	31.53±5.54	0.997+
	31.00 (28.00-34.00)	32.00 (27.00-36.00)	
	(n, %)	(n, %)	
Education level			
Uneducated	9 (8.3)	8 (11.0)	0.436†
Primary school	64 (58.7)	37 (50.7)	
High school	17 (15.6)	9 (12.3)	
University	19 (17.4)	19 (26.0)	
Employment status			
Employed	29 (26.6)	20 (27.4)	1.000*
Unemployed	80 (73.4)	53 (72.6)	
Family income level			
1600 TL	37 (33.9)	25 (34.2)	0.993†
1601-2500 TL	37 (33.9)	25 (34.2)	
2501-5000 TL	15 (13.8)	9 (12.3)	
>5000 TL	20 (18.3)	14 (19.2)	

+Mann-Whitney U test, †Pearson chi-square test, *Continuity correction
BMI: Body mass index

Discussion

In this study, obese and overweight mothers who were employed and had a high appetite were found to have more obese and overweight children. Additionally, the children who were breastfed for less than 4 months were more likely to be obese and overweight than children who were breastfed for more than 6 months.

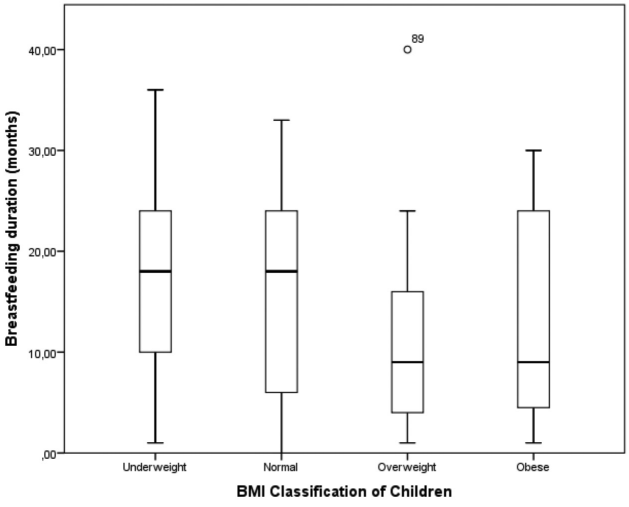

Figure 1. Boxplot of breastfeeding duration (months) and Children's body mass index classification
BMI: Body mass index

Parents are important as a role model in the physical appearance and health of their children (12). Parental obesity has been shown to increase the risk of the development of obesity in children (13,14). The mother is especially the determinant of nutrition for her child, as she is the principal caregiver and the person shaping nutrition (6). Stunkard et al. (15) showed a weak relationship between the weight of mothers and the weight of their children in the first 2 years. The first years are a transitional period in which the prenatal environmental impact decreases and the genetic and shared common environment and parental characteristics become more pronounced (4). Therefore, this study did not include children less than 2 years of age.

In a study in which children under 5 years of age were followed for about 14 years, it was shown that mothers' positive weight gain increased the likelihood of positive weight gain in pre-school and school children. However, no similar relationship was found between fathers and their children (5). In our study, we found a positive correlation between the weight, weight percentile and weight SDS values of the obese or overweight mothers and their

Table II. The relationship between breastfeeding duration, initiation time of a complementary diet, maternal appetite, mother's body mass index classification, mother's working status and body mass index classification of children

		BMI classification of children								p value
		Obese		Overweight		Normal		Underweight		
		n	%	n	%	n	%	n	%	
Breastfeeding duration	<4 months	4	15.4	4	15.4	15	57.7	3	11.5	0.687†
	4-6 months	2	13.3	3	20	8	53.4	2	13.3	
	>6 months	13	9.5	14	10.2	79	57.7	31	22.6	
Initiation time of complementary diet	<4 months	2	40	0	0.0	3	60	0	0.0	0.375†
	4-6 months	5	12.5	5	12.5	22	55	8	20	
	>6 months	12	8.8	17	12.4	79	57.6	29	21.2	
Maternal appetite	Very low	0	0.0	0	0.0	0	0.0	1	100	0.005†
	Low	2	20	0	0.0	3	30	5	50	
	Normal	1	2.4	6	14.3	27	64.3	8	19	
	Strong	5	6.6	6	8	46	61.4	18	24	
	Very strong	11	20.4	10	18.5	28	51.9	5	9.2	
BMI classification of mothers	Obese or overweight	14	12.8	16	14.7	61	56.0	18	16.5	0.170†
	Normal	5	6.8	6	8.2	43	58.9	19	26.0	
Mother's working status	Employed	7	14.3	11	22.4	26	53.1	5	10.2	0.015†
	Unemployed	12	9.0	11	8.3	78	58.6	32	24.1	

†Pearson chi-square test
BMI: Body mass index

children. Also, BMI percentiles were higher in the children of obese or overweight mothers.

It has been shown that young mothers with low education levels are not aware of their weight status and do not worry that their children are overweight (16). In a study from Sweden, it was reported that the children of obese and low-educated parents were at risk of the development of obesity (17). In a study from the United States, the relationship between the number of a mother's working hours (for mothers with higher education levels) and child BMI was associated with the child's duration of television viewing (18). In this study, the number of obese and overweight children was higher for employed mothers, and the number of underweight children was higher for unemployed mothers. In children between 2 and 5 years of age, have been reported to be more important in the prevention of obesity, rather than longer working hours, more standard working hours for parents and reduced access of children to sugary drinks (19).

It has been reported that exclusive breastfeeding has a positive effect on the weight of children, as well as their weight in adolescence and adulthood (20). There is also a positive relationship between the mother's >30 BMI and a duration of less than 4 months breastfeeding (21). In a study that evaluated 5-year-old children, it was reported that there was a weak relationship between a duration of breastfeeding of less than 4 months and obesity, but there was no statistical significance, and exclusive breastfeeding was not protective for obesity (21). In this study, we did not find a relationship between breastfeeding duration and obesity. However, it was seen that children who were breastfed for less than 4 months were more likely to be obese and overweight than children who were breastfed for more than 6 months.

A complementary feeding period provides the opportunity to protect children from becoming obese and overweight (22). Complementary nutrition that is applied between 6 and 24 months becomes an important period affecting long-term health (23). The European Society for Paediatric Gastroenterology Hepatology and Nutrition states that complementary nutrition should not be initiated before the 17th week or after the 26th week and that exclusive breastfeeding or predominantly breastfeeding in the diet for 6 months is preferential (24). This study did not find a relationship between the initiation time of a complementary diet and obesity. Therefore, it is important to provide appropriate nutritional support in this period, considering the positive effects of complementary nutrition on a child's development and on their long-term health (25).

Study Limitations

The limitation of the study was evaluating the mothers' and children's appetite according to the mothers' declaration. Furthermore, larger sample size studies on this issue will be useful.

Conclusion

Obesity is a preventable public health problem. In this respect, it is important to identify influential factors and take necessary measures to prevent children from becoming obese and overweight. This study determined that the mothers' characteristics of having a BMI classification of overweight or obese, having an excessive appetite and being employed may be risk factors in the development of overweight and obese children. Increasing the awareness of mothers about their excess weight and their children's excess weight and providing appropriate training for mothers about the healthy feeding of their children can help prevent obesity in childhood.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained from the Ethics Committee of İzmir University of Health Sciences, Tepecik Training and Research Hospital (approval number: 2019/7-25).

Informed Consent: Informed consent was obtained from all mothers participating in the study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Y.Ç.A., B.A., M.B., Concept: Y.Ç.A., M.B., Design: Y.Ç.A., M.B., O.B., B.A., Data Collection or Processing: Y.Ç.A., B.A., T.T., E.B., O.B., Analysis or Interpretation: Y.Ç.A., B.E., Literature Search: Y.Ç.A., B.E., T.T., E.B., Writing: Y.Ç.A., M.B.

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Original Article

Association of Neck, Wrist and Hip Circumferences with Kidney Function in Children and Adolescents: The CASPIAN- V Study

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ABSTRACT

Aim: Some evidence exists concerning the relationship between anthropometric measurements and chronic kidney disease. This study aims to investigate the association of neck circumferences (NC), wrist circumferences (WC) and hip (HC) circumferences with kidney function in a pediatric population.

Materials and Methods: In this national study, 4.200 students aged 7-18 years were selected by random cluster sampling from 30 provinces of Iran. NC, WC and HC were measured according to standard protocol and were categorized to either low or high according to their age-sex specific median values. The estimated glomerular filtration rate (eGFR) was calculated based on the "updated" Schwartz equation.

Results: The response rate was 91.5% (n=3.843). The mean standard deviation of eGFR was 96.71 (19.46), 96.49 (21.69), and 96.59 (20.66) mL/minimum/1.73 m^2 for girls, boys and the total population, respectively. Compared to other participants, those in the high NC group had significantly higher eGFR (102.12±21.31 vs 90.65±18.18, p<0.001) and high creatinine (Cr) (0.66±0.14 vs 0.63±0.11 mg/dL, p<0.001). Individuals categorized as high WC had significantly higher eGFR (102.12±21.31 vs 90.83±18.16, p<0.001) and Cr (0.66±0.15 vs 0.63±0.10) mg/dL, p<0.001). In the multivariate model, high NC, WC and HC were associated with higher eGFR (p<0.001). Moreover, each one-unit (cm) increment in NC, WC and HC increased eGFR by 1.42, 3.24 and 0.46 units, respectively.

Conclusion: The findings of this large population-based study suggest that simple anthropometric measurements, such as WC and NCs, can be used in epidemiological studies to determine those children and adolescents that might be at risk of kidney dysfunction.

Keywords: Kidney function, neck circumference, wrist circumference, children, prevention

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Introduction

Chronic kidney disease (CKD) is an important health problem with complicated associations with other disorders such as cardiovascular diseases (1). Studies conducted in the United States (between 1988-1994 and 1999-2004) have reported that the prevalence of CKD is increasing from 10% to 13.1%. Limited studies exist about CKD in non-Western populations. In Iran, its incidence is reported as 27.8% in females and 14.2% in males (2,3).

CKD will cause a poor quality of life and also a huge economic burden as the patient may need kidney transplantation or dialysis (4). The disease is asymptomatic at the beginning and is not usually detected until the progression and development of complications. This makes the prevention of kidney failure or other outcomes very hard (5). Early detection of the disease can delay the progress to end stage renal disease or other severe complications (6).

Obesity is a growing worldwide problem in both developing and developed countries. It is a major determinant of most chronic disorders including CKD (7,8). Body mass index (BMI) is the most commonly used index for determining weight status. BMI is easy to calculate, but it has some limitations in describing body compositions. Waist circumference is largely used for determining the visceral obesity that is related to complications of obesity (9,10). Measurement of waist circumference differs according to body position and breathing phase, and it is hard to measure it in routine primary care visits and some situations where adequate body exposure are difficult, therefore some other parameters including neck and wrist circumferences (WCs) are described and used in epidemiological studies (11). In the current study, we aim to determine the association of kidney function with neck and WCs in children and adolescents.

Materials and Methods

This multicentric cross-sectional study was conducted as part of the fifth survey of a national school-based surveillance program entitled "Childhood and Adolescence Surveillance and Prevention of Adult non-communicable Disease" study (2015). Detailed methodology has been described previously (12).

Ethical Considerations

The Research and Ethics Committee of Isfahan University of Medical Sciences approved this study (approval number: 194049). Participation in this study was voluntary. After a complete explanation of the study objectives and protocols, written informed consent and verbal consent were obtained from the parents and students, respectively.

