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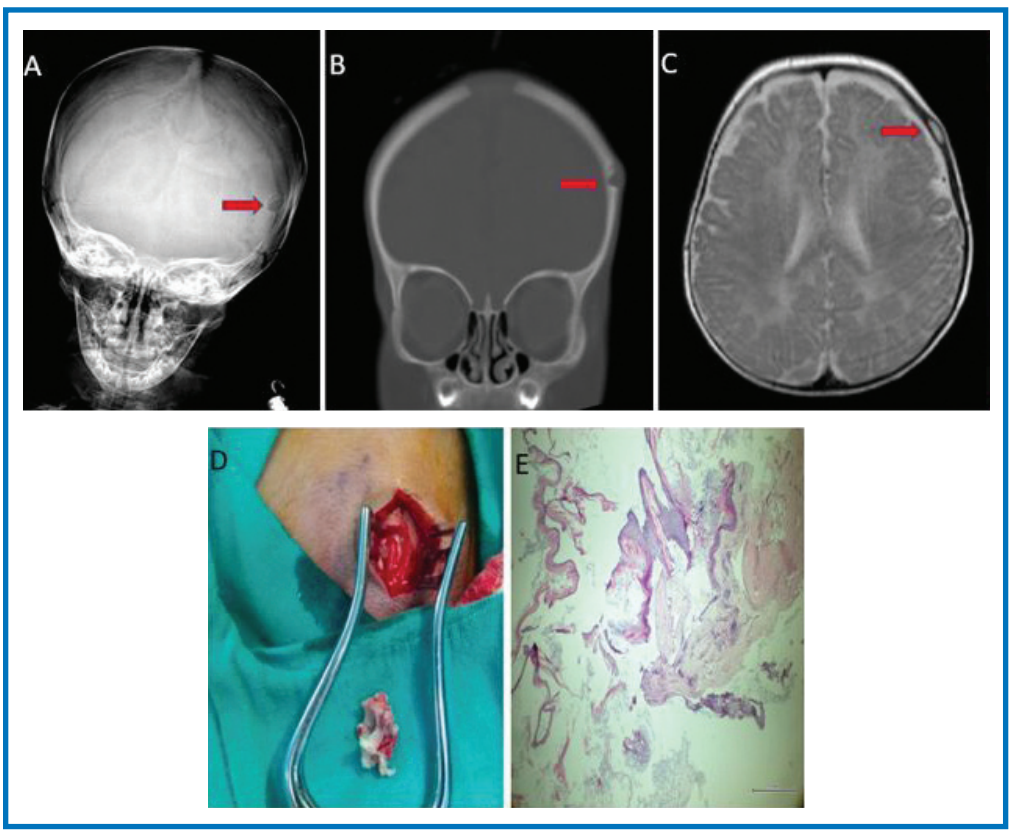

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Editorial

Dear readers,

We would like to express that we are very happy to publish the third issue of this year. The current issue includes three original articles, two case reports and a comprehensive review of infectious diseases and anesthesia in children.

I would like to thank all of authors and reviewers who have contributed to the success of our journal.

Sincerely,

Ahmet Anık
Editor-in-chief

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Review

Infectious Diseases and Anesthesia in Children

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ABSTRACT

Due to vaccination and better socioeconomic conditions, childhood infectious diseases have dramatically decreased in recent years. Respiratory tract infections (RTI) are common childhood infection diseases. Although most of the upper respiratory tract infections are usually self-limited and resolve within 7-10 days, some patients have persistent symptoms for more than 3-4 weeks. Presence of both respiratory comorbidities and recent RTI can be independent predictors for adverse events during anesthesia. A RTI can increase the risk of perioperative respiratory complications from 2-7 times, hence postponement of anesthesia for elective surgeries for several weeks is applied in daily practice. The complications are most frequent during an active respiratory infection, however, bronchial hyper-reactivity can persist for 6 weeks or more even after the disappearance of clinical symptoms. In general, signs of an active lower respiratory infection, and presence of a systemic illness should warrant canceling an elective procedure. Minimum 2 weeks, up to 6 weeks of interval is advised. The potential risks of RTIs during the perioperative period lead to the cancellation of elective procedures until at least being asymptomatic. This cancellation can have important social, economic, and emotional consequences for both the child, his/her family, and the medical team. In general, signs of an active lower respiratory infection, and presence of a systemic illness should warrant canceling an elective procedure.
A consensus guideline derived from multidisciplinary points of view can provide a detailed and valid algorithm for especially challenging cases. In addition, ongoing exclusive educational and training programs could aid the clinicians in their everyday practice.

INFECTIOUS DISEASES IN CHILDREN

Due to vaccination and better socioeconomic conditions, childhood infectious diseases have dramatically decreased in recent years.

Although infectious diseases in childhood are decreasing, children come across in different situations in anesthesia practice as.[1]

1. Recently vaccinated
2. Recently exposed to an infectious disease
3. Ill with an infectious disease

Respiratory tract infections (RTI) are common childhood infectious diseases. The highest incidence rates of acute respiratory infections (ARI) are during the first 2 years of life where on average infants experience six to eight ARIs each year.[2] Although most of the upper respiratory tract infections (URTIs) are usually self-limited and resolve within 7-10 days, some patients have persistent symptoms for more than 3-4 weeks. A variety of respiratory viruses, such as influenza, parainfluenza, rhinovirus, human bocavirus, and human metapneumovirus are responsible for RTIs. Their common feature is to invade the respiratory mucosa and result in airway inflammation, edema, and bronchoconstriction which sensitize the airway to secretions and volatile agents.[3] Viral infections also induce an increased acetylcholine secretion and consecutive bronchoconstriction due to the inhibition of host cholinergic M2 receptors.[2]

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Presence of both respiratory comorbidities and recent RTI can be independent predictors for adverse events during anesthesia.[4] Recently, a prospective observational multicentre cohort study of children from birth to 15 years of age undergoing elective or urgent anesthesia for diagnostic or surgical procedures (APRICOT study) was performed in 261 hospitals in Europe.[5] Among 31,127 anesthetic procedures in 30,874 children, the incidences of severe perioperative critical events was 5.2%, respiratory events was 3.1%, and cardiovascular events was 1.9%. A RTI can increase the risk of perioperative respiratory complications from 2-7 times,[6] hence postponement of anesthesia for elective surgeries for several weeks is applied in daily practice. The complications are most frequent during an active respiratory infection, however, bronchial hyper-reactivity can persist for 6 weeks or more even after the disappearance of clinical symptoms.[7] In this period, the airway becomes ëhyper-reactiveí resembling the pathophysiological mechanisms seen in those of asthma. Eventual bronchial changes can result in perioperative severe complications such as, functional obstruction of the upper (laryngospasm) and the lower airways (bronchospasm).[8] Laryngospasm incidence increases in children with RTI or any airway anomaly. Using a laryngeal mask can also be a contributor factor during general anesthesia.[9] Perioperative RTIs also contribute to the occurrence of oxygen desaturation and long-term cough in children.[10] Increase in dysphoria and sputum production and neurological developmental disorders and sequela secondary to hypoxia are additional complications in these children.[11,12]

Risk factors for perioperative complications in children with RTIs:

• *Symptoms and signs*: RTIs consist of variable distinct infections, including sinusitis, otitis media, pneumonia, and bronchiolitis, etc. Although nasal congestion, purulent secretions, moist cough, or detectable focus are well-known to be more risky, without an obvious focus, even a serous, clear nasal discharge can trigger perioperative adverse events.[10] In a recent study, it was shown that while patient height increases, airway resistance decreases and airway compliance decreases in patients undergoing adenotonsillectomy.[13] Rales detected during preoperative auscultation and sputum suction were also associated with intraoperative airway resistance and compliance in these children. Anesthesiologists generally accept fever, productive cough, wheezing, rales, and rhonchus as contraindications for cancellation of elective surgeries.[14] For prediction of perioperative adverse events, anesthesiologists and pediatricians declared to prefer to perform laboratory and radiological tests, such as hemogram, C-reactive protein, and chest radiograph.[14,15]

• *Underlying disorders*: Children with asthma have an elevated risk of perioperative respiratory adverse events due to elevated risks for bronchospasm and hypoxemia[16]. Prematurity is also a challenging disorder because general anesthesia brings a high risk of morbidity, in particular when the babies have intraventricular hemorrhage, patent ductus arteriosus, necrotizing enterocolitis, or bronchopulmonary dysplasia.[17] Cystic fibrosis is another disorder with potential risks, for which elective surgeries need optimization as much as possible. More intense daily physiotherapy and nebulized drugs will be appropriate. The risk of pulmonary complications will increase on the event that duration of surgery/anesthesia increases, or the surgical site is upper abdominal and thoracic regions, or nasogastric tube insertion is used.[18] Children with infection due to respiratory syncytial virus can suffer more frequently from morbidities when they are anesthetized.[19]