Study Population and Sampling Framework

Participants consisted of students, aged 7-18 years, living in urban and rural areas of 30 provinces of Iran. They were selected by a multistage, stratified cluster sampling method. Using the proportional to size method and with an equal sex ratio, sampling within each of the provinces was conducted according to the student's area of residence (urban or rural) and level of education (primary and secondary). Moreover, the number of samples of different educational grades in urban and rural areas was estimated according to the number of students in each grade. The total sample size was calculated as 480 students in each province (48 clusters of 10 students); in each province, 14 clusters were randomly selected for biochemical testing, i.e. a total of 4.200 students.

Procedure and Measurements

Two sets of questionnaires were developed for students and their parents. The students' questionnaire was derived from the World Health Organization-Global School Student Health Survey. The validity and reliability of the Farsi-translated questionnaire was assessed previously (13,14). During the interviews, not only demographic information, but also complementary information on physical activity (PA), screen time (ST), and socio-economic status, was completed for all participants.

Through the executive process of the survey, all examinations were conducted with calibrated instruments and the recording of information was completed through validated checklists which were designed and conducted under the standard protocol by trained health care professional teams (15,16).

Neck circumference (NC), hip and WC were measured using a non-elastic tape to the nearest 0.1 cm over the skin. NC was measured by a tape underneath the Adam's apple in contact with the patient's skin in a comfortable position (15,17).

WC was measured with subjects in a seated position for both wrists at distal to the prominences of the radial and ulnar and an average was taken (18,19). Neck, wrist and hip were categorized as either low or high according to an age-sex specific median.

Blood Sampling

Eligible students were referred to the laboratory, while one of the parents accompanied him/her. There, 6 mL

venous blood samples were collected after 12-hr overnight fasting. All collection tubes were centrifuged at 2.500-3.000 x g for 10 minutes. Immediately after centrifugation, serum samples were aliquot into 200 microliter tubes and stored at -70 °C. All samples were transferred by cold chain to the Isfahan Mahdieh Laboratory. Serum creatinine (Cr) was measured enzymatically by the Hitachi auto-analyzer (Tokyo, Japan) (20,21).

Definition of Terms

Socio-economic Status

The method, validity and considered variables for calculating the socio-economic status (SES) of Iranian families was approved previously through the Progress in the International Reading Literacy Study (22). Considering that, the principal component analysis of variables including parental education, parents' job, ownership of a private car, school type (public/private), and having a personal computer in the home were summarized in one main component. This component explained 72.0% of variance. This main component was categorized into tertials. The first tertial was defined as a low SES, the second tertial as an intermediate and the third tertial as a high SES.

Screen Time

To assess ST behaviors, the average number of hours per day that participants spent watching TV/VCDs, using personal computers (23), or playing electronic games was asked, then the total cumulative time spent for ST was estimated. Information was recorded separately for weekdays and weekends. The analysis of the correlates of ST was carried out according to the international ST recommendations and ST was categorized into two groups; less than 2 hours per day (low), and 2 hours per day or more (high) (24-26).

Physical Activity

Through a validated questionnaire, information regarding the past week's frequency of leisure time PA outside school was collected (12). PA was considered as at least a 30-minute duration of exercises that led to heavy sweating or a large increase in breathing or heart rate. Based on this, participants described their weekly PA habits via four available responses as follows; none, 1-2 days, 3-6 days, and every day. With the aim of analysis, weekly frequency of PA was categorized into three groups; less than two times per week (mild), two to four times a week (moderate) and more than 4 times a week (vigorous) (27).

Glomerular Filtration Rate

GFR describes the flow rate of filtered fluid through the kidney (28). The estimated eGFR is used to screen for the early detection of kidney damage, to help diagnose CKD, and to monitor kidney status. It is a calculation based on the results of a blood Cr test adjusted for age and sex based on the equation used (28). In the present study, eGFR was calculated based on the "updated" Schwartz equation formula (29):

$$\text{eGFR} = \frac{0.413 \times \text{height (cm)}}{\text{serum creatinine } (\frac{\text{mg}}{\text{dL}})}$$

Statistical Analysis

Continuous and categorical variables are expressed as mean [standard deviation (SD)] and number (percentage) respectively. The Kolmogorov-Smirnov test was used to examine the normality of continuous variables. Associations of continuous and categorical variables with age groups were compared by ANOVA and the chi-square test, respectively.

The mean of eGFR and Cr across categorized levels of hip, neck, and WCs was compared by t-test. Linear regression analysis was used to examine the association of hip, neck and WCs with eGFR and Cr.

Three models were applied: Model I: the crude model (without adjustment); Model II: was adjusted for age, area of residence (urban or rural), sex, PA, ST and SES; and Model III: was additionally adjusted for BMI. All statistical analyses were performed using a survey analysis method, and were conducted using the statistical program STATA package version 11.0 (stata statistical software: Release 11. College Station, TX: StataCorp LP. Package). P values of less than 0.05 were considered as statistically significant.

Results

The study participants consisted of 3.843 students with a mean age of 12.28±3.15 years, without any significant difference between boys and girls. From them, 50.6% were boys and 71.4% were from urban areas. The characteristics of the participants are presented in Table I. It shows that PA and SES were significantly different between the age groups. Whereas, eGFR and Cr, respectively, with an overall mean ± SD of 96.59±20.66 and 0.65±0.14 (mg/dL), showed significant ascending differences between the age groups (p-trend<0.001). Likewise, BMI, NC, WC and HC, with means of 18.51±4.71 (kg/m^2), 29.84±3.99 (cm), 14.72±1.89 (cm), and 79.14±14.64 (cm) followed an ascending trend with increasing age (p-trend<0.001).

Considering the mean ± SD of eGFR and Cr according to NC, WC and HC; participants in the high NC group had significantly higher eGFR (102.12±21.31 vs 90.65±18.18, p<0.001) and Cr (high; 0.66±0.14 vs 0.63±0.11 mg/dL, p<0.001). Except for Cr levels in girls, these significant associations were also documented in other groups. Likewise, those participants who were categorized as the high WC group had significantly higher eGFR (102.12±21.31 vs 90.83±18.16, p<0.001) and Cr [(0.66 ±0.15 vs 0.63 ±0.10) mg/dL, p<0.001] than their counterparts. Except for Cr levels of girls, this significant association existed in other groups as well. Regarding the two groups of high and low HC, both boys and girls had higher eGFR in the high HC groups (boys: 103.66±22.38, girls: 102.10±19.43 mg/dL, p<0.001) (Table II).

Table III shows the association of NC, WC and HC as continuous and categorical variables with eGFR and Cr in linear regression analysis. In a multivariate model, NC, WC and HC, as continuous and categorical variables, were associated with eGFR; participants with high NC, WC and HC, compared with their other counterparts, had significantly higher eGFR (p<0.001). In a multivariate model (Model III), each one unit (cm) increment in NC, WC and HC increased eGFR by 1.42, 3.24 and 0.46 units, respectively.

The multivariate model on the association of NC, WC and HC, as continuous and categorical variables, with Cr, showed that only continuous NC and WC were associated with Cr levels; per each one unit (cm) increment in NC and WC, Cr increased significantly by 0.002 and 0.004 mg/dL, respectively.

Table I. Characteristics of participants by gender and age group: The CASPIAN-V study

	Age			Total	p value
	7-10 y	11-14 y	15-18 y		
Mean age (year)[1]	8.74±1.03	12.51±1.08	16.41±1.04	12.28±3.15	<0.001
Sex[2]					
Boy	2.358 (48.7)	2.826 (50.5)	2.044 (53.2)	7.228 (50.6)	<0.001
Girl	2.485 (51.3)	2.765 (49.5)	1.796 (46.8)	7.046 (49.4)	
Area of residence					
Urban	3.235 (66.8)	3.683 (65.9)	3,276 (85.3)	10.194 (71.4)	<0.001
Rural	1.608 (33.2)	1.908 (34.1)	564 (14.7)	4.080 (28.6)	
BMI (kg/m^2)[1]	16.18±4.03	18.99±4.41	21.21±4.42	18.51±4.71	<0.001
Physical activity[2]					
Low	1.470 (32.6)	1.683 (32.3)	1.301 (36.1)	4.454 (33.4)	0.001
Medium	1.482 (32.9)	1.784 (34.3)	1.158 (32.1)	4.424 (33.2)	
High	1.554 (34.5)	1.739 (33.4)	1.147 (31.8)	4.440 (33.3)	
Screen Time[2]					
Low	4.023 (85.4)	4.553 (84.2)	3.068 (81.5)	11.644 (83.8)	<0.001
High	688 (14.6)	857 (15.8)	698 (18.5)	2.243 (16.2)	
SES[2]					
Low	1.524 (32.9)	1.830 (34.4)	1.205 (32.8)	4.454 (33.4)	0.06
Medium	1.514 (32.7)	1.723 (32.4)	1.278 (34.8)	4.424 (33.2)	
High	1.595 (34.4)	1.764 (33.2)	1.193 (32.5)	4.440 (33.3)	
Neck circumference[1]	27.25±3.06	29.97±3.42	32.93±3.54	29.84±3.99	<0.001
Waist circumference[1]	13.44±1.47	14.92±1.62	16.03±1.71	14.72±1.89	<0.001
Hip circumference[1]	69.08±10.57	80.32±1245	90.18±13.39	79.14±14.64	<0.001
eGFR1	87.23±15.72	99.30±19.76	102.60±23.20	96.59±20.66	<0.001
Creatinine (mg/dL)[1]	0.63±0.10	0.64±0.11	0.69±0.16	0.65±0.14	<0.001

[1]Data are presented as mean (standard deviation), [2]Data are presented as number (percentage)
CASPIAN-V: BMI: Body mass index, SES: Socio-economic status, eGFR: Eestimated glomerular filtration rate, 0.413* height (cm)/serum creatinine (mg/dL)

Table II. Mean ± standard deviation of estimated glomerular filtration rate and creatinine according hip, neck and wrist circumference: The CASPIAN-V study

Variable	eGFR			Creatinine (mg/dL)		
	Total	Boy	Girl	Total	Boy	Girl
Neck circumference[a]						
Low	90.65±18.18	90.02±19.07	91.31±17.17	0.63±0.10	0.64±0.11	0.62±0.10
High	102.12±21.31	102.28±22.34	101.99±20.08	0.66±0.14	0.67±0.14	0.66±0.15
p value	<0.001	<0.001	<0.001	<0.001	<0.001	0.008
Wrist circumference[b]						
Low	90.83±18.16	89.76±19.24	91.87±16.97	0.63±0.10	0.64±0.11	0.62±0.10
High	102.12±21.33	102.18±22.07	102.04±20.39	0.66±0.15	0.66±0.16	0.66±0.14
p value	<0.001	<0.001	<0.001	<0.001	<0.001	0.007
Hip circumference[c]						
Low	89.78±17.98	89.17±18.3	90.49±17.53	0.63±0.11	0.64±0.11	0.62±0.10
High	102.89±20.99	103.66±22.38	102.10±19.43	0.66±0.15	0.66±0.14	0.66±0.15
p value	<0.001	<0.001	<0.001	<0.001	0.004	0.005

[a]According to age-sex specific median, [b]According to age-sex specific median, [c]According to age-sex specific median, CASPIAN-V: eGFR: estimated glomerular filtration rate

Discussion

As the first study of its kind in a non-Western population, we investigated the association between some anthropometric measurements including hip, neck and WCs with renal function in a large national pediatric population. The results demonstrated that in different age groups of girls and boys, those participants with lower hip, neck and WCs had better kidney function than their counterparts. Adjusted models of logistic regression analysis showed that the association between GFR and the afore mentioned anthropometric measurements was more prominent than that of Cr.

Recently, the evaluation of the associations between anthropometric indices, including neck and WCs, and disease-related biological markers have gained more interest; which is due to its low cost and non-invasive method of measurement (30).

NC is considered as the representative anthropometric parameter of upper-body subcutaneous fat (31). The appropriate inter and intra reliability of NC among 6-16 year-old children and adolescents have been reported on previously (32). Accordingly, multiple measurements are not necessary for this index. In addition, its measurement has a simple method that can be easily performed by health care professionals (32).

Some studies have indicated the association between NC and obesity, cardio metabolic risk factors and insulin resistance in children (33,34). Moreover, some studies demonstrated that the association between NC and cardiometabolic risk factors is more significant than other anthropometric parameters such as waist circumference or BMI (35).

Although some studies exist regarding the usefulness of measuring NC for predicting renal function in adults, to the best of our knowledge, there is no study in this field based on a pediatric population.

Recently, Yoon et al. (36) in a prospective cohort study (Korean Genome and Epidemiology Study cohort) have evaluated the association between NC and incident CKD. They revealed that NC could be used as an independent predictor for CKD. Their observed association persisted even after adjustment for other anthropometric measurements such as BMI and waist-to-hip ratio, baseline eGFR and traditional risk factors of CKD. They also found that this association would be more prominent in the presence of obesity and elevated BMI.

The findings of the Liu et al. (37) study suggested that NC, as an indicator of upper-body subcutaneous fat, could have a pathogenic role in the occurrence of renal dysfunction. They showed that NC is associated with other indicators of renal function including uric acid, micro albuminuria, 24-hr Cr clearance rate and eGFR based on the Cockcroft and Gault formula as well as cardiovascular risk factors such as serum lipid levels and hs-C-reactive protein.

Table III. Association of hip, neck and wrist circumference with estimated Glomerular Filtration Rate and Creatinine in logistic regression analysis: The CASPIAN-V study

	eGFR			Creatinine (mg/dL)		
	β	SE	p value	β	SE	p value
Neck circumference (cm)						
Model I	1.42	0.08	<0.001	0.004	0.001	<0.001
Model II	0.88	0.10	<0.001	0.001	0.001	0.03
Model III	0.80	0.11	<0.001	0.002	0.001	0.01
Neck circumference, High/Low[a]						
Model I	11.47	0.64	<0.001	0.03	0.007	<0.001
Model II	6.73	0.80	<0.001	0.004	0.005	0.45
Model III	6.55	0.86	<0.001	0.004	0.005	0.43
Wrist circumference (cm)						
Model I	3.24	0.17	<0.001	0.01	0.002	<0.001
Model II	2.07	0.22	<0.001	0.003	0.001	0.01
Model II	2.17	0.25	<0.001	0.004	0.001	0.006
Wrist circumference, High/Low[b]						
Model I	11.29	0.64	<0.001	0.03	0.007	<0.001
Model II	7.15	0.78	<0.001	0.002	0.005	0.63
Model III	7.07	0.84	<0.001	0.003	0.005	0.62
Hip circumference (cm)						
Model I	0.46	0.02	<0.001	0.001	0.00	<0.001
Model II	0.34	0.02	<0.001	0.00	0.00	0.62
Model II	0.38	0.03	<0.001	0.00	0.00	0.51
Hip circumference, High/Low[c]						
Model I	13.11	0.63	<0.001	0.03	0.007	<0.001
Model II	8.93	0.81	<0.001	-0.002	0.005	0.64
Model III	9.18	0.22	<0.001	-0.002	0.006	0.67

[a]According to age-sex specific median, [b]According to age-sex specific median, [c]According to age-sex specific median, Model I: Without adjustment, Model II: Adjusted for age, living area, sex, physical activity and screen time, SES, Model III: Additionally adjusted for BMI
eGFR: Estimated glomerular filtration rate, SES: Socio-economic status

To the best of our knowledge, the current findings are the first to show a significant association between NC in children and GFR, which is considered as the most important and earliest indicator of renal dysfunction. It seems that this anthropometric index could be applicable both in epidemiological studies and clinical practice for screening for renal dysfunction in the pediatric population.

The association between obesity and the development of CKD has been documented in some studies (38,39). Moreover, the relationship between obesity and end stage renal disease has a direct correlation irrespective of underlying factors such as hypertension or diabetes (39).

WC is another simple anthropometric measurement, which has a safe and non-invasive method with appropriate intra- and inter-operator reliability (40). In addition, it is related to skeletal frame size, and is not affected by body fat variations (40).

A study in Iranian adults reported that WC, as a novel anthropometric measurement, can be considered as an independent predictor for incident hypertension and cardiovascular disease among non-centrally obese women (41). However, in another study in the same population, WC had significant correlation with lipid profile, but not with metabolic syndrome or cardiovascular diseases (42).

Some other studies indicated that WC is associated with insulin resistance both in children and adults (43), as well as with diabetes in the adult population (44).

A recent study in Italy showed that WC could be used as an indicator of insulin resistance in obese youth (40). A cohort with 30 years of follow up showed that this measurement is an indicator of insulin resistance and BMI in children but not in adults (45).

Thus, considering the association between obesity, insulin resistance and abnormal glucose metabolism with CKD, as well as the current finding on the association between WC and GFR, it is suggested that WC can be used as a predictor of CKD in children.

In this study, although the mean serum Cr level was higher in those participants with higher measurements of hip, neck and WCs, it had no significant correlation with these anthropometric measurements. In addition, these very small differences are of no clinical importance.

This investigation had a cross-sectional design, which is considered as its main limitation. In addition, the results of this study would be more applicable if the association of the afore mentioned anthropometric indices with other markers of kidney function, such as cystatin C, had been investigated.

This study was conducted as a part of a national study with a large sample size and, to the best of our knowledge, this was the first national study in the pediatric population which has evaluated the association of neck and WCs with renal function.

Conclusion

The findings of this large population-based study suggest that both neck and WCs are appropriate, simple, non-invasive and easy to detect anthropometric measurements that can be used in epidemiological and clinical studies for determining those children and adolescents who are at risk of kidney dysfunction.

Ethics

Ethics Committee Approval: The Research and Ethics Committee of Isfahan University of Medical Sciences approved this study (approval number: 194049).

Informed Consent: Written informed consent and verbal consent were obtained from the parents and students, respectively.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: R.K., M.E.M., Concept: R.H., M.E.M., M.Q., R.K., Design: R.H., M.Q., R.K., Data Collection or Processing: M.T., T.A., G.S., A.M.G., S.Z., Analysis or Interpretation: M.Q., Literature Search: A.M.G., S.D., A.A., Writing: M.M., A.M.G.

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Original Article

Platelet Indices and the Severity of Dengue Infection in Children

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ABSTRACT

Aim: Dengue is becoming endemic in India. The reported case-fatality rate in India is 3-5%. Thrombocytopenia is the most common finding. Platelet indices are gaining importance in the illness. To study the platelet indices in children with dengue infection and to note their relationship with the severity of disease.

Materials and Methods: Observational record-based study done over 12 months at a medical college hospital in costal Karnataka. Platelet parameters were noted from the hospital-based data system and compared with the severity of disease (Bleeding score, Severity score, Warning signs and Duration of stay).

Results: Out of 125 dengue positive patients studied, 83% had mean platelet volume below 9fl, 68% had platelet distribution width below 18, 64% had plateletcrit (PCT) below 0.1%, 57% had a platelet count fall below 1 lakh during their illness. PCT showed a significant correlation (p=0.001) with decreasing and increasing trends of the platelet count and a similar relation to the severity of the disease. Patients had a longer duration of stay (>4days) when platelet counts decreased to less than 1 lakh during their illness compared to those with more than 1 lakh (73% vs 35%). Platelet counts below 1 lakh were noted in 85% (37 of 44) of patients with warning signs as compared to 41% (34 of 81) of patients without warning signs.

Conclusion: Platelet indices are decreased in dengue infection. A decreased platelet count and PCT correlate with the severity of the infection.

Keywords: Platelet indices, dengue infection, severity

Introduction

Dengue illness remains a significant clinical and public health challenge globally. More than 2.5 billion people in the tropics and subtropics are at risk of infection (1) and an estimated 390 million dengue infections occur annually in around 125 countries worldwide (2). Increases in the incidence of dengue outbreaks are seen during the monsoon and post-monsoon seasons. Children and young adults are the population that are most affected. It is a vector borne arboviral disease transmitted by Aedes mosquitoes (3).

One of the most common laboratory findings in dengue is thrombocytopenia (3). Possible mechanisms of thrombocytopenia could be, direct bone marrow suppression by the virus, anti-dengue antibody-mediated platelet destruction, peripheral consumption of the platelets and isolated viral replication in the platelets. Thrombocytopenia leads to bleeding although the platelet count may not directly correlate with the bleeding manifestations (4). Bleeding in dengue can vary from minor petechiae to severe haemorrhage causing the death of the patient (5).

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Platelet indices like mean platelet volume (MPV), platelet distribution width (PDW) and Plateletcrit (PCT) are being investigated as prospective platelet activation indicators. MPV is a useful independent predictor of bleeding. It is a surrogate indicator of bone marrow activity. Low MPV indicates bone marrow suppression and suggests a risk of bleeding. The normal range for MPV is 8.9-11.8 fL (6). PDW is a marker of volume variability in platelet size and is elevated in the presence of platelet anisocytosis. It directly measures variability in platelet size and changes occurring with platelet activation, and also suggests the heterogeneity in platelet morphology. The normal range for PDW is 10.0%-17.9% (7). PCT is the volume occupied by platelets in the blood as a percentage and calculated by the formula PCT = platelet count × MPV/10.000. The normal range for PCT is 0.22-0.24% (5).

Platelet indices are reported by most automatic and semi-automatic cell counters used in most hospitals. Despite advances in diagnostic modalities and treatment strategies, there is limited data on dengue fever in the paediatric population and its relation with platelet parameters. This study aims to fill in some of these gaps by describing the severity of dengue infection in children, particularly with relation to platelet indices.

Materials and Methods

It is an observational record based study done over a period of 12 months between July 2017 to July 2018. 125 cases coming under the inclusion criteria admitted as an inpatient in our Medical college Hospital were included in the study. The approval was obtained from the Father Mullers Medical College Institutional Ethics committee and the waiver of consent was approved with approval number: FMMCIEC/CCM/453/2018.

All children aged less than 15 years (1 month to 15 years) presenting with features of suspected or probable dengue as per WHO guidelines with positive serology (NS1 or immunoglobulin M (IgM) positive by rapid card test or ELISA) were included in the study. Children who were IgM or NS1 negative (those who cannot be proven as "probable or confirmed dengue") and children with a pre-existing chronic disease which may interfere with the assessment of the complications of dengue infection were excluded from the study.

Demographic features, clinical features, warning signs and duration of stay were noted from inpatient records. Serology and platelet parameters were noted from the hospital-based data system. Bleeding score, severity score, warning signs and duration of stay were the parameters used to assess the severity of illness.

The study population was divided into two categories with respect to each platelet indices. Normal reference ranges were used in categorizing the study population. A platelet count of 1 lakh, PCT of 0.22, MPV of 9fl and PDW of 18 were considered as cut off points (4-7) to categorize the cases into two subgroups. Severity parameters were compared between the 2 subgroups with respect to each platelet indices.