• *Age, Passive smoking:* Pulmonary complications due to a respiratory infection are inversely correlated with age. Children younger than 5 years have a significantly increased risk compared to the older children.[7] A recent study investigating the effect of recent URTI on the incidence of perioperative complications in children undergoing therapeutic cardiac catheterization revealed that small age, passive smoking, and presence of rhinorrhea or moist cough were the independent risk factors for perioperative respiratory adverse events in these children.[11]

• *Airway management*: Orotracheal intubation has an increased probability of complications when compared with laryngeal mask airway and facemask[6]. The risk of respiratory complications are 11 times more in children with endotracheal intubation when respiratory infectious symptoms

are present. It is better to use a mask airway instead of tracheal intubation to minimize the risk if appropriate.[6,20] Surgeries associated with upper airways result in an increased incidence of perioperative adverse events.[21]

• *Parental considerations*: If parents declare that their child has a 'cold' on the day of surgery and the child has snores, these can be assumed as predictors of anesthetic adverse events.[6]

• *Anesthetic agents*: Desflurane causes lesser episodes of laryngospasm than sevoflurane. Additionally, the emergence time and the quality of recovery are better with sevoflurane. Also, desfluraneís bronchoconstrictive effects should also be kept in mind.[22,23]

The duration for cancellation in elective surgeries

The potential risks of RTIs during the perioperative period lead to the cancellation of elective procedures until at least being asymptomatic. This cancellation can have important social, economic, and emotional consequences for both the child, his/her family, and the medical team. Re-planning and eventual disorganization in addition to delays in treatments of critical and cancer patients happen. Unfortunately, there is not any consensus guideline, but there are lots of studies and scoring systems to deal with these patients perioperative management.[2,12,24,25] In general, surgeons give the decision for elective surgeries together with anesthesiologists. New onset or ongoing RTI symptoms require pediatrician consultation.[26] There are no definitive rules for canceling a procedure when there is any RTI. From the point of some authorsí view, children with a mild URTI can be safely anesthetized because no big problems are encountered and they are easily treated without long-term sequelae.[27] In general, signs of an active lower respiratory infection, and the presence of a systemic illness should warrant canceling an elective procedure.[28] Minimum 2 weeks, up to 6 weeks of an interval is advised.

Strategies during the perioperative period

Generally, except for sufficient history and clinical examination, any additional investigation is not routinely advised in most children presenting with URTI. If any proven or probable underlying disorders, such as asthma or a bacterial infection are suspected, consultation from the specialist should be made to initiate appropriate investigations (respiratory function test, cultures, etc.) and treatments (bronchodilators, steroids, antibiotics, etc.).

• If the patients do not have any underlying respiratory disorders, such as allergy, corticosteroids and other adjunctive therapies result in inconsistent results.[29,30] Therefore, they should be used with caution.

• The least invasive method should be chosen. If it is sorted, the order is as facemask > laryngeal mask airway > endotracheal tube.[31] Additionally, uncuffed endotracheal tubes are superior to cuffed ones. Experienced anesthetists should do the airway control. Premature babies are among the special populations. Their cardiorespiratory systems are fragile and any intervention can aggravate cardiac and respiratory instability. Hence, they are sensitive to both respiratory infections and bronchospastic episodes.[17] Sedoanalgesia and avoidance of endotracheal intubation would be the most suitable anesthetic technique for them.

• In high-risk children, it is better to choose IV propofol rather than inhalational drugs during induction.[31] Intravenous anesthetic agents are superior when intraoperative laryngospasm is present. On the other hand, volatile anesthetic agents are more suitable for intraoperative bronchospasm. Sevoflurane has advantages over the other volatile anesthetic agents.

In our clinic, elective surgeries of children with preoperative upper respiratory tract infections are cancelled until 2 weeks after the symptoms are asymptomatic. In this process, a pediatric consultation is requested to receive appropriate treatment for the current infection. As a conclusion, a child with a RTI can also be safely anesthetized, only if the physician follows appropriate perioperative anesthesia evaluation and management approaches. A consensus guideline derived from multidisciplinary points of view can provide a detailed and valid algorithm for especially challenging cases. In addition, ongoing exclusive educational and training programs could aid the clinicians in their everyday practice.

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Original Article

Evaluation of Success Rate of Exogenous Obesity Management with an Intensive Follow-up Program

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ABSTRACT

Objective: *Obesity critically affects the quality and expectancy of life with its physiological, hormonal, metabolic, and social aspects. This study has assessed the success rate of exogenous obesity management consisting of lifestyle changes with an intensive follow-up in prepubertal children.*
Methods: *Twenty-two obese prepubertal children between ages 4 and 9 years were enrolled in this study. Eating habits were surveyed, and individually tailored diet programs were introduced. Additionally, an exercise coach prepared individualized exercise programs. Patients were recalled monthly for six months. At each monthly visit, weight, height, BMI, waist circumference, body fat percentages were measured, and compliance with the diet and exercise programs was reviewed. Wilcoxon signed-rank test was used for statistical analysis.*
Results: *The patients showed statistically significant reductions in BMI, waist circumference, and body fat percentage ($p<0.001$ for each).*
Conclusion: *This study demonstrates that in prepubertal obese children, lifestyle changes implemented by intensive follow-up and monitoring could increase the success rate of exogenous obesity management.*

INTRODUCTION

Obesity is well known to affect the quality and expectancy of life with its detrimental ramifications in physiological, psychological, hormonal, metabolic, and social dimensions. The incidence of obesity is globally increasing among both adults and the pediatric population.[1] Obesity is a multifactorial condition that arises from an imbalance between energy intake and energy consumption.[2] Obesity is described by the World Health Organization (WHO) as an increase in the amount of body fat to a level that impairs health.[3]

While there are many known and potential causes for childhood obesity, an underlying disorder cannot

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be identified in most cases. This form of obesity is called “simple” or “exogenous” obesity and is the most common cause of childhood obesity. When obesity is caused by endocrinological, genetic, or other conditions, it is called “secondary” or “endogenous” obesity. These factors affect the basic equation of “energy intake equals to energy usage,” and in exogenous obesity, energy intake exceeds energy usage.[6]

Several severe health issues are associated with childhood obesity. Most remarkably, more than half of the individuals who are obese in adolescence become obese adults if obesity is not seen as a severe condition to be treated by families or health care providers.[7] Moreover, increasing incidence of obesity has led to raised occurrences of chronic diseases typically seen in adults, such as Type 2 diabetes, metabolic syndrome, and hypertension in children.

Lifestyle modification is the only option in managing childhood obesity as neither bariatric surgery nor pharmacological interventions are recommended in children with obesity. Thus, we hypothesized that childhood obesity could be better managed with a closer clinical follow-up. In this study, we have observed a higher success rate in the management of exogenous obesity by an intensive follow-up after lifestyle interventions in prepubertal patients with exogenous obesity. However, this required close and sustained cooperation of the families.

MATERIAL and METHODS

We enrolled 22 consecutive prepubertal girls and boys aged 4-9 years who were diagnosed with exogenous obesity in the pediatric endocrinology outpatient clinic. Obesity was defined as BMI >2 SD score, according to the World Health Organization criteria.[4] Standard deviation (SD) scores for weight, height and BMI were determined using the reference created for the Turkish population by Neyzi et al.[5] The pubertal stage of each case was determined according to Tanner pubertal staging.[8] The patients and families were interviewed about the age of onset of obesity, birth weight, gestational age, duration of breastfeeding, duration of TV watching, eating habits and choices, family history of obesity, monthly income and educational status of the parents.

Twenty obese children (16 girls, and six boys) were enrolled. The ethics committee of the Cukurova University, Faculty of Medicine, approved this study and informed consents were obtained from legal guardians. We had initially planned 80 patients as the study population. However, 58 (72.5%) of 80 patients dropped out in the second or third months of the study.

Weight, height, body mass index (BMI), waist circumference, body fat percentage, and biochemical parameters were determined. Body mass index (BMI) was calculated by dividing body weight (kg) by height squared (m^2).[4,5] Waist circumference (WC) was measured at the end of a gentle expiration in a patient without clothing using a non-stretchable tape with sensitivity of 0.1 cm, between the midpoint of the lowest rib cage and the iliac crest. WC percentiles and SD scores were calculated according to age and gender regarding the data for Turkish children.[9] All measurements were made by the same investigator (GS).

Body fat percentage measurements were made by determining the level of visceral adipose tissue (VAT) and body fat percentage (FM%) using a bioelectrical impedance measurement device (BIA, TANITA BC 420MA). The bioelectrical impedance analysis method is based on the electrical permeability differences between the adipose tissue and other tissues. We instructed families that foods and drinks should not be consumed for 4 hours and physical exercise must not be performed for 12 hours preceding the measurements.

An individualized nutrition plan was generated for each patient. Patients received individualized exercise plans prepared by the same investigator, who is a registered exercise coach (GK). The patients were scheduled for a monthly follow-up for a 6-month-period. Weight, height, BMI, waist circumference, and body fat percentage were measured at each visit. Compliance with the nutritional and exercise program was reviewed. At the end of the sixth month, measurements were re-evaluated and compared.