Severe abdominal pain, persistent vomiting, bleeding gums, vomiting blood, rapid breathing, and fatigue/restlessness were considered as warning signs as described by the World Health Organization. Based on the site and type of bleeding (data obtained from inpatient case records), a bleeding score was assigned to each patient as depicted in Table I (8). Each patient was classified into one of the four vascular leakage categories as depicted in Table II according to the overall severity of hemo-concentration and/or the development of shock (9).

Statistical Analysis

Data was entered into Microsoft Office Excel Sheet 2010. Statistical analysis was done using SSPS-21 software. Statistical analysis of the data included descriptive analysis and differences between groups (based on dengue severity scores) as Pearson's correlation or chi-square tests. Any p value of <0.05 was considered as significant.

Results

A total of one hundred and twenty-five cases were

Table I. Bleeding scores

Bleeding score	Description
0	No bleeding
1	Petechiae
2	Epistaxis or gingival bleeding, menorrhagia
3	Gastrointestinal bleeding
4	Intracranial bleed, intrapulmonary bleed

Table II. Severity scores

Severity score	Description
1	10% or less change in hematocrit
2	10% to 20% change in hematocrit
3	20% or more change in hematocrit and/or evidence of fluid accumulation on a radiograph or ultrasound image.
4	Dengue shock syndrome

included in the study. Among these, 42% (52) were females and 58% (73) were males. The age-related demographics showed that 17% (21) of patients belonged to the age group of 6 months to 5 years, 34% (42) patients were in the age group of 5-10 years and 49% (62) were in the age group of 10-15 years. Serological parameters showed that 77% (96) of patients were positive for NS1, 12% (15) were positive for IgM, 11% (14) were positive for NS1 and IgM. Platelet indices of all the enrolled cases were analysed and minimum values noted during the stay were considered for grouping.

Out of one hundred and twenty-five cases considered, 57% had their platelet count fall to less than 100.000 (10.4% to less than 25.000; 9.6% between 25.000-50.000; 36.8% between 50.000-100.000) compared to 43% of cases in whom the platelet count persisted above 100.000 during their illness. 78% of our cases had PCT fall to less than 0.22 (10.4% were less than 0.025; 14.4% ranged between 0.025-0.05; 39% were between 0.05-0.1; 14.2% ranged from 0.1 to 0.22) compared to 22% of them who had PCT persistently above 0.22 during their illness. MPV had fallen to less than 9fl in 83% (29% were less than 8 fl and 54% were between 8-9 fl) of cases compared to 17% of cases who had MPV persistently above 9fl during their illness. PDW was less than 18 in 68 % (29% were less than 17 and 39% ranged from 17 to 18) of cases whereas 32% of cases had PDW persistently above 18 during their illness.

A significant positive correlation ($p<0.01$, $r=0.93$) was noted between rising and falling trends of platelet counts with PCT. A negative correlation ($p<0.05$, $r=-0.350$) was noted between falling and rising trends of platelet count and MPV. Similarly, a negative correlation was noted between falling and rising trends of PCT and MPV ($p<0.01$, $r=-0.390$).

Out of one hundred and twenty-five cases considered in our study, 69% had no bleeding manifestations (bleeding score of 0) while 31% had bleeding scores of 1 and above (28% had a score of 1 and 3% had a score of 2). In respect to severity scores, 68% had severity scores of 1 while 32% had severity scores of 2 and above during their illness. Warning signs were present in 35% of the cases while 65% of cases had no warning signs. In relation to the duration of stay, 44% of the population were discharged within 3 days while 56% had a hospital stay of 4 days or more.

Severity parameters were compared between the 2 subgroups as described in the methodology. The tabulated data is depicted in Table I. As shown in the Table, a higher proportion of the population with a platelet count less than 1 lakh and PCT less than 0.22 had higher disease severity parameters during their illness compared to the other group in the corresponding platelet indices categories. Low MPV and PDW did not show any effects on the severity of disease. However, a higher proportion of the population with PDW more than 18 had higher disease severity parameters (Table III).

Discussion

Platelet counts have no role in determining the need for transfusion in dengue. Transfused platelets are as likely to be destroyed by the antibodies as one's own

Table III. Comparison of severity parameters in platelet indices categories

Parameters	Platelet count		Plateletcrit		MPV		PDW	
	<1 lakh	>1 lakh	<0.2	>0.2	<9 fL	>9 fL	<18	>18
Bleeding scores								
0 (No bleeding)	51%	93%	36%	96%	68%	71%	79%	48%
1 or above	49%	7%	64%	4%	32%	29%	21%	52%
Severity score								
1	56%	83%	49%	88%	67%	71%	79%	45%
2 or above	44%	17%	51%	12%	33%	29%	21%	55%
Warning signs								
Present	49%	11%	67%	7%	35%	24%	25%	50%
Absent	51%	89%	33%	93%	65%	76%	75%	50%
Duration of stay								
<3 days	25%	67%	28%	82%	44%	38%	48%	32%
>4 days	75%	33%	72%	18%	56%	62%	52%	68%

MPV: Mean platelet volume, PDW: Platelet distribution width

platelets and hence platelet transfusions have a limited role in the management of dengue (7). Platelet indices give information on whether the platelet destruction is ongoing (necessitating an impending platelet transfusion) or whether the bone marrow is responsive and so platelet transfusions can be put on hold. Low platelet count, low MPV, low PCT and high PDW may be used as probable indicators for dengue in endemic areas and also as a predictor of the severity of the dengue infection.

In the acute stage of dengue fever, thrombocytopenia is due to bone marrow depression. Low MPV with low platelets implies marrow suppression as a mechanism of thrombocytopenia. Increasing MPV with ongoing thrombocytopenia represents peripheral destruction (10) and signals a need for a platelet transfusion while an increase in MPV together with a stable platelet count possibly indicates recovery. Decreased MPV with severe thrombocytopenia with hemorrhagic tendencies could be an ominous sign in dengue and could indicate the need for a red cell transfusion (11). In our study, we found that MPV was decreased in the early stages of dengue and low MPV with thrombocytopenia was associated with higher disease severity parameters and bleeding. These findings indicate that bone marrow suppression by dengue virus could be one of the causes of thrombocytopenia and bleeding in dengue infection.

PDW is higher in hyper-destructive patients when compared with hypo-productive thrombocytopenic patients. The high PDW in platelet destruction could be explained by the fact that newly produced platelets are larger than circulating platelets, which tend to decrease in size with age in circulation similar to reticulocytes with respect to red blood cells. As a result, in patients with thrombocytopenia secondary to peripheral destruction, the PDW is increased reflecting active bone marrow compensation with the release of young platelets (12). In our study, the PDW increased during the recovery phase indicating increased production from the bone marrow and release into circulation. Part of our study population had a PDW of more than 18% indicating that hyper-destruction could be a mechanism of thrombocytopenia in dengue infection. No relation was found between PDW and the severity of disease in our study. PCT, a product of platelet count and MPV had similar effects on the illness as MPV and platelet count. Low PCT was associated with higher disease severity and bleeding.

Wiwanitkit (13) observed that MPV in patients with Dengue hemorrhagic fever was not decreased and was similar to the healthy population. A study by Bashir et al. (14) observed that patients with dengue fever had lower levels of MPV and platelet count; however, PDW values were increased in patients with dengue fever. Navya et al. (15) observed that platelet count was a predictive parameter of dengue fever and they also showed that low MPV and high PDW sensitivity were related to dengue fever. Hardeva et al. (16) recorded a significant association between platelet counts and the severity of the disease. Low platelet count, low MPV, low PCT and high PDW show considerable sensitivity and specificity for dengue fever and can be used as a predictor of the severity of dengue infection. Similar findings were noted by Krishnamurthy et al. (17) and Kumar et al. (18).

In our study, we found that platelet indices are depressed during dengue illness. Our analysis showed a significant correlation between low platelet count, MPV and PCT with different severity parameters. Low MPV and increased PDW during the course of the illness suggested that hypo-production and hyper-destruction are the two possible mechanisms of thrombocytopenia in dengue infection.

Study Limitations

This is a record-based retrospective study so the clinical parameters collected were from records rather than direct observation which would have led to bias in assigning bleeding scores and severity scores.

Conclusion

Platelet indices are decreased in dengue infection. Decreased platelet count, MPV and PCT correlate with the severity of the infection. No significance was noted with PDW and the severity of the disease.

Ethics

Ethics Committee Approval: The approval was obtained from the Father Mullers Medical College Institutional Ethics committee and the waiver of consent was approved with approval number: FMMCIEC/CCM/453/2018.

Informed Consent: Informed consent was obtained.

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Authorship Contributions

Surgical and Medical Practices: C.S.B., K.S.A., Concept: C.S.B., K.S.A., Data Collection or Processing: C.S.B., K.S.A., Analysis or Interpretation: C.S.B., K.S.A., Literature Search: C.S.B., K.S.A., Writing: C.S.B., K.S.A.

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Original Article

The Role of Interleukin-1 Beta C-511T as a Modifier Polymorphism in Cryopyrin-associated Periodic Syndromes

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ABSTRACT

Aim: Cryopyrin-associated Periodic Syndromes (CAPS) are a subgroup of the Periodic fever syndromes, caused by mutations in the *NLRP3* gene. *NLRP3* gene mutations can cause three clinically different phenotypes. It is known that even the same mutations in the *NLRP3* gene can cause different phenotypes. To investigate this situation, we have constructed a hypothesis that if an individual with the Interleukin-1 Beta (IL-1β)-511 T/T genotype which is associated with overexpressed IL-1β levels, he/she might have a more severe CAPS phenotype.

Materials and Methods: Thirty-six NLRP3 Exon three variant-positive patients with detailed clinical data and 30 healthy controls were selected for the IL-1β genotype investigation. For the analysis of IL-1β-511 allele, the SNP rs1143634 was genotyped using the TaqMan 5'-exonuclease allelic discrimination assay.

Results: Neither the Muckle Wells Syndrome patients (severe phenotype) with a p.Val198Met mutation nor symptomatic patients with the p.Gln703Lys variant showed an increased IL-1β-511T/T genotype frequency.

Conclusion: We suggest that IL-1β-511 T/T polymorphism is not a modifying factor regarding the clinical severity of CAPS patients. However, to expand this theory and in order to find other modifying genetic factors, other polymorphisms of IL-1β or other genes in the inflammasome pathway such as caspase-1 or ASC should be analyzed.

Keywords: NLRP3, polymorphism, cryopyrin, IL-1β, association

Introduction

Cryopyrin-Associated Periodic Syndromes (CAPS) are a subgroup of the periodic fever syndromes (PFSs) which are characterized by episodic fever and abdominal pain attacks (1). In addition to these, some severe neurological or systemic complications can result in life-threatening situations (2). CAPS are inherited in an autosomal dominant fashion with an estimated prevalence of 1/360.000 people and they are caused by mutations in the *NLRP3* gene (3).

The *NLRP3* gene encodes cryopyrin (NALP3) protein. When activated by the NACHT domain, NALP3 recruits ASC and caspase-1 and creates inflammasome. Inflammasome increases an inflammation by the activation and secretion of interleukin (IL)-18 and IL-1 beta (IL-1β). The gain of function mutations in the NACHT domain of the NLRP3 protein leads to the overproduction of IL-1β by the activation of inflammasome and this causes fever, recurrent exaggerated systemic inflammatory response and the other systemic features of CAPS (4).

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Since most of the mutations in the *NLRP3* gene are located in exon 3, which encodes the NACHT domain, the basic diagnostic strategy of CAPS includes sequence analysis of at least the exon 3 of the gene (5). *NLRP3* gene mutations, even some identical mutations, can cause 3 clinically different phenotypes:

Familial Cold Autoinflammatory Syndrome

Familial Cold Autoinflammatory Syndrome (FCAS) is the mildest form of these 3 conditions. Cold exposure triggers a urticarial rash and fever. Conjunctivitis, arthralgia, fatigue, myalgia, and headaches are also common symptoms. Secondary amyloidosis is uncommon, unlike the other types of CAPS (6).

Muckle-Wells Syndrome

Muckle-Wells syndrome (MWS) is a more severe type of CAPS. Progressive sensorineural hearing loss and renal failure due to amyloidosis are serious complications of MWS (6).

Chronic Infantile Neurological Cutaneous and Articular Disease or Neonatal Onset Multisystemic Inflammatory Disease

Chronic infantile neurological cutaneous and articular/neonatal onset multisystemic inflammatory disease (CINCA/NOMID) is the most severe form of CAPS. The urticarial rash starts just after birth. Apart from severe inflammatory symptoms, dysmorphic features, skeletal problems, central nervous system findings and eye involvement can also be seen (4).

As in many single gene disorders, identical mutations in NLRP3 can lead to different phenotypes (FCAS, MWS and CINCA/NOMID) in CAPS. It is known that single gene disorders caused by the same mutation in the same gene can be affected by background modifiers (7). Since the main pathogenic mechanism underlying CAPS is an overproduction of IL-1β, and the *IL-1β* gene contains several single nucleotide polymorphisms, we hypothesized that if an individual with a specific IL-1β polymorphism is producing more IL-1β than others, he/she might have a more severe CAPS phenotype.

IL-1β polymorphisms have been investigated previously in other conditions and one of the polymorphisms, C-511T, which is located in the promoter region of the *IL-1β* gene, has been associated with increased IL-1β production in T/T state (8-10). Thus, we decided to investigate whether there is a role of IL-1β C-511T polymorphism in modifying disease severity.

Materials and Methods

The study was approved by the Local Research Ethics Committee University of Health Sciences, İzmir Tepecik Training and Research Hospital (approval number: 2018/14-12, date: 22.11.2018). Written informed consent was obtained from the patients or the parents of the patients and members of the healthy control group.

Thirty-six NLRP3 Exon 3 variant-positive patients whom we had previously reported in molecular genetic evaluation of periodic fever syndromes and 30 healthy controls were selected for the IL-1β genotype investigation.

To investigate whether there is a role of IL-1β C-511T polymorphism in modifying disease severity, the patients with an NLRP3 variant were classified:

The patients with the p.Val198Met mutation (13 patients) were classified as either FCAS (7 patients) or MWS (6 patients).

The patients with the p.Gln703Lys variant (21 patients) were classified as either asymptomatic (8 patients) or symptomatic (13 patients).

For the investigation of the role of the IL-1β genotype, C-511T polymorphism was analyzed. For the analysis of IL-1β -511 allele, the SNP rs1143634 was genotyped using the TaqMan 5'-exonuclease allelic discrimination assay. Allele-specific fluorescence was measured with a real-time PCR system.

Results

The heterozygous T/C genotype of IL-1β was the most common genotype both in patients with the NLRP3 variants and the healthy control groups. The homozygous C/C was the second most common genotype in both groups.

When evaluated in terms of allele frequency, the C allele was the most common allele both in patients with the NLRP3 variants and the healthy control group.

As for the analysis of those patients with the p.Val198Met mutation, genotype frequencies of IL-1β C-511T showed that T/T allele was unexpectedly higher in those patients with FCAS (less severe phenotype) compared to those with MWS (severe phenotype) and the healthy control group (28.6% vs 0% and 20%).

In those patients with the p.Gln703Lys variant, IL-1β-511, T/T allele was again unexpectedly higher in the asymptomatic patients compared to the symptomatic group (12.5% vs 0%).

The genotypes and allele frequencies of IL-1β C-511T in those patients with the NLRP3 variants and the healthy control samples are shown in Table I.

The comparison of genotypes according to clinical severity is summarized in Table II.

Discussion

The main pathogenic mechanism underlying CAPS is an overproduction of IL-1β. The gain of function mutations in the NACHT domain of the NLRP3 protein leads to the overproduction of IL-1β by the activation of inflammasome and this causes fever, recurrent exaggerated systemic inflammatory response and the other systemic features of CAPS (6). In CAPS, although there is a clinical classification, a lack of correlation exists between genotype and phenotype.

It is well known that the same variants can lead to different phenotypes and this association can be explained by variable penetrance and expressivity. Researches have shown that variable phenotypes can be caused by a number of factors, such as modifier genes, environmental factors, allelic variations and complex genetic and environmental interactions (11). Modifier genes can affect transcription, change gene expressions and they are also capable of altering the effects of mutations (7).

In CAPS, the effects of background genetic factors such as other PFS-related genes (MEFV, TNFRSF1A and MVK) are possibly leading to these variable phenotypes. This suggestion was supported by several recent studies that have reported the coexistence of *MEFV* and *NLRP3*, *TNFRSF1A* or *MVK* gene variants that caused synergistic effects (12,13). This selection of patients with mutations in multiple autoinflammatory genes show presentations which are challenging to delineate, such as atypical phenotypes (13).

One of the other possible explanations for variable and unexpected phenotypes in CAPS may be due to somatic mosaicism. Several studies have identified NLRP3 somatic mosaic mutations in children with CINCA/NOMID and MWS (14). Those patients with somatic mutations are probably missed by Sanger sequencing and will only be detected by the use of new technologies (14). Rowczenio et al. (15) suggested that when a mutation occurs in early embryonic life, it will cause mosaicism affecting more cells of the body. These data suggest that the emergence time and the level of mosaicism is associated with different phenotypes or different severity levels.

As a new candidate for these modifier genetic factors, we have constructed a hypothesis stating that since the main pathogenic mechanism is the overproduction of IL-1β and if an individual with a specific IL-1β polymorphism is producing more IL-1β than others, he/she might have a more severe CAPS phenotype. One of the IL-1β polymorphisms, C-511T, which is located in the promoter region of the *IL-1β* gene, has been associated with increased IL-1β production in T/T state (8,10).

In our previously studied patient group, the same p.Val198Met mutation was causing FCAS (less severe) and MWS (more severe) phenotypes in different patients, and the same p.Gln703Lys variant was leading to asymptomatic and symptomatic patients (16). Thus, we have compared the IL-1β-511 genotype within the p.Val198Met and the p.Gln703Lys groups and also compared them with the healthy controls. As a result, Neither the MWS patients (more severe phenotype) with p.Val198Met mutation nor

Table I. Interlekuin-1 beta-511 genotype and allele frequencies of patients and controls

IL-1β	**Patients with NLRP3 variants (36)**					**Healthy controls (30)**
-	**Genotype frequency**					**Genotype frequency**
-	Total (36)	p.Q703K (21)	p.V198M (13)	p.R327Q (1)	p.K510N (1)	Total (30)
T/T	3 (8.3 %)	1	2	0	0	6 (20 %)
T/C	17 (47.3 %)	10	6	0	1	16 (53.3 %)
C/C	16 (44.4 %)	10	5	1	0	8 (26.7 %)
-	-	-	-	-	-	-
-	**Allele frequency**					**Allele Frequency**
-	Total (72)	-	-	-	-	Total (60)
T	23 (31.9 %)	-	-	-	-	28 (46.7 %)
C	49 (68.1 %)	-	-	-	-	32 (53.3 %)

IL-1β: Interlekuin-1 beta

Table II. Interlekuin-1 beta-511 genotype and allele frequencies according to clinical severity			
IL-1β	**Patients with p.V198M Mutation (13 Patients)**		**Healthy controls (30 Samples)**
	Familial cold autoinflammatory syndrome (7 Patients)	**Muckle-Wells Syndrome (6 patients)**	**-**
-	Genotype frequency	-	**Total (30)**
T/T	2 (28.6%)	0 (0%)	6 (20%)
T/C	3 (42.8%)	3 (50%)	16 (53.3%)
C/C	2 (28.6%)	3 (50%)	8 (26.7%)
-	Allele frequency	-	Total (60)
T	7 (50%)	3 (25%)	28 (46.7%)
C	7 (50%)	9 (75%)	32 (53.3%)
IL-1β	Patients with p.Q703K Variant (21 Patients)		Healthy Controls (30 Samples)
-	Asymptomatic (8 Patients)	Symptomatic (13 Patients)	-
-	Genotype Frequency	-	Total (30)
T/T	1 (12.5%)	0 (0%)	6 (20%)
T/C	3 (37.5%)	7 (53.8%)	16 (53.3%)
C/C	4 (50%)	6 (46.2%)	8 (26.7%)
-	Allele Frequency	-	Total (60)
T	5 (31.3%)	7 (26.9%)	28 (46.7%)
C	11 (68.7%)	19 (73.1%)	32 (53.3%)

IL-1β: Interlekuin-1 beta

symptomatic patients with the p.Gln703Lys variant showed an increased IL-1β-511 T/T genotype frequency over the less severe phenotype groups and the healthy controls. Furthermore, IL-1β-511 T/T genotype frequency in MWS patients with p.Val198Met mutation and symptomatic patients with the p.Gln703Lys variant was 0%.

Conclusion

In this study, we couldn't confirm our hypothesis and we suggest that IL-1β-511 T/T polymorphism is not a modifying factor regarding the clinical severity of CAPS patients. The failure of our hypothesis may be due to the small sample size and improper selection of the genetic modifier. We suggest that, to expand this theory and in order to find additional mechanisms, other modifying genetic factors such as other polymorphisms of IL-1β or other polymorphisms of the genes in the inflammasome pathway (caspase-1, ASC, etc.) should be analyzed.

Additionally, to obtain a full clinical interpretation, it is necessary to consider the possibility of somatic mosaicism and polygenic inheritance in molecular genetic evaluation by using next generation techniques.

Ethics

Ethics Committee Approval: The study was approved by the Local Research Ethics Committee University of Health Sciences, İzmir Tepecik Training and Research Hospital (approval number:2018/14-12, date: 22.11.2018).

Informed Consent: Written informed consent was obtained from the patients or the parents of the patients and members of the healthy control group.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: B.Ö., T.R.Ö., Concept: B.Ö., T.R.Ö., Design: B.Ö., T.R.Ö., Data Collection or Processing: B.Ö., T.R.Ö., Analysis or Interpretation: B.Ö., T.R.Ö., Literature Search: B.Ö., T.R.Ö., Writing: B.Ö., T.R.Ö.

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Case Report

Cerebral Involvement of Hemophagocytic Lymphohistiocytosis in Griscelli Syndrome

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ABSTRACT

Type II Griscelli Syndrome (GS) is caused by a mutation in the *RAB27A* gene and usually manifests with silvery-gray hair, immune deficiency and the development of hemophagocytic lymphohistiocytosis (HLH). A hematopoietic stem cell transplantation is the curative treatment for HLH and reduced-intensity conditioning prevents the morbidity/mortality in the transplantation related to myeloablative conditioning. We report on a 21-month old boy with cerebral involvement of HLH related to GS.