Laboratory tests: Venous blood samples were obtained following 8-hour fasting. Fasting blood glucose (FBG), fasting insulin, C-peptide, HbA1c, serum lipid profile, total cholesterol, High Density Lipoprotein (HDL), Low Density Lipoprotein (LDL), triglycerides, fT4, and thyroid stimulating hormone (TSH) values were determined.

The diet program: Daily energy requirement was calculated for each patient according to his or her age, sex, and target weight. The diet list was generated for each patient to include necessary nutrients according to patients' age and socio-economic and cultural background as follows: 50-55% of the daily energy requirement from carbohydrates, 15-20% from proteins, and 30% from fats. Previous nutritional habits were ascertained, and healthy alternatives were specified. Patients were given a balanced diet according to their target weight.[10,11] A registered pediatric dietitian followed up patients during and after the study.

Exercise program: All 22 patients were included in the home exercise program. An experienced exercise trainer created the exercise program. Before the exercise program, body composition analysis was conducted using TANITA BC 420 MA, and waist circumference was measured. The type of exercise given to the home exercise group was chosen as aerobic exercise (walking, cycling, swimming, climbing stairs, dancing) and strength exercise using their own weight. An exercise follow-up chart was created to chronicle patients' workout sessions. Each child received a written monthly exercise plan and an exercise follow-up chart. The exercise follow-up chart would make the children feel in control, keep them motivated and let the exercise coach follow up the patients. Children were invited every month and evaluated for exercise compliance. Children having problems with compliance were given advice on possible solutions.[12]

Statistical Analysis: SPSS Software package v20.0 was used to analyze the data statistically. Categorical measurements were summarized as number and percentage, whereas continuous measurements were summarized as mean and standard deviation (or median, minimum-maximum where applicable). In the comparison of pretreatment and post-treatment values at the 1st and 6th months, Wilcoxon signed ranks test was used, as parametric test assumptions were not met with number of participants fewer than 30. A significance level of 0.05 was set.[13]

RESULTS

Comparisons of the physical measurements at the 1st and 6th months are presented in Table 1. The waist circumference and BMI measurements were significantly lower in the 6th month after treatment, while height measurement was significantly higher. However, the weight measurements were not statistically different.

Comparisons of the body fat percentages at 1 and 6

Table 1. Comparisons of the physical measurements at 1 and 6 months after treatment (n=22)

						Percentiles			
		Mean	Standard deviation	Minimum	Maximum	25th	50th (Median)	75th	p
Height (cm)	1. month 6. month	131.173 134.827	9.7894 10.1155	109.0 111.5	147.0 152.0	127.750 130.900	132.000 136.000	138.500 142.250	<0.001
Weight (kg)	1. month 6. month	41.841 40.891	8.6834 9.1703	23.4 22.0	59.6 59.0	37.150 33.600	40.750 41.450	48.150 45.325	0.144
Waist circumference (cm)	1. month 6. month	74.200 69.082	7.7364 7.4180	65.0 58.0	90.0 81.0	67.750 63.000	74.000 67.000	79.000 77.250	<0.001
BMI (kg/m^2)	1. month 6. month	24.127 22.345	2.5921 2.8475	19.7 17.3	29.6 28.0	22.375 20.500	24.100 22.000	25.825 24.400	<0.001

Wilcoxon Signed Ranks Test
BMI: Body mass index

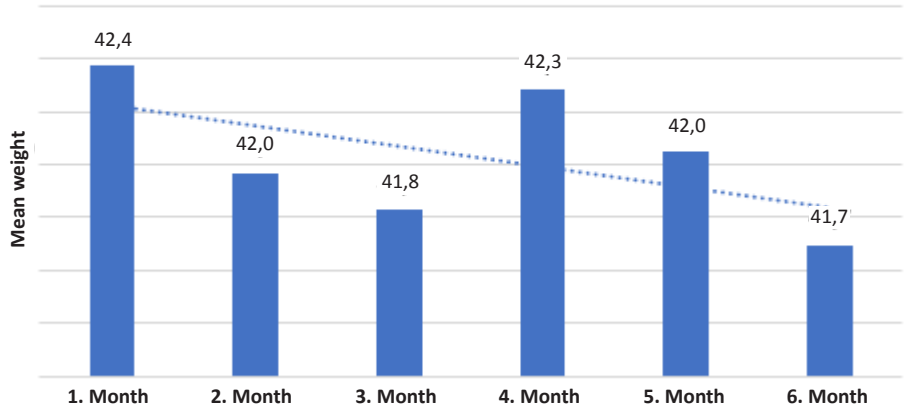

Figure 1. Changes in the weight measurements during the study period in girls (n=16)

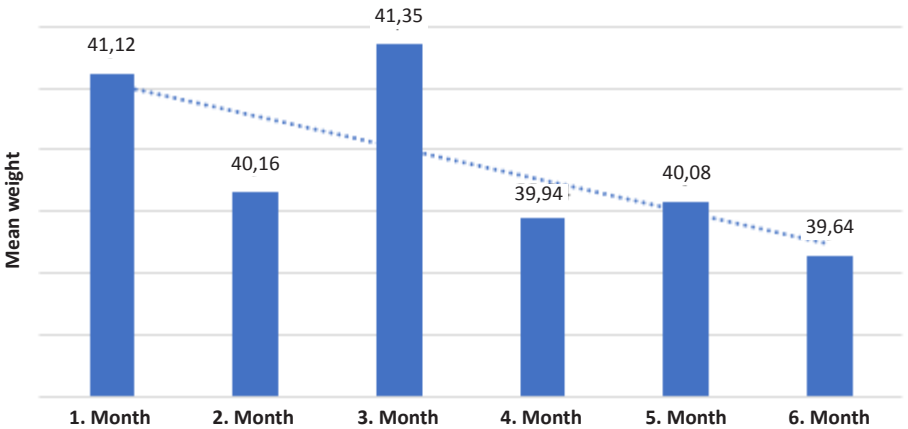

Figure 2. Changes in the weight measurements d uring the study period in boys (n=6)

Table 2. Comparisons of the body fat percentages at 1 and 6 months after treatment (n=22)

						Percentiles			
		Mean	Standard deviation	Minimum	Maximum	25th	50th (Median)	75th	p
Body fat percentages (%)	1. month 6. month	36,00 31,886	3.918 4.7082	29 21.9	43 40.0	34.10 29.375	36.90 33.150	38.00 34.075	<0.001

Wilcoxon Signed Ranks Test

months after treatment are presented in Table 2. The body fat percentages were significantly lower in the 6th month.

Comparisons of the laboratory measurements at 1 and 6 months after treatment are presented in Table 3. No statistically significant difference was observed in any of the parameters.

DISCUSSION

Obesity is an energy metabolism disorder caused by excessive accumulation of fat in the body that may cause physical and psychological problems. Obesity and its serious complications have raised heightened interest in simple and effective methods to prevent and treat obesity. Lifestyle modification that includes

Table 3. Comparisons of the laboratory measurements at 1 and 6 months after treatment (n=22)

						Percentiles			
		Mean	Standard deviation	Minimum	Maximum	25th	50th (Median)	75th	p
TSH (mIU/L)	1. Month 6. Month	3.0527 2.8941	1.09816 1.37619	1.07 1.05	5.72 6.49	2.2175 1.9325	3.1700 2.5300	3.6825 3.5450	0.543
Free T4 (ng/dL)	1. Month 6. Month	1.1768 .9236	.86666 .12089	.61 .65	4.63 1.23	.8850 .8500	.9600 .9250	1.0450 .9825	0.523
HbA1c (%)	1. Month 6. Month	5.359 5.417	.4204 .3957	4.7 4.9	6.1 6.1	5.085 5.053	5.370 5.385	5.613 5.823	0.380
Glucose (mg/dL)	1. Month 6. Month	85.36 85.41	7.762 4.717	72 79	98 94	79.75 80.75	83.00 85.50	92.25 89.25	0.985
Insulin (IU)	1. Month 6. Month	11.125 9.483	11.4256 7.7337	2.1 2.5	53.0 38.5	4.460 4.450	8.735 7.910	13.188 12.525	0.465
HOMA IR (mmol/L)	1. Month 6. Month	44.5 36.5	50.2 31.2	7.4 9.0	230.6 153.9	15.8 17.4	32.4 28.6	51.2 46.9	0.338
Total cholesterol (mg/dL)	1. Month 6. Month	140.00 136.18	32.773 37.821	74 30	203 198	119.25 114.00	142.50 136.50	156.50 172.25	0.436
Triglyceride (mg/dL)	1. Month 6. Month	87.95 82.33	43.023 31.819	23 29	185 133	51.00 57.50	78.00 79.00	121.00 114.00	0.821