Keywords: Griscelli Syndrome, hemophagocytic lymphohistiocytosis, hematopoietic stem cell transplantation

Introduction

Griscelli Syndrome (GS), which is a rare autosomal recessive disease which is characterized by cellular immune deficiency and partial albinism, was first described in 1978. Clinical manifestations of GS are silvery-gray hair, abnormal regulation of immunity and different degrees of cyto- and pancytopenia (1). GS is classified into three different subtypes regarding its clinical and molecular features. Type II GS is caused by a mutation in the *RAB27A* gene and usually manifests with silvery-gray hair, recurrent infections due to immune deficiency and development of hemophagocytic lymphohistiocytosis (HLH) (1,2). HLH related to uncontrolled hemophagocytosis and fever, severe cytopenia, hepatosplenomegaly, skin rash, jaundice, hyponatremia, hypoalbuminemia and hyperferritinemia are well-known clinical manifestations of the disease. Also, the central nervous system (CNS) is involved in patients with HLH with an incidence of more than 33% to 75% (3). Hematopoietic stem cell transplantation (HSCT) is the curative treatment for primary HLH like GS, with or without CNS involvement. Recently, reduced-intensity conditioning (RIC), which possesses risks like primary graft failure and the loss of chimerism, has been reported to reduce the high mortality in transplantation compared to the myeloablative conditioning regimens (4). In this case report, we evaluated a 21-month old boy with cerebellar involvement of HLH related to GS. He was treated with allogeneic HSCT, RIC and donor lymphocyte infusion (DLI) for a mixed chimera.

Case Report

A 21-month old boy was admitted to the emergency unit for 3 days due to fever. A viral upper respiratory tract system infection was suspected. However, physical examination revealed silvery-gray hair, eyebrows and

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eyelashes. At first sight, his silvery-gray hair attracted our attention and a microscopic evaluation of the hair shaft showed typical large irregular melanin granules instead of small homogeneous pigment granules as in normal hair. His parents were consanguineous and there was no evidence of similar conditions in his family history. The family was informed about GS and a blood sample was sent to a laboratory for the identification of a mutation of the *RAB27A* gene. The immunoglobulin (Ig) levels were checked and the IgG level was 452 mg/dL (normal range: 300-1240 mg/dL), the IgM level was 67 mg/dL (normal range: 45-200) and the IgA level was 28 mg/dL (normal range: 18-150 mg/dL). Lymphocyte profiling was normal according to a pediatric immunology consultant. Approximately one month later, the patient was admitted again to the clinic for 5 days suffering from fever. Physical examination showed pallor, tachycardia due to the fever and hepatosplenomegaly (the liver was palpable 2 cm below the right costal margin and the spleen was palpable 3 cm below the left costal margin). Laboratory data revealed bicytopenia (anemia and neutropenia) and hyperferritinemia. Hemophagocytosis was detected in the bone marrow smear. In light of all these findings, the patient was diagnosed with HLH. As a mutation in the *RAB27A* gene was detected [homozygous mutation for p.L26P (c.77T>C)], the final diagnosis of the patient was confirmed as GS Type II. In line with the Treatment Protocol of HLH 2004, a combination therapy with dexamethasone, cyclosporine A (CsA) and etoposide was administered. Donor screening was concomitantly started to find a matched donor for HSCT. Intrathecal treatment was not considered as there were no neurologic findings in the physical examination. No pleocytosis or no abnormal protein level in cerebrospinal fluid (CSF) were observed. After the patient entered remission at the end of the induction therapy, maintenance therapy was initiated. The patient developed irritability, hypotonia and fever at the 16th month of treatment, while he was being treated with CsA and waiting for a matched unrelated donor (MUD). CSF examination revealed abnormal findings like pleocytosis and elevated protein. The cranial magnetic resonance imagination (MRI) showed cerebral involvement of HLH. The MRI demonstrated periventricular localized profound hyperintense nodules and subcortical diffuse hyperintense areas in the temporal and frontal lobes (Figure 1). Treatment was restarted according to the first-line therapy principles of the HLH-2004 protocol. The patient underwent allogeneic HSCT obtained from a MUD at the 9th month of the reactivation of HLH, while the disease was not in the active phase, and was successfully engrafted after 22 days. The RIC regimen consisted of 0.2 mg/kg alemtuzumab for 5 consecutive days (days -12 to -8), fludarabine 30 mg/m^2 for 5 consecutive days (days -8 to -4), melphalan 140 mg/m^2 for 1 day (day -3). CsA and methylprednisolone 1 mg/kg/day were administered for prophylaxis against Graft versus Host Disease. At the eighth month, due to the presence of mixed chimerism (30% donor chimerism), DLI was performed to prevent graft failure while the patient was in remission. He has been in remission for over 12 months after HSCT. At the ninth month, cranial MRI was almost normal without any finding of CNS involvement for 21 months with mixed

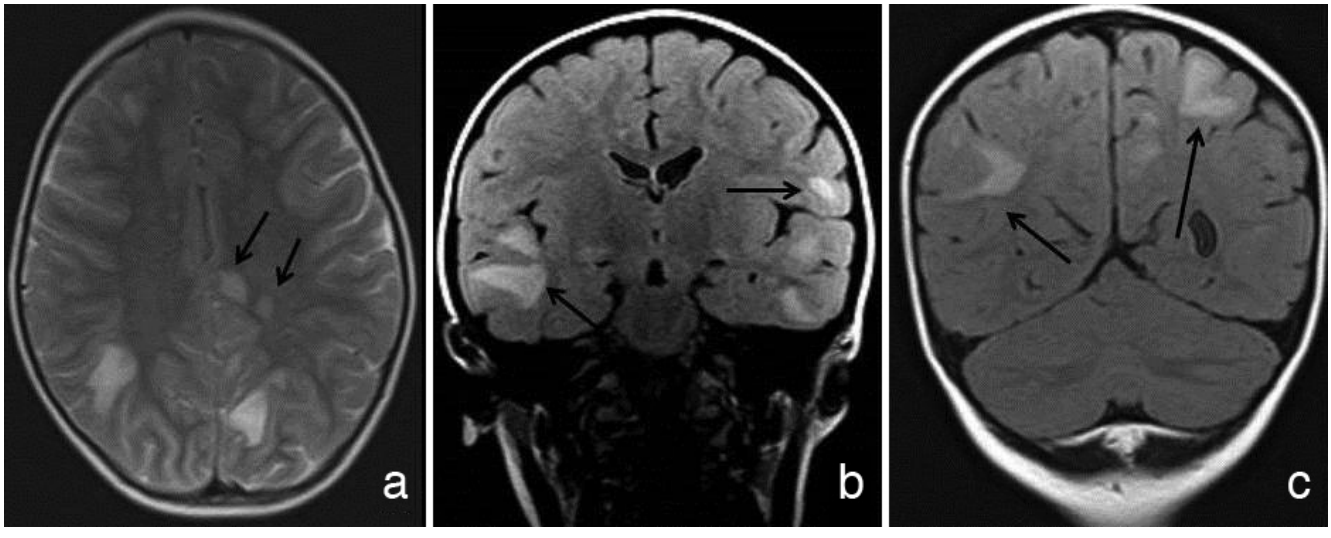

Figure 1. a) T2-weighted axial image shows periventricular profound-localized hyperintense nodules, (b,c) coronal FLAIR images demonstrate subcortical diffuse hyperintense areas in bilateral temporal and frontal lobes

chimerism. There was evident regression in hyperintense nodules and complete disappearance of subcortical diffuse hyperintense areas in MRI. The general neurological and mental development was summarized as his speech and motor functions were delayed but his emotional and cognitive abilities were similar to his peers. Informed consent was received from family.

Discussion

GS is a rare hereditary disease although the frequency is relatively higher in some ethnic groups with a high incidence of consanguineous marriages. HLH is a troublesome condition that involves the *RAB27A* gene mutation associated with the Type II GS. CNS involvement of HLH is a variable condition that can be detected at any time during the follow-up of the disease and shows heterogeneous characteristics regarding the clinical presentation, ranging from irritability, headache, convulsions, ataxia, central nerve palsies and from stupor to coma. Involvement of CNS can be detected via CSF examination and neuroradiological examination. Abnormal findings of CSF are elevated leukocyte cell count (pleocytosis) and/or protein levels. There is a correlation between the neuroradiological findings and histopathological stages of CNS involvement of HLH as previously reported. Considering the stages; stage 1 is defined as a mild and common presentation with leptomeningeal inflammatory infiltrates, stage 2 involves perivascular infiltration and stage 3 is characterized by massive tissue infiltration-necrosis and vascular destruction. The neuroimaging of the CNS involvement in HLH includes focal or diffuse abnormalities like periventricular hyperintensity in T2 images, expanded perivascular areas, white-gray matter changes and parenchymal atrophy without any specific features (5,6). In our case, we observed periventricular hyperintense nodules and subcortical diffuse hyperintensity. Although these findings are not specific for CNS involvement in HLH, certain concomitant findings supported the diagnosis.

HSCT is a unique way to cure patients with primary HLH like GS Type II. In the literature, there are few cohort studies and case reports which described allogeneic HSCT for GS Type II (7-9). Pachlopnik Schmid et al. (9) reported that 7 of 10 patients with HLH had CNS involvement before HSCT and 5 of them had irreversibly suffered from a neurological deficit. The overall survival rate of these 10 patients was 70%. In another study, 7 of 11 patients with HLH had CNS involvement before HSCT. The overall survival of these patients with GS Type II who underwent allogeneic HSCT was more than 75%. Unfortunately, 4 of the 7 patients with CNS involvement had a neurological deficit such as developmental delay or speech abnormality (10). As Al-Ahmari et al. (10) emphasized, HSCT could be a good choice for the treatment of the disease and to prevent neurological complications when performed before the emergence of HLH. In our case, abnormal findings in CSF and neurological examination have resolved after HSCT.

Conclusion

Only a few cases with cerebral involvement of HLH related to GS Type II who were treated with allogeneic HSCT have been published. In our case, HSCT was performed with non-myeloablative conditioning. Eighteen months after HSCT was performed, the patient was in remission and had no neurological findings in spite of mixed chimerism. RIC prevented the morbidity/mortality in the transplantation related to the myeloablative conditioning and mixed chimerism would be sufficient for the prevention of the disease activation. DLI is an effective method for preventing graft failure.

Ethics

Informed Consent: Informed consent was received from family.

Peer-review: Externally peer-reviewed.

Authotship Contributions

Surgical and Medical Practices: E.T., Y.A., S.A., T.H.K., Y.O., Design: E.T., Y.A., Data collection or Processing: E.T., Y.A., Analyses or Interpretration: Y.A., S.A., Literature Search: E.T., Y.A., Writing: E.T.

Conflict of Interest: No conflict of interest was declared by the authors.

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Case Report

A Newborn with Giant Cell Tumor of the Occipital Bone: Case Report

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ABSTRACT

Giant cell tumors of bone (GCTB) are commonly benign neoplasms and characterized by regional progressive and destructive lesions. They have a malignant potential and the capacity to metastasis. Incidents of GCTB are reported in 20% of all benign and 5% of all malignant bone tumors and pediatric cases account for less than 5% of all them. The first line treatment strategy for GCTBs is surgical resection. A male baby presented at our hospital on his 10th day of life suffering from respiratory distress and persistent vomiting. His blood and urine panels were within normal parameters. CMRI was performed to evaluate his condition. The CMRI report noted a "suspected 4x3 cm contrasted bone-derived malignant-looking mass at the left posterior fossa of the cranium". The biopsy confirmed: "A grade 1-2 giant cell tumor of bone". Surgical resection was not possible because of the location of the mass and its proximity to blood vessels but chemotherapy was the one strategy available in this particular case. The chemotherapy regimen consisted of cisplatin 1 mg/kg/day (1-3 days) and doxorubicin 1 mg/kg/day (1,2 days) and was applied four times every month. Using CMRI, we noted a reduction in mass of more than 50% after two sessions and complete regression after four sessions. The patient was given regular follow-ups with no evidence of recurrence and co-morbidity were observed over the next 60 months. We recommend chemotherapy as a successful alternative strategy when surgical resection, radiotherapy, and other therapies are not applicable for GCTBs.

Keywords: Giant cell tumor of bone, newborn, chemotherapy

Introduction

Giant cell tumor of bone (GCTB) are generally localized at the epiphysis of long bones and are characterized by regional progressive and destructive lesions. GCTs of bone are commonly benign neoplasms but they have malignant potential and the capacity to metastasis (1,2). The first line treatment strategy for GCTBs is surgical resection and other alternatives are localized radiotherapy or chemotherapy. The mainstay molecular pathology of GCTB has been discovered recently in that GCTB overexpress receptors activator of nuclear factor-kappa B (RANK) and its ligand (RANKL) in stromal cells. This interaction causes bone resorption due to the activation of osteoclasts. Denosumab, a monoclonal humanized antibody to RANKL, block RANK-RANKL interaction, has been reported as curative in some patients over 12 years old (3). A newborn presented with GCT of the occipital bone and was treated with chemotherapy and we concluded that chemotherapy is a successful alternative strategy when surgical resection, radiotherapy, and other therapies are not applicable for GCTBs.

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Case Report

A male baby weighing 3.6 kg at birth and delivered via C-section at the 39th week of pregnancy presented at our hospital on his 10th day of life suffering from persistent vomiting. Cranial magnetic resonance imaging (CMRI) was performed to evaluate his condition and a "suspected 4x3 cm bone-derived malignant-looking mass at the left posterior fossa" was noted (Figure 1). Surgical resection was not possible because of the location of the mass, especially its proximity to major blood vessels. The biopsy showed spindle cells with pleomorphic cells and a variable proliferation index with some areas as high as 20% as demonstrated by Ki-67 staining. Given this information, the presence of giant cell areas and spindle cell areas containing necrosis indicated a grade 1-2 GCT according to the classification by Jaffe et al. (4). Metastasis was not observed in computed tomography of the thorax. Loss of hearing in the left ear was determined via brainstem auditory evoked potential (BAEP) and was probably due to the mass. The patient was not suitable for surgery or radiotherapy, but chemotherapy was the one strategy available in this particular case. The chemotherapy regimen consisted of cisplatin 1 mg/kg/day (1-3 days) and doxorubicin 1 mg/kg/day (1,2 days) and was applied four times monthly. Using MRI, we noted complete regression after four sessions. The patient was given regular follow-ups with no evidence of recurrence or co-morbidity over the next 60 months. The CMRI showed no residual mass at posterior fossa at the 60th month after chemotherapy (Figure 2 a,b,c,d). Bilateral BAEP has proven normal as has his general neurological and mental development during this time with his motor functions and speech as well as his emotional and cognitive abilities testing appropriate to his age. Informed consent was received from family.

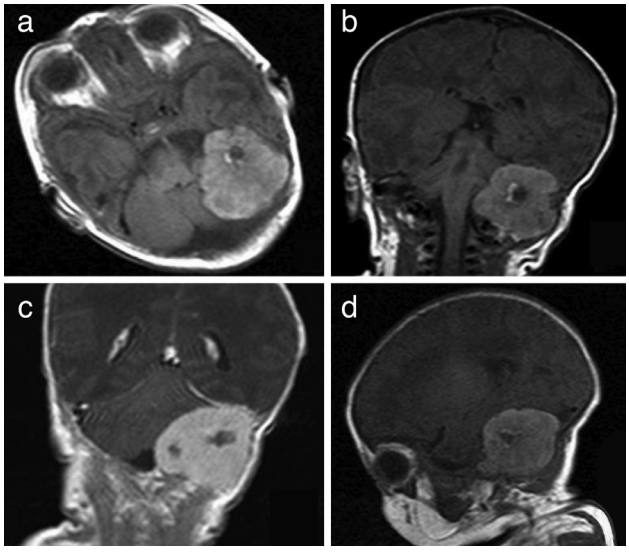

Figure 1. (a,b,c,d) Pretreatment magnetic resonance imaging revealing a mass lesion at the left posterior fossa of cranium

Discussion

Pain is the leading symptom when GCTB is localized in the long bones but neurologic symptoms or failures are revealed when GCTB is present in the skull. Unfortunately, various benign or malignant tumors may be confused with GCTB (3). Histological examination of GCTB shows a heterogeneous tumor occurring in stromal cells and multinucleated giant cells with over-expressed RANK and RANKL (2,4). The preferred treatment of GCTB is resection with surgery or extended intralesional curettage, but this is not always suitable given the location and size of the tumor. Radiotherapy has been used as a treatment option in combination with surgery or chemotherapy for GCTBs, but this carries the risk of malignant transformation, local recurrence and some side effects (1,2).

Table I lists the pediatric cases of GCTB in the skull reported in the literature since 2000. They are mostly adolescents with base of the skull treated with surgical intervention, radiation or embolization (5-10). Our case was one of the youngest patients described in the literature. Treatment is determined by location and age. The location of the mass and patient's age prohibited us from performing wide resection, radiotherapy or using denosumab in this case. Conventional chemotherapy was used following an

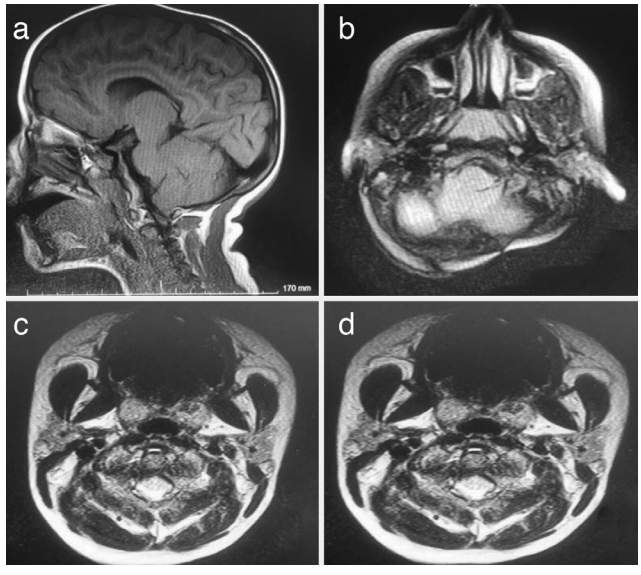

Figure 2. (a,b,c,d) Magnetic resonance imaging shows any residual mass lesion at the left posterior fossa of cranium after 5 years of chemotherapy.

Table I. Pediatric cases of giant cell tumor of bone at skull in literature

Case No	Reference	Age/Gender	Location	Treatment	Outcome
1	Sharma et al. (6)	17 years/male	Sphenoethmoidal	Partial resection and radiotherapy	Two years follow-up with no recurrence
2	Sharma et al. (6)	12 years/female	Petroclival	Close to all resection	After 1 year locale recurrence
3	Bibas-Bonet et al. (7)	8 years/female	Temporopetroidal	Radiotherapy	Eight years follow-up with neurologic sechel and no recurrence
4	Elder et al. (5)	2 years/female	External auditory canal	Embolization and resection	Thirteen months follow-up with no recurrence
5	Elder et al. (5)	7 weeks/female	External auditory canal	Close to all resection	Eleven months follow-up with no recurrence
6	Gupta et al. (8)	17 years/female	Sphenoid bone	Resection and radiotherapy	Two years follow-up with no recurrence
7	Karamanakos et al. (9)	5 weeks/female	Temporal bone	Partial resection	Died after 4 weeks
8	Inoue et al. (10)	16 years/male	Sphenoid bone	Close to all resection and denosumab	Ten months with monthly denosumab treatment and no recurrence

informed consensus between the physician and the infant's family. The patient has had no recurrence or co-morbidity, nor was any toxicity as a result of chemotherapy detected over five years of follow-up.

Although the pathology prognosis in our case was not completely compatible with malignant (grade 3) GCTB according to the classification by Jaffe et al. (4) the chemotherapy response has led us to believe that that the mass would have become malignant. We recommend chemotherapy as a successful option for treating GCTB if other strategies are not possible or suitable.

Ethics

Informed Consent: Informed consent was received from family.

Peer-review: Externally and internally peer-reviewed.

Authotship Contributions

Surgical and Medical Practices: E.T., B.D., Ş.Ç., T.T., B.D., Design: E.T., B.D., Data collection or Processing: E.T., B.D., Analyses or Interpretration: E.T., B.D., Literature Search: E.T., B.D., Writing: E.T., B.D.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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- All persons who have made substantial contributions to the work reported in this manuscript (e.g., technical assistance, writing or editing assistance, data collection, analysis) but who do not fulfill authorship criteria are

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İlk adımdan ilk başarılara

BEXSERO, MenB* aşılamasında 2. aydan itibaren endike olan tek aşıdır.[1,2]

BEXSERO
Meningokok Grup B Aşısı
(rekombinant, adsorbe)

Dünya genelinde **30 milyondan fazla doz** dağıtılmıştır.[3]

Dünya genelinde **41'den fazla ülkede** ruhsatlıdır.[4]

BEXSERO: Geniş bir popülasyonda koruma sağlamaya yardımcı olur[1]

Geniş yaş aralığı

BEXSERO,
2. aydan itibaren kullanılabilir.[1]

Geniş kapsayıcılık

BEXSERO,
4 farklı antijeni hedefler: fHbp, NadA, PorA ve NHBA[1,5-8]

Gerçek dünya deneyimi

BEXSERO,
ulusal bağışıklama programlarında bebekler için kullanılmaktadır.[9-11]

Esnek doz seçenekleri

BEXSERO,
rutin aşılama ziyaretlerine uygun çeşitli program seçenekleri sunar.[1]

*Meningokokal hastalık, serogrup B.

Referanslar: 1. BEXSERO KÜB, Eylül 2018. **2.** Pfizer Ltd. Trumenba, European publc assessment report, Annex I: Summary of product characterstcs. EMA; June 2017. Avalable from: <http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Informaton/human/004051/WC500228995.pdf>. Accessed June 2017. **3.** Data on file;2017N320400_04;1-2 **4.** DOF 2016N297580_01 Bexsero countries commercialized-coversheet-18Jul2018. **5.** Biagini M, Spinsanti M, De Angelis G, et al. Expression of factor H binding protein in meningococcal strains can vary at least 15-fold and is genetically determined. Proc Natl Acad Sci USA. 2016;113:2714-2719. **6.** Livorsi DJ, Stenehjem E, Stephens DS. Virulence factors of gram-negative bacteria in sepsis with a focus on Neisseria meningitidis. Contrib Microbiol. 2011; 17:31–47. **7.** Hao W, Ma JH, Warren K, et al. Extensive genomic variation within clonal complexes of Neisseria meningitidis. Genome Biol Evol. 2011;3:1406–1418. **8.** Vogel U, Taha M-K, Vasquez JA, et al. Predicted strain coverage of a meningococcal multicomponent vaccine (4CMenB) in Europe: a qualitative and quantitative assessment. Lancet Infect Dis. 2013;13:416-425. **9.** Meningococcal B. National Immunisation Office website. http://hse.ie/eng/health/immunisation/hcpinfo/OtherVaccines/meningococcalb/. Accessed April 3, 2017. **10.** Piano Nazionale Prevenzione Vaccinale PNPV 2017-2019. Ministero della salute website. http://www.salute.gov.it/imgs/C_17_pubblicazioni_2571_allegato.pdf. Accessed April 3, 2017. **11.** Guidance: Meningococcal B vaccine: JCVI position statement. Gov.UK website. https://www gov.uk/government/publications/meningococcal-b-vaccine-jcvi-position-statement. Accessed February 13, 2017.