Wilcoxon Signed Ranks Test
TSH: thyroid stimulating hormone, HbA1c: hemoglobin A1c, HOMA IR:Homeostatic Model Assessment for Insulin Resistance

diet, exercise, and behavioral motivation is the mainstay in all forms of exogenous obesity regardless of the patient age and availability of pharmacological or surgical interventions. Lifestyle modification is practically the only available method for obesity in prepubertal children. The main principles of nutritional management in obese children include decreasing calorie intake according to daily requirements and modification of eating habits. The goal of dietary treatment is to make patients reach their ideal weight and maintain this weight through healthy eating habits all their lives. In children, however, the goal of diet treatment varies with the severity of obesity. As long as the patient is not morbidly obese, the goal of treatment is to maintain the same body weight instead of weight loss. As the children become taller, BMI is expected to be normalized.[14]

A committee made up of pediatric obesity specialists has recommended a comprehensive staged-care approach for treating childhood obesity.[15] Patients in our study would be classified in Stage 2 (structured weight management) for that stratification. The Expert Committee stated that "monthly office visits are probably most appropriate at this level." They did not cite a study or provide data to substantiate this recommendation. However, this level of intense follow-up may not be available to most obese children. It is a well-known fact that management of obesity with lifestyle modification has a rather low success rate. In clinical practice, lifestyle interventions only reduce mean BMI by −1 to −2 kg/m^2, and the long-term success rate (a decrease in BMI SD score of <0.25) at two years is <10%.[16] Thus, we hypothesized that lifestyle changes in the management of childhood obesity could be better implemented with a close and sustained clinical follow-up. In this study, we observed that patients with an intensive follow-up have encouraging results regarding the most critical obesity parameters such as BMI, waist circumference, and body fat percentage. Since each of our patients served as his/her own control in a prospective longitudinal set-up, our results are free from confounding variables, therefore scientifically valid and valuable.

We generated a nutritional plan suitable for the age,

Table 4. Comparison of clinic parameters obtained before and 6 months after treatment

	Standard follow-up group (n=20)			Intensive follow-up group (n=22)			
	Before treatment Mean±SS	6 months after treatment Mean±SS	P	Before treatment Mean±SS	6 months after treatment Mean±SS	P	P
Height (cm)	127.1±10.5	130.1±10.2	0.0001	131.2±9.8	134.8±10.1	0.0001	0.051
Height SDS	1.0 (-1.5-4.0)	1.4 (-0.7-4.6)	0.0001	0.0 (-1.3-3.1)	0.6 (-0.4-3.7)	0.0001	0.273
Weight (kg)	37.6±8.5	40.8±8.5	0.0001	41.8±8.7	40.9±9.2	0.144	0.0001
Weight SDS	2.3 (1.2-3.7)	2.7 (1.4-4.5)	0.0001	2.0 (1.1-3.4)	2.0 (0.2-3.1)	0.068	0.0001
BMI (kg/m^2)	23.1±2.4	24.1±2.5	0.0001	24.1±2.6	22.3±2.8	0.0001	0.0001
BMI SDS	2.2 (1.1-3.3)	2.4 (1.4-3.9)	0.005	2.2 (1.3-3.1)	1.9 (0.1-2.8)	0.0001	0.0001
Waist circumference (cm)	68.7±5.7	70.5±5.7	0.0001	74.2±7.7	69.1±7.4	0.0001	0.0001
Waist circumference SDS	3.1 (1.1-5.7)	3.4 (1.8-6.3)	0.0001	3.7 (1.8-7.5)	2.3 (0.7-6.0)	0.0001	0.0001
Body fat percentage %	33.6±4.7	36.2±4.7	0.0001	35.5±4.4	31.9±4.7	0.0001	0.0001

p= Dependent T-Test; p: Wilcoxon Test; pα= Repeated measures ANOVA*

socio-economic status, and cultural tendencies of each patient in the intensive follow-up group. Nutritional habits were discussed with patients and their families. We recommended that the entire household should participate in healthy eating practices. We promoted natural and additive-free nutritional habits. In the monthly visits, we offered alternatives to food items that patients did not want to eat.

The combination of diet and exercise result in more weight loss than diet alone. In the long run, exercise is indispensable to maintain current weight. We followed up the exercise habits monthly by using an exercise follow-up chart. Thus, our patients saw their own progress and felt that they were in control. After the study was completed, we recommended that children continue exercise training all their lives.

In this study, we raised awareness through frequent control visits and thus achievement of weight loss and its maintenance more likely. In the standard clinical practice, diet and exercise recommendations are made, and patients are called for a follow-up control visits within 3-6 months. On the other hand, we monitored our patients every month and evaluated their compliance with the recommended lifestyle modifications. We predicted the difficulties in putting these lifestyle modifications into practice, and instead of waiting for six months according to the routine obesity care practice, we made the necessary interventions in time. This way, we ensured that the recommended lifestyle changes were implemented in our patients' lives in a most practical way. We managed this with the help of two critical professionals, namely, dietitian and training coach. The principal investigator (GS) was the primary contact person of patients and families. Another critical aspect of the study was that we involved at least one parent during follow-up visits, enlisting the whole family's help to put the lifestyle modifications into practice. Andreson et al., in support of our study, found that promoting positive relationships between parents/caregivers and children holds promise to prevent childhood obesity.[17]

The mechanisms that let intensive follow-up leading to better outcomes are unknown, but increased awareness, good relations with other professionals, addressing the needs in an expedited manner, answering questions in time, and positive motivation are thought to play essential roles.

As the weaknesses of this study, the number of study participants was lower than expected. Also, the high rate of drop-out at the beginning of the study underscored the crucial problem of motivation on behalf of patients and families in managing obesity.

CONCLUSION

Given the alarming global increase in the prevalence of childhood obesity and the unavailability of alternative treatment options like pharmacotherapy or bariatric surgery in prepubertal children, the

question of how to better implement lifestyle changes becomes crucial. Our findings support a close, frequent, and sustained clinical follow-up with the help of nutrition and exercise professionals for the successful management of childhood obesity.

Ethics Committee Approval: Approval was obtained from the Non-Invasive Clinical Research Ethics Committee of Çukurova University Faculty of Medicine (Ethics Committee approval number: 28/14.02.2014).
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Original Article

Prognostic Value of Myeloid Marker Positivity and its Association with Prognostic Factors in Pediatric Acute Lymphoblastic Leukemia

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ABSTRACT

Objective: *The aim of this study is to investigate the effect of myeloid marker positivity on prognosis and its relationship with classical prognostic factors in acute lymphoblastic leukemia (ALL).*
Methods: *Cases who were newly diagnosed with ALL, followed up in our hospital were included. CD13, CD14 and CD33 were used as myeloid markers by immunophenotyping with flow cytometry in the bone marrow samples. Any parameter higher than 20% was accepted as positive.Modified BFM-2000 protocol was used in treatment and ALL-BFM-95 residual protocols were used in relapses. Risk groups were determined according to the Trall-BFM-2000 protocol. Clinical, laboratory and demographic characteristics of participants such as age, gender, leukocyte count at the time of diagnosis, were all recorded. Patients were divided into three groups according to myeloid markers; those with negative myeloid markers (Group-I), positive one of the myeloid markers (Group-II), those with multiple positive myeloid markers (Group-III). For overall survival, death only was accepted, relapse or death were taken as failure for event free survival (EFS).*
Results: *A total of 96 ALL cases were included. 44 of the patients were male and 52 were female. Their ages were between 10-204 months and median value was 4.5 years. Nine patients were T-ALL (9.4%), one had biphenotype ALL (1%), and 86 had B precursor cell ALL (89.6%). Group-I had 47 patients. One or more myeloid markers were found to be positive in 49 patients (51.1%). While 42 of them consisted group-II, group-III had 7 patients. The EFS distribution for all patients was between 43,16-52 months, with a median of 45.58 months. There was no difference between the groups in terms of EFS (p 0.871).*
Conclusion: *This study revealed that myeloid markers had no effect on prognosis. When compared with parameters with prognostic significance, no difference was found except between FAB morphology and myeloid markers. Therefore, studies involving more patients are needed to obtain more precise information on the subject.*

INTRODUCTION

Hematopoietic malignancies account for more than 40% of childhood malignancies. While leukemias constitute 25-30% of childhood cancers, approximately 97% consists of acute leukemias. Acute lymphoblastic leukemia (ALL) is five times more common in children under the age of 15 than acute myeloblastic leukemia (AML) and the incidence of ALL in 0-14 years of age is 41.4/1.000.000 in our country.[1,2] While the response and survival rate to ALL treatment was about 10% in the 1960s, remission can be achieved at a rate of 80-90% with current treatment protocols arranged according to the biological characteristics of leukemia cells.[1]

In parallel with the advances in diagnosis and treatment, some clinical and laboratory findings have been found to be effective on prognosis and treatment according to risk has come to the fore.

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Additionally, the age and leukocyte values at the time of diagnosis, biological features such as cytogenesis, immunophenotype and clinical conditions such as central nervous system (CNS) involvement, the presence of an extranodal mass were used in determining the risk groups and the treatments to be applied accordingly. Thus, appropriate chemotherapy is determined for patient groups with low and high recurrence risk. Protocols aimed to apply the treatment with the least side effects as possible and to use more intensive treatment in high-risk groups.[3,4] However, by the implementation of more effective treatment regimens, some of these prognostic factors have lost their importance and the rapid response to treatment has become the most determining prognostic factor. While the prognosis is shaped according to the treatment, new prognostic information is obtained by evaluating the response to the treatment.[4,5] Although it is not studied well, existing data are conflicting on the prognostic role of myeloid markers in ALL so far. Therefore, this study aimed to investigate the effect of myeloid marker positivity on prognosis and its relation with classical prognostic factors in childhood ALL.

MATERIALS and METHODS

Pediatric ALL cases newly diagnosed in a period of four years and treated in our hospital were included in the study. Ethics committee approval was received from study hospital's local ethics committee for this study. Informed consent was obtained from parents and children. Age, gender, leukocyte count at the time of diagnosis, hemoglobin value, hepatomegaly, splenomegaly, lymphadenomegaly (LAM), CNS involvement, mediastinal mass and presence of extramedullary involvement, FAB classification, immunophenotype, associated translocations, risk group, myeloid markers, number of blasts in the smear on treatment day 8, blast rate in the bone marrow on the 15th and 33rd days, the time of recurrence, if occured, and the time of death if occurred, and the time of treatment initiation were recorded and evaluated by recording clinical and demographic data. Hepatosplenomegaly was noted in case of the abnormal enlargement of liver and spleen according to the age matched precentile values. Death was accepted as only death for overall survival, and relapse or death as failure for event-free survival (EFS). The follow up period was 52 months. EFS time was taken as the time from diagnosis to relapse or from diagnosis to disease-related death.

Diagnosis and Extramedullary Involvement

Physical examination findings were recorded following detailed anamnesis of all patients with cell morphology and surface antigen compatible with ALL. After routine laboratory analyzes (complete blood count, peripheral blood smear, biochemical tests, virological tests, coagulation tests), bone marrow aspiration was performed, stained with Giemsa and morphologically examined under a light microscope. The percentage of blasts in the bone marrow was determined by FAB criteria (L1: Childhood ALL, L2: Adult type ALL, L3: Burkitt type ALL). Periodic-Acid-Schiff (PAS), Sudan Black and myeloperoxidase staining were performed on bone marrow aspiration (BMA) materials, as well as immunophenotyping with flow cytometry. CD13, CD14 and CD33 as myeloid markers in immunophenotyping; CD19, CD20, CD22, CD24 and CD10 for the B cell line as lymphoid markers; CD3, CD5, CD7 were used for the T cell line. More than 20% of any parameter and for CD34 a value higher than 10% was accepted as positive. t(9; 22), t(4; 11), t(1; 19) and t(12; 21) were studied for all cases. The presence of a mediastinal mass was investigated by chest radiographs of the patients. CNS involvement was investigated by cytological and biochemical examination of the cerebrospinal fluid (CSF) sample taken by lumbar puncture.

The patients were divided into three groups according to their myeloid markers; Those with negative for myeloid markers (Group I), positive for one of the myeloid markers (Group II), and those with more than one positive myeloid markers (Group III).

Diagnosis and Evaluation of Response to Treatment During Follow-up

Modified Berlin-Frankfurt-Munster 2000 (BFM-2000) protocol was applied to the patients and ALL BFM-95 Residual protocols were applied in relapse cases. BFM HR blocks were applied to patients who did not respond to treatment or had a partial response and patients included in the high-risk group. The blast

rate in peripheral blood smear was counted on the 8th day of the treatment protocol. A blast count of <1000/mm^3 was considered as remission. A leukocyte count of >100,000/mm^3 was defined as hyperleukocytosis. The blast rate in bone marrow preparations on the 15th day was evaluated as M3 bone marrow if it was 25% or above, 5-24% as M2 bone marrow, and <5% as M1 bone marrow. A blast rate of <5% in bone marrow preparations on the 33rd day showed remission.

Risk Classification

Our patients were divided into standard, medium and high risk groups according to the Turkish ALL-BFM 2000 (TRALL-BFM 2000) protocol.

Standart Risk Group (SRG): Patients meeting all of the following criteria were taken as SRG; age ≥ 1 year or <6 years, initial leukocyte count <20,000/mm^3, leukemic cell count <1000/mm^3 in peripheral blood on the eighth day after 7 days of prednisolone treatment, without T-cell immunology, complete remission on day 33 and cases without t (9;22) or t(4;11) translocations.

Moderate Risk Group (MRG): Patients with at least one of the criteria were taken as MRG; Cases with leukocytes ≥20,000/mm^3, age <1 year or ≥6 years, or T-cell immunology. Also; should meet all of the following conditions; number of leukemic cells in the peripheral blood on the eighth day is <1000/mm^3, complete remission on the 33rd day, no t (9;22) and t(4;11) translocations.

High Risk Group (HRG): Patients with at least one of the criteria were evaluated as HRG; cases with leukemic cell count >1000 mm^3 in peripheral blood on the eighth day, incomplete remission on the 33rd day or positive one of the t(9;22) and t(4;11) translocations.

Statistical Analysis

Data were presented as mean±standard deviation (SD) for parametric tests and median (min-max or 25-75 percentile or interquartile range) for non-parametric tests. Survival analyzes were performed by using the Kaplan-Meier test. Log-rank and Breslow tests were used to compare the survival rates of the groups. SPSS version 21.0 (SPSS, Chicago, IL) was used for statistical analysis. Statistical significance was accepted when the probability (p) value was <0.05 and changes were referred to as significant at this P value.

RESULTS

A total of 96 ALL patients, 44 male and 52 female, diagnosed during a one-year period and aged between 10-204 months (median age 4.5 years) were included in the study (Table 1). In the physical examination at the time of first application, hepatosplenomegaly (HSM) was detected in 32% of the patients and lam in 11.5%. Four patients had a mediastinal mass and were diagnosed with T-cell leukemia. CNS involvement was detected at the time of diagnosis in a patient with biphenotype morphology. Two patients had skeletal involvement and one patient had parotid gland involvement. In laboratory tests, it was seen that 80% (n=77) of the patients had anemia, 44 (46%) had leukocytosis (>20,000/mm^3) and 11 (11.5%) of the patients with hyperleukocytosis had a leukocyte count >100,000/mm^3.

Table 1. The distribution of the participants according to the clinical characteristics

	Number of cases	
	n	%
Sex		
Male	44	45.8
Female	52	54.2
Age (years)		
<1	2	2.0
≥1- <6	64	66.7
≥ 6	30	31.3
HSM		
Yes	31	32.3
No	65	67.7
LAM		
Yes	11	11.5
No	85	88.5
Mediastinal mass		
Yes	4	4.2
No	92	95.8
SSS involvement		
Yes	1	1.0
No	95	99.0
Extramedullary involvement		
Yes	3	3.1
No	93	96.9

75% of BMA smears of the patients were evaluated in FAB-L1 and 25% in FAB-L2 morphology. In the immunophenotypic evaluation, it was determined that nine patients had T cell phenotype, one patient

Table 2. Immunephenotypes of the participants

	Number of cases	
Immunephenotype	**n**	**%**
B cell	86	89.6
Early Pre B	6	6.3
Pre B	2	2.1
CALLA+ B	78	81.2
T cell	9	9.4
Biphenotype	1	1.0

had biphenotypic characteristics, and 86 (89.6%) patients had B precursor cell phenotype (Table 2).

When the patients were evaluated according to risk groups, 32.3% (n=31) belonged to the standard risk group, 59.4% (n=57) to the medium risk and 8.3% (n=8) to HRG.

In cytogenetic examination, three (3.1%) patients had only t(9;22), two (2.1%) patients had only t(4;11), any translocations were detected in 85 (88.7%) patients and there were no cases where two of them were positive either. The results of six (6.1%) patients, who died before the final analysis of translocation, could not be reached.

According to myeloid markers, 7 patients had more than one myeloid marker positivity (Group III), 42 patients had one myeloid marker positivity (Group II), and 47 patients had no myeloid marker (Group I). Overall myeloid marker positivity (Group II + Group III) was 51.1% (n=49). Immunophenotype distribution according to the myeloid markers of the patients is summarized in Table 3.

With treatment, 84 (87.5%) patients developed remission within one month of remission induction therapy. It was observed that a patient who did not proceed to remission was CD13 positive (group II) at HRG. Although this patient was in remission with BFM HR Block treatment, relapse developed 15 months after the initiation of treatment and the patient who was applied ALL BFM 95 Residive protocol died of sepsis 63 days after relapse, while 11 patients died in the first 30 days due to various reasons. One of these patients was t (4; 11) positive, one patient was at HRG, one patient was CD13 positive (Group II) and the other was both CD13 and CD33 positive (group III). Of the patients who died within the first 30 days, six were at MRG and only one patient was in group II, while the others were found to be group I. The remaining 3 patients were at SRG, and only one patient was in group II, while the others were in group I. One of the two patients followed up in remission developed bone marrow recurrence in the 4th month, and the other had a recurrence of the bone marrow and mediastinal mass in the 12th month. Both of these patients were in MRG and T-cell ALL immunophenotype, one of them was only CD13 positive (Group II), while the other had both CD13 and CD33 positive (Group III) (Table 4). These two patients died within two months after relapse. Six patients died within 2-9 months

Table 3. Immunephenotypes of the participants between the groups

Immunephenotype	**Group I %**	**Group II %**	**Group III %**	**Total %**
Early Pre B	5.2	1.0	0.0	6.3
Pre B	1.0	1.0	0.0	2.1
CALLA+B	39.5	36.5	5.2	81.2
T cell	3.2	5.2	1.0	9.4
Biphenotype	0.0	0.0	1.0	1.0

Table 4. Current outcomes of the participants between the groups

	Group I		Group II		Group III		Total	
Current Outcome	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Survival	38	39.6	33	34.4	5	5.2	76	79.2
Exitus	9	9.4	9	9.4	2	2.0	20	20.8
Total	47	48.9	42	43.8	7	7.3	96	100

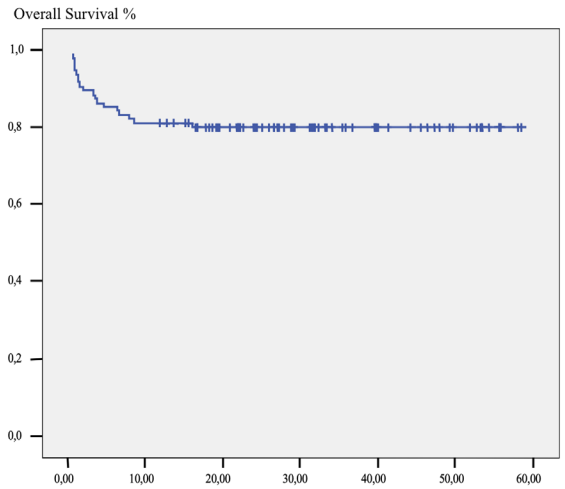

Figure 1. The overall survival rate and the overall survival time were shown as months in Figure 1.

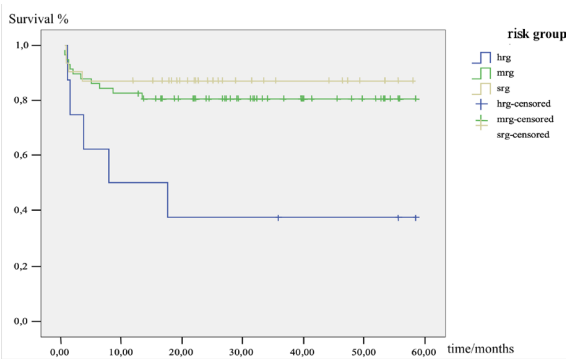

Figure 2. Survival periods of the risk groups were seen in Figure 2.

while in remission. 79.2% (n=76) of our patients survive after 52 months of follow-up. The overall survival rate was 79.9% and the overall survival time was 47.64 months (43.24-51) (Figure 1). Survival periods of the risk groups were shown in Figure 2 (Figure 2). The 52-month EFS was found to be 80.3%. The EFS distribution for all patients was between 43.16-52 months, with a median of 45.58 months. EFS values according to gender were 76.8% in boys and 82.4% in girls (p 0.061).

Various clinical and laboratory characteristics of our patients (age, gender, hemoglobin value, leukocyte count, HSM, lam, mediastinal mass, CNS involvement, extramedullary involvement, blast morphology, immunophenotype, cytogenesis, blast number in peripheral blood on day 8, day 15 and 33, blast rate in bone marrow on the 1st day) was evaluated, it was seen that only immunophenotype and bone marrow response on the 15th day statistically affected the prognosis, while other factors did not affect the prognosis. It was observed that the prognosis (EFS 84.9%) in patients with non-T immunophenotype was better than biphenotype and T-ALL (EFS 29.6%) (p <0.001). Although not used in risk classification, EFS values were found to be significantly different according to the 15th day bone marrow M1, M2 and M3 (p <0.001). When the EFS of our patients were evaluated according to the risk group, it was seen that the EFS of HRG (37%) was significantly lower than the other groups (p 0.008).

None of the cases had all three of the myeloid markers were positive, concurrently. Other myeloid markers were found to be negative in patients with positive CD14. Therefore, in Group III, where two myeloid markers were positive, only CD13 and CD33 were found to be positive either. The effects of these groups on prognosis are given in Table 5. Although the EFS value of Group III seemed to be shorter numerically, no statistically significant difference was found between the EFS. When the groups formed according to myeloid markers were compared with other prognostic factors, it was observed that there was a significant difference between the patients with only FAB-L1 and FAB-L2 blast morphology in

Table 5. Association between the myeloid markers positivity and EFS

	Number of Cases				
	n	%	EFS (month)	EFS (%)	p
Group I	47	48.9	47.92±3.1	81.3±0.05	
Group II	42	43.8	44.44±3.2	77.7±0.06	0.871
Group III	7	7.3	25.87±4.89	68±0.1	

EFS: Event free survival
Kaplan-Meier test

terms of distribution of the groups (p 0.012). It was observed that the positive myeloid markers of our patients did not affect the peripheral blood smear and bone marrow blast response. It was found that mortality rates in Group I, II and III did not differ. The number of patients with relapse was very low, and there was no significant difference between the groups in terms of relaps rates.

DISCUSSION

Acute leukemias are the most common malignant diseases in childhood. Many factors such as age, gender, leukocytosis and cytogenetic values have prognostic importance in childhood ALL. These prognostic factors are also used in classifying patients into risk groups. Given relapses can occur in even patients without poor prognostic factors, current prognostic evaluation is required to be improved. Therefore, it is necessary to search for new prognostic factors in childhood ALL.[6]

In series including larger patient population, the incidence of ALL in male patients was higher than girls, while it was found to be 45.8% in this study.[7] Boys are known to have a worse prognosis than girls who receive the same treatment.[8] Similarly, in this study, although the EFS of males was lower than females, a statistically significant difference was not found, probably due to our relatively low number of cases.

Age at the time of diagnosis is a notable prognostic parameter in ALL.[9] The worst prognosis is seen under one year of age, related to the certain features such as CNS involvement, high blast load and slower response to treatment are common in this age group.[9] Especially, under 3 months has the worst prognosis, while the prognosis is better in the range of 6-12 months.[1,4] The best prognosis is seen between the ages of 2-6 in all age groups.[9] In our study, the median age at the time of diagnosis was 4.5 years and had similar results with studies in Germany and Korea.[10,11] Besides, the median age was stated to be around 6 years in different studies.[12-14]

Leukocyte count at the time of diagnosis is also defined as another prognostic factor, of which higher rate is associated with an increased risk of recurrence, especially in B-ALL.[9] Significant higher or lower leukocyte counts at the time of diagnosis may delay the diagnosis of ALL. Leukocytosis (>20,000/mm^3) was not detected in more than half of our cases. There are different approaches to the cut-off value of leukocyte count.[12,13] When taken the commonly used value of 20,000/mm^3 as cut-off in our study, it was seen that there was no difference between the EFS of the cases with the leukocyte count above 20.000/mm^3 and the cases with less than 20,000/mm^3.

While anemia, which is present in more than 80% of the patients at the time of diagnosis, indicates that leukemia has been present for a relatively long time, normal hemoglobin (Hb) values suggest a rapid course of leukemia. It is thought that patients presenting with higher Hb levels or mild anemia are detected at an early stage of the disease. Therefore, they may be more susceptible to chemotherapeutic interventions.[1,2,15,16] In a study investigating the effect of Hb level on prognosis, complete remission rates were reported as 63% when Hb level was <8 g/dl, 70% between 10-12 g/dl and 60% when >12 g/dl. It has been stated that the level does not affect the life span.[17] In our study, there was no statistically significant effect of Hb level on EFS.

In the literature, fever, organomegaly, lymphadenopathy and pallor have been defined as the most common clinical features.[16] Patients with hepatomegaly and/or splenomegaly at the time of ALL diagnosis, had been shown to have an almost four times higher risk of recurrence.[18] Studies examining the relationship between splenomegaly/hepatomegaly and survival have conflicting results.[19] In our study, HSM, LAM, and the presence of a mediastinal mass, which are among the poor prognostic parameters, was not found to be effective on prognosis due to the possible low number of patients.

In the past, all lymphoblasts were classified according to FAB criteria. Currently, this classification is not recommended due to the lack of independent prognostic significance and being subjective. However, it still has a place in clinical practice, as it can provide diagnostic accuracy in some cases. Additionally, the FAB system is preferred in developing

countries such as our country, given its advantages of being practical and not requiring much resources.[16,20] L1 morphology is more common in children (about 74%) than adults (about 66%).[21] In accordance with the literature, distribution of our patients in L1 and L2 according to the morphological classification was 75% and 25%, respectively. When the sole effect of blast morphology on prognosis was examined, it was seen that the EFS values of L1 and L2 did not differ.

Approximately 2-3% of children with ALL, have t(4; 11) and t(9; 22), which is known as Philadelphia chromosome, was found in 2.9% of them.[19] These translocations are known to be associated with poor prognosis.[19,20] In this study, t (9; 22) and t (4; 11) was found to be 3.1% and 2%, respectively. However, due to the low number of patients with positive translocations in our study, a statistical evaluation could not be made.

Immunophenotyping in leukemic lymphoblast cells forms the basis of diagnostic evaluation, since these cells lack specific morphological and cytochemical properties. Expression of CD markers is widely used to classify hematological malignancies, including leukemia and lymphoma.[2,22] This study evaluated myeloid surface antigens such as CD13, CD14 and CD33, which are not found in normal T or B lymphocytes, with a lower limit of 20% in fluorescence analysis. In our series, the myeloid marker positivity with 51.1% is much higher than the 4-22% reported in the literature. Uckun et al. reported that they used only CD13 and CD33 antigens with a lower limit of 30% in fluorescence analysis in 1557 patients and their myeloid antigen positivity was 16.6%.[23] Using the lower limit of 20%, similar to our study, Putti et al. found the myeloid marker positivity to be 32% in their series of 908 patients.[24]. The researchers stated that screening CD13 and CD33 myeloid markers will reveal the presence of all myeloid antigens in childhood ALL.[24] We tried to create a wider panel by looking at CD14 in addition to these antigens. In this study, CD13 was found to be the most detected myeloid marker in 44% of patients. CD14 and CD33 were found positive in 4% and 9%, respectively. When our patients with T-biphenotype and B precursor cell ALL were evaluated according to the distribution of myeloid marker positivity, it was observed that there was no statistically significant difference (p 0.52). Similar to our results, Putti et al. found that the percentage of myeloid marker positivity was similar between these two immunophenotypes.[24] When the association of ALL and myeloid marker positivity was compared with other prognostic values such as age, gender, high leukocyte count, hemoglobin value, HSM, presence of translocations and immunophenotype, no statistically significant difference was found. When evaluated only in terms of blast morphology, it was observed that myeloid marker positivity was higher in L2 morphology, which was considered to show a relatively poor prognosis (p 0.012). Uckun et al. showed that patients with myeloid antigen negative B precursor cell ALL have more clinical and laboratory values such as higher leukocyte count, splenomegaly and low platelet count, which show worse prognosis compared to patients with myeloid antigen positive B precursor cell ALL.[23] There are also previous studies, from different countries, which obtained data similar to ours.[24,25] On the other hand, Fink et al. reported that myeloid antigen positive patients presented with higher leukocyte count; but EFS of these cases did not differ than others.[26]

Clinical importance of myeloid marker positivity has been presented in the literature since 1990. Although most of the studies showed that myeloid markers have no effect on the prognosis, the results are contradicting. Wiersma et al. stated that myeloid antigen positivity was the most important indicator of poor prognosis, while other studies reported that myeloid antigen positive patients had better prognosis than myeloid antigen negative ones.[26,27] Mejstríková et al. showed that CD13 and CD33 markers have prognostic value and 5-year EFS is lower in myeloid antigen negative ones.[28] Despite it was not evaluated a prognostic factor, children with myeloid markers and Philedelpia choromosome positive ALL was shown to have a poor early response to treatment, which resulted in a low CR rate.[29]

However, in their study with a large ALL population, Uckun et al. found that 4-year EFS was similar in both myeloid antigen positive and negative ones.[23] Pui et al. reported that the myeloid antigen found in 105 of 334 patients with newly diagnosed ALL, but this did not affect EFS although it was associated with

specific genetic anomalies.[29] There are also several studies reporting that myeloid antigen positivity does not affect the prognosis.[22,24,25,31,32] In our study, it was seen that EFS was not affected by myeloid markers.

Limitations

This study has some limitations such as restricted number of participants. Including larger numbers of participants may provide a more strengthened study.

CONCLUSION

This study revealed that myeloid markers had no effect on ALL prognosis. When compared with other prognostic parameters, no difference was found except FAB morphology. In conclusion, myeloid antigen positivity is a common condition in patients with childhood ALL, and its prognostic significance is controversial. Although there is no objective data to explain the positive myeloid markers in the patient group with FAB-L2 blast morphology showing only a relatively poor prognosis, it was thought that the low number of our patients led to this situation. Therefore, studies involving more patients are needed to obtain more precise information on the subject.

Ethics Committee Approval: The study was approved by local Ethics Committee of study hospital (Ethics Committee approval number: 154/2008.06.26).
Conflict of Interest: The authors have no conflicts of interest to disclose.
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Informed Consent: Informed consent was obtained from the parents prior to participation in the study.

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Original Article

Prevalance of Epilepsy in School-age Children in Erzurum

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ABSTRACT

Objective: *This study aimed to investigate the prevalence of epilepsy in school children in Erzurum and compare it with prevalence studies in Turkey and worldwide.*
Methods: *This is a cross-sectional study conducted in the center of Erzurum. From the universe formed by 74,732 students, 5,571 people were selected through the "proportionate stratified sampling method" and 4,560 (80%) of the 5,700 questionnaires distributed were collected. Based on the data obtained, 563 students were accepted as possible epilepsy cases and examined for epilepsy.*
Results: *TOf the students participating in the study, 51.3% were female and 48.6% male. Six girls (3/1000) and 10 boys (5/1000), a total of 16 cases (4/1000) were detected to be followed-up for epilepsy. Prevalence rates were found to be 4.5/1000, 2.6/1000 and 3.6/1000 for males, females and the total population, respectively. The prevalence of active epilepsy was determined to be 4/1000, 2/1000, and 3/1000 for males, females and the sum of both, respectively.*
Conclusion: *Epilepsy is an important health problem for our region. The prevalence of epilepsy among school-age children in Erzurum was close to the prevalence rate seen in developed countries. Febrile convulsion, low educational level and low socioeconomic level are the risk factors for epilepsy.*

INTRODUCTION

Epilepsy is a condition characterized by sudden, recurrent epileptic seizures that are not triggered by an identifiable event due to abnormal and excessive electrical discharges in cortical neurons.[1] Epilepsy adds to society's burden by adversely impacting children's physical and social lives. Preventive and curative health services can help to change this situation. Epidemiological studies are needed to reveal the frequency and causes of epilepsy, to prevent its development, and to determine appropriate treatment approaches.[2]

In studies conducted to date, the mean prevalence of epilepsy has been found to be 18.5/1000 (between 2.8 and 44/1000).[3,4] The prevalence of epilepsy was reported to be 8-17/1000 in a limited number of studies performed in Turkey.[4,5] Many studies have shown differences in prevalence rates. To determine the prevalence values, many studies should be carried out in the different regions of Turkey.

The aim of this study is to determine the prevalence of epilepsy in school-age children aged 7-16 in Erzurum city center, to evaluate the risk factors in patients diagnosed with epilepsy, and as a result of the data obtained, to contribute to the prospective approaches for the follow-up and treatment of epilepsy for our country.

MATERIALS and METHODS

Study area and Population

Erzurum is the largest city in the Eastern Anatolia Region. Its total population is approximately 784,941.

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This study was planned in order to determine the prevalence of epilepsy in children in primary education and high school age in Erzurum. According to the data of Erzurum Provincial Directorate of National Education and Statistics Department, 54,580 students study in 184 primary schools and 20,152 students in 29 high schools,ie. a total of 74,732 students in 213 schools within the boundaries of the metropolitan city.

Sample Selection

The study's sample included 5571 students selected from the population of elementary and high schools within the boundaries of Erzurum Metropolitan using the "proportional stratified sampling method". The elementary and high schools were grouped separately, and their weight in the population was determined, and they were represented in the sample in proportion to their weight. Considering that each elementary school consists of 8 classes with an average of 25 students and the high schools consist of 4 classes with 20 students, each school was considered a cluster, and 13 clusters were included in the sample. While determining the sample size, epilepsy prevalence (p) was taken as 0.56% d 0.02 and the formula n=Nt2p.q / d2 (N-1) + t2pq was used at 95% confidence interval. The sample size was calculated to be 5064, but it was aimed to use 5571 questionnaires, assuming that 10% of the questionnaires would be excluded from the study.

Questionnaire Form

Approval was obtained from Atatürk University Faculty of Medicine Ethics Committee. The study was conducted in two stages. In the first stage, 11 questions were about the socio-demographic characteristics of the cases. 15 questions were prepared according to the "Guidelines for Epidemiologic Studies" proposed by the "ILAE-CEP-1993" in the prevalence study conducted by Karaağaç et al. in Silivri, and these questions were asked during realization of the study.[6] We added ten questions to increase the sensitivity of the survey. The sensitivity and specificity of these survey questions were detected as 99% and 76%, respectively. In accordance with the Principles of Helsinki Declaration, an "informed consent" form was obtained from the parents who participated in the study. Scoring was made by evaluating the data obtained in the first stage.

Statistical Analysis

The data were evaluated using the SPSS 15.0 package program. Data were expressed as number, percentage, mean and standard deviation. Prevalence of epilepsy, age, gender, socio-economic status, social security, consanguineous marriage, residence, parents' educational level, family history of epilepsy, and febrile convulsion, risk factors related to epilepsy and febrile convulsion history in the child were analyzed with Fisher-Freeman-Halton Test and chi-square test. Level of statistical significance was taken as $p<0.05$. The reason of using chi-square test was to find the significant differences between the expected frequencies and observed results to understand whether the distribution of categorical variables differ from each other. The independent variables of the study were age, gender, social security, consanguineous marriage, homeownership, and monthly income, and parental educational level, family history of epilepsy, and febrile convulsions, risk factors associated with epilepsy and history of febrile seizures in children. The dependent variables of the study were related to the prevalence of epilepsy.

RESULTS

Stage One; **Socio-Demographic Characteristics:**

A total of 5,571 questionnaires were distributed and 4,560 responses were received, with an 81.8% return rate. Of the questionnaire forms, 2,784 (61.0%) were taken from primary education schools and 1,773 (38.9%) forms from high schools. The mean age of the questionnaire was 12.7±3.4, and 51.33% of the students were female and 48.6% were male. In terms of educational level, 57.4% of fathers and 67.9% of mothers were primary school graduates. When examined in terms of consanguinity; 11.7% of the parents were 1st degree relatives. Monthly income of 34.1% of the cases was low. There was a history of epilepsy in 6.5% and febrile seizure in 25.4% of the families. The results are shown in Table 1.

Second Stage Findings; Prevalence Findings

The data obtained in the first stage were evaluated. Study participants who scored 3 over 9 questions (n=563) were accepted as possible epilepsy cases.

Table 1. Family history of epilepsy and febrile seizures

	n	%
Epilepsy in the family		
Yes	295	6.47
No	4262	93.53
Family members, and relatives with a history of epilepsy		
Mother	32	11.31
Father	35	12.37
Siblings	76	26.86
Aunt, uncle,	81	28.62
Cousin or nephew	59	20.85
Family history of a febrile seizure		
Yes	1156	25.37
No	3401	74.63
Family members, and relatives with a history of febrile seizures		
Mother	75	6.78
Father	115	10.39
Siblings	604	54.56
Aunt, uncle,	106	9.58
Cousin or nephew	207	18.70

Table 2. The questionnaire for the possible epilepsy cases

1. Does your child have epilepsy?
2. How does your child have seizures?
3. If you answered yes to the first question, how many seizures had your child had in the last five years?
4. How often do the seizures occur in your child?
6. How many years has your child had a seizure?
7. Have you ever had an EEG done on your child?
8. If yes, what were the results of the EEG?
9. Is your child taking medication for epilepsy?
10. How many years has your child been taking medication?
11. If your child is on treatment, what medication is he/she taking?
12. Has the medication resulted in a decrease in seizures?
13. What is the blood level of the medication your child is taking?
14. Has your child ever had meningitis or encephalitis?
15. Did your child not receive oxygen at birth?
16. Has your child ever had a sudden stroke?
17. Has your child ever had a concussion?
18. Does anyone in your family have epilepsy?
19. If so, who has it?
20. Does anyone in your family have a febrile seizure?
21. If so, who or what has it?
22. Has your child ever had a febrile seizure?
23. At what age did your child have his or her first febrile seizure?
24. Has your child had more than one febrile seizure? If yes, how often?
25. Has your child taken medication for a febrile seizure?
26. If yes, what medication did he/she take?

Potential epilepsy cases were summoned to Atatürk University Medical Faculty Paediatrics Department Polyclinic to be examined for definite epilepsy. The questionnaire shown in Table 2 was applied to the respondents. While 250 out of 563 participants were examined in the hospital. 150 persons who did not wish to come to the hospital were examined by telephone and screened for epilepsy. The families of participants who might have epilepsy were persuaded and called to the hospital. Fifty-seven individuals were evaluated in terms of epilepsy in their schools, whereas 106 individuals could not be reached because school counseling services were unavailable, and telephone communication was not possible.

Cases participating in the study were evaluated for drug use due to epilepsy (active or inactive epilepsy) or febrile seizures. Active epilepsy patients were defined as patients who had at least one seizure in the past five years, whether treated or not. Inactive epilepsy was used for patients who were untreated or seizure-free in the last five years. Epilepsy was defined as the presence of two or more unprovoked seizures. Febrile seizures were defined as the most common seizures in childhood, usually between the ages of 3 months and five years, associated with fever and without evidence of intracranial infection. As a result of the study, 13 (2.3%) possible epilepsy cases were classified as active epilepsy, 3 (0.5%) as inactive epilepsy, and 80 (14.2%) as febrile convulsions (Table 3). In the second stage of the study, 334 (59.3%) of 563 possible epilepsy cases were not evaluated as epilepsy. When the family history of epilepsy in epileptic cases was evaluated, epilepsy was found in the family in 7 (43.7%) of 16 patients, 3 of 6 female patients and 4 of 10 male patients. When evaluated in terms of febrile seizures in the family, positive history was found in 4 of 6 female patients

Table 3. Distribution of cases with possible epilepsy

	n	%
No epilepsy	334	59.3
Inactive epilepsy	3	0.5
Active epilepsy	13	2.3
Febrile convulsion	80	14.2
Conversion	3	0.5
Panic attack	1	0.2
Syncope	22	3.9
Syringomyelia	1	0.2
Could not be reached	106	18.8
Total	563	100.0

Table 4. Distribution of risk factors in epileptic individuals

	n	%
Having meningitis		
Yes	1	6.2
No	15	93.8
Oxygen deprivation at birth		
Yes	3	18.7
No	13	81.3
Sudden paralysis		
Yes	0	0.00
No	16	100
Having a concussion		
Yes	2	12.5
No	14	87.5

Table 5. Comparison of socio-demographic findings in epileptic and non-epileptic subjects

		Epilepsy group					
		With epilepsy		Without epilepsy			
		n	%	n	%	Chi-square, Fisher-Freeman-Halton Test*	p
Gender	Female	6	46.2	234	53.9		
	Male	7	53.8	200	46.1	0.306	0.580
Health insurance	Health card for uninsured people in Turkey	4	30.8	161	37.1		
	SSI (Social İnsurance İnstitution)	7	53.8	177	40.8		
	Bagkur (Social security organization for artisans and the self-employed)	1	7.7	52	12.0		
	Paid Retirement Fund	0	0.0	13	3.0		
		1	7.7	31	7.1	0.89*	0.873
Consanguineous marriage	1st Degree Kinship	3	23.1	78	18.0		
	2nd Degree Kinship	1	7.7	86	19.8		
	No Kinship	9	69.2	270	62.2	1.142*	0.564
Home ownership	Own	8	61.5	258	59.4		
	Rent	5	38.5	160	36.9		
	Dwelling-House	0	0.0	16	3.7	0.033*	1.000
Monthly income	<500 TL	7	53.8	171	39.8		
	500-999 TL	3	23.1	162	37.7		
	1000-1999 TL	3	23.1	80	18.6		
	≥ 2000 TL	0	0.0	17	4.0	1.56*	0.619
Father's educational level	Illiterate	1	7.7	39	9.0		
	Primary School Graduate	10	76.9	273	62.9		
	High School	1	7.7	102	23.5		
	University	1	7.7	20	4.6	2.372*	0.407
Mother's educational level	Illiterate	3	23.1	143	32.9		
	Primary School Graduate	9	69.2	262	60.4		
	High School	0	0.0	24	5.5		
	University	1	7.7	5	1.2	4.118*	0.237

Table 6. EEG findings of possible epilepsy cases

EEG Findings	n	%
Normal	47	38.5
Focal epileptic form	3	2.5
Generalized epileptic form	3	2.5
Suspected epileptic form	1	0.8

Table 7. Distribution of epilepsy prevalence by gender

	With epilepsy		Without epilepsy			
Gender	Number	%	Number	%	Total	p
Female	6	0.26	2333	99.74	2339	0.30
Male	10	0.45	2211	99.55	2221	
Total	16	0.35	4544	99.65	4560	

Table 8. Age-adjusted prevalence of epilepsy in females and males

	MALE		FEMALE		TOTAL	
GRADE	Total population	Expected case	Total population	Expected case	Total population	Expected case
7-10	14,160	130	13,324	38	27,484	167
11-14	14,039	41	13,057	53	27,096	94
15-18	11,518	26	8,634	10	20,152	36
TOTAL		39,717	179	35,015	74,732	269
Age-adjusted prevalence (prevalence/1000)		**4.5**		**2.6**		**3.6**

and 4 of 10 male patients, a total of 8 patients (50%), and no statistically significant difference was found (p>0.05).

In the epileptic cases, a positive history of epilepsy was found with a frequency of 2.8% in the father, 6.6% in the siblings, and 1.7% in the cousins and nephews. The 1st degree consanguinity was 25%, and 2nd degree consanguinity was 6.2%. This finding was not found to be statistically significant (p>0.05). The fathers, and mothers of epileptic cases were found to be primary school graduates, in 75% and 68.7% of the cases, respectively. When the history of febrile convulsion