BEXSERO Kısa Ürün Bilgisi
BEXSERO 0.5 mL IM Enjeksiyonluk Süspansiyon İçeren Kullanıma Hazır Enjektör Çok bileşenli Meningokok grup B Aşısı (rekombinant, adsorbe) **Etkin maddeler:** Bir doz (0.5 mL) şu etkin maddeleri içerir: Rekombinant Neisseria meningitidis grup B NHBA füzyon proteini 50 mikrogram, rekombinant Neisseria meningitidis grup B NadA proteini 50 mikrogram, rekombinant Neisseria meningitidis grup B fHbp füzyon proteini 50 mikrogram, PorA P1.4 içeren toplam protein miktarı olarak ölçülen Neisseria meningitidis grup B suşu NZ98/254'ten dış membran vezikülleri (OMV) 25 mikrogram. **Yardımcı maddeler:** Sodyum klorür, histidin, sükroz, enjeksiyonluk su, alüminyum hidroksit. **Farmasötik form:** Enjeksiyonluk süspansiyon içeren kullanıma hazır enjektör. Beyaz, opak sıvı süspansiyon. **Terapötik endikasyonlar:** BEXSERO, 2 ay ve üzeri yaştaki kişilerin, Neisseria meningitidis grup B'nin neden olduğu invazif meningokok hastalığına karşı aktif bağışıklanması için endikedir. İnvazif hastalığın farklı yaş gruplarındaki etkisi ile birlikte grup B suşlarının farklı coğrafi bölgelerdeki antijen çeşitliliği de aşılama sırasında göz önünde bulundurulmalıdır. **Pozoloji ve uygulama şekli:** 2 ila 5 aylık bebekler için aşı programı: her biri 0.5 ml'lik üç primer doz (ilk doz 2 aylıkken verilir), primer dozlar arasındaki süre en az 1 ay olmalıdır ve 12 ay ile 23 ay arasında bir rapel doz uygulanır. 6 ila 11 aylık aşılanmamış bebekler için aşı programı: her biri 0.5 ml'lik iki primer doz, primer dozlar arasındaki süre en az 2 ay olmalıdır ve primer seri ile rapel doz arasında 2 aylık süre bırakılarak yaşamın 2. yılında bir rapel doz uygulanır. 12 ila 23 aylık aşılanmamış bebekler için aşı programı: her biri 0.5 ml'lik iki primer doz, primer dozlar arasındaki süre en az 2 ay olmalıdır ve primer seri ile rapel doz arasında 12-23 aylık süre bırakılarak bir rapel doz uygulanır. 2 ila 10 yaş çocuklar için aşı programı: her biri 0.5 ml'lik iki primer doz, primer dozlar arasındaki süre en az 2 ay olmalıdır ve rapel doz için gereklilik belirlenmemiştir. 2 ila 10 yaş çocuklar için aşı programı: her biri 0.5 ml'lik iki primer doz, primer dozlar arasındaki süre en az 2 ay olmalıdır ve rapel doz için gereklilik belirlenmemiştir. Adölesanlar (11 yaşından itibaren) ve erişkinler için aşı programı: her biri 0.5 ml'lik iki primer doz, primer dozlar arasındaki süre en az 1 ay olmalıdır ve rapel doz için gereklilik belirlenmemiştir (50 yaşın üzerindeki erişkinlerde veri mevcut değildir). **Uygulama şekli:** Aşı, tercihen bebeklerde uyluğun anterolateral bölgesine ve daha büyük hastalarda üst kolun deltoid kası bölgesine derin intramüsküler enjeksiyon şeklinde yapılmalıdır. **Kontrendikasyonlar:** Bu tıbbi ürün etkin maddeye ya da yardımcı maddelere karşı bilinen aşırı duyarlılığı olan kişiler kullanmamalıdır. **Özel kullanım uyarıları ve önlemleri:** BEXSERO uygulaması akut şiddetli ateşli hastalık geçiren kişilerde ertelenmelidir. Bununla birlikte, soğuk algınlığı gibi minör enfeksiyon varlığında aşılama ertelenmemelidir. İntravasküler yolla enjekte edilmemelidir. BEXSERO trombositopenisi ve kanama bozuklukları olan kişilere intramüsküler uygulama kontrendike olacağından uygulanmamalıdır. Bu kişilere ancak potansiyel yararın risklerden fazla olması durumunda uygulanabilir. BEXSERO'nun dolaşımdaki tüm meningokok grup B suşlarına karşı koruma sağlaması beklenemez. Birçok aşıda olduğu gibi, sağlık mesleği mensupları, bebekler ve çocukların (2 yaş altı) aşılanmasından sonra vücut sıcaklığında olabilecek yükselmelerin bilincinde olmalıdır. Aşılama zamanında ve aşılamadan kısa bir süre sonra profilaktik antipiretik uygulaması, aşılama sonrası febril reaksiyonların insidansını ve şiddetini azaltabilir. Antipiretik ilaçlara, bebekler ve çocuklara (2 yaş altı) yönelik yerel kılavuzlar doğrultusunda başlanmalıdır. BEXSERO'nun 50 yaş ve üzeri kişilerde kullanımına ilişkin veri bulunmamaktadır. Çok prematüre bebekler (gebeliğin 28. haftası ve öncesinde doğanlar) ve özellikle solunum sistemi gelişimi eksikliği hikayesi olanlarda primer bağışıklama serilerinin uygulanmasında potansiyel apne riskine karşı 48-72 saat solunum sisteminin izlenmesi gerekmektedir. Bu grup bebekte aşılamanın yararı yüksek olduğundan, aşılama alıkonmamalı ve ertelenmemelidir. Enjektörün uç kapağı doğal kauçuk lateks içerebilir. Latekse bağlı alerjik reaksiyon gelişme riski çok düşük olmakla birlikte, latekse karşı hipersensitivite öyküsü bilinmeyen kişilerde risk yarar oranı göz önünde bulundurulmalıdır. **Diğer tıbbi ürünler ile etkileşimler ve diğer etkileşim şekilleri:** BEXSERO, parantez içerisinde belirtilen aşı antijenlerinin herhangi birinin monovalan ya da kombinasyon şeklindeki aşıları ile (difteri, tetanoz, aselüler boğmaca, Haemophilus influenzae tip b, inaktif çocuk felci aşısı, hepatit B, 7-valanlı konjüge pnömokok, kızamık, kabakulak, kızamıkçık ve su çiçeği ve meningokok grup C-CRM konjuge aşısı) eşzamanlı olarak uygulanabilir. BEXSERO ile burada listelenen diğer aşıların eş zamanlı uygulanması sonrasında daha sık ortaya çıkan ateş, enjeksiyon yerinde hassasiyet, yeme alışkanlıklarında değişiklik ve iritasyon nedeniyle mümkün olduğu durumlarda aşılamaların farklı zamanlarda yapılması düşünülebilir. Profilaktik parasetamol kullanımı, BEXSERO ya da rutin aşılara immünojenisiteyi etkilemeksizin ateş insidansını ve şiddetini azaltır. Parasetamol dışında diğer antipiretiklerin immün yanıt üzerindeki etkisi çalışılmamıştır. **Gebelik ve laktasyon: Gebelik kategorisi: B. Gebelik dönemi:** Gebeliklerde maruz kalmaya ilişkin klinik veri mevcut değildir. Hayvanlar üzerinde yapılan çalışmalar, gebelik / embriyonal / fetal gelişim / doğum ya da doğum sonrası gelişim ile ilgili olarak doğrudan ya da dolaylı zararlı etkiler olduğunu göstermemektedir **Laktasyon dönemi:** Emzirme sırasında kadınlar ve çocuklarda aşının güvenilliği ile ilgili veri mevcut değildir. **İstenmeyen etkiler:** Yeme bozuklukları, uykulu olma, alışılmışın dışında ağlama, baş ağrısı, ishal, kusma, döküntü, artralji, ateş, irritabilite, enjeksiyon bölgesinde eritem, enjeksiyon bölgesinde şişlik, enjeksiyon bölgesinde sertlik, egzema, ürtiker, deri renginde solukluk, Kawasaki sendromu, hipotonik-hiporesponsif atak, nöbetler, alerjik reaksiyonlar. **Doz aşımı:** Doz aşımı deneyimi sınırlıdır. Doz aşımı durumunda tüm yaşamsal fonksiyonların izlemi ve olası semptomatik tedavi önerilmektedir. **Raf ömrü:** 36 ay. **Saklamaya yönelik özel tedbirler:** 2-8°C arası sıcaklıklarda (buzdolabında) saklayınız. Dondurmayınız. Işıktan koruyunuz. **Ambalajın niteliği ve içeriği:** Piston tıpa (Tip I bromobütil kauçuk) ve koruyucu uç kapaklı (Tip II kauçuk), iğneli veya iğnesiz kullanıma hazır dolu enjektör (Tip I cam) içinde 0.5 mL süspansiyon. **Ruhsat sahibi:** GlaxoSmithKline ilaçları Sanayi ve Ticaret A.Ş. Büyükdere Cad. No:173 1. Levent Plaza B Blok 34394, 1.Levent / İSTANBUL **Ruhsat numarası:** 2018/470. **Ruhsat tarihi:** 06.09.2018 **Fiyatı:** 19 Şubat 2019 itibari ile KDV dahil perakende satış fiyatı 403,92 TL. **Reçete ile satılır.** GSK ürünleri ile ilgili advers olayları GSK'ya doğrudan e-posta (ist_tr_safety@gsk.com) ve telefon aracılığı ile (444 54 75) veya T.C. Sağlık Bakanlığı, Türkiye İlaç ve Tıbbi Cihaz Kurumu, TÜFAM'a (Türkiye Farmakovijilans Merkezi: e-posta: tufam@titck.gov.tr; faks: 0312 218 35 99; tel: 0312 218 30 00) iletebilirsiniz. Daha geniş bilgi için firmamıza başvurunuz. GlaxoSmithKline İlaçları San. ve Tic. A.Ş. Büyükdere Cad. 1. Levent Plaza B Blok No: 173 1. Levent 34394 İSTANBUL Tel: 0212 339 44 00 www.gsk.com.tr. **KÜB özeti onay kodu:** PI-0234

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▼ Bu ilaç ek izlemeye tabidir. Bu üçgen yeni güvenlilik bilgisinin hızlı olarak belirlenmesini sağlayacaktır. Sağlık mesleği mensuplarının şüpheli advers reaksiyonlarını bildirmeleri beklenmektedir. Raporlama yapılması, ilacın yarar/risk dengesinin sürekli olarak izlenmesine olanak sağlamaktadır. Herhangi bir şüpheli advers reaksiyonu Türkiye Farmakovijilans Merkezi (TÜFAM)'ne (www.titck.gov.tr; e- posta: tufam@titck.gov.tr; tel: 0 800 314 00 08; faks: 0 312 218 35 99) ve/veya GSK Ürün Güvenliği Departmanı'na doğrudan e-posta (ist_tr_safety@gsk.com) ve telefon aracılığı ile (444 5 475) bildirmeniz gerekmektedir.

DAHA GENİŞ BİLGİ VE KISA ÜRÜN BİLGİSİ İÇİN FİRMAMIZA BAŞVURUNUZ.
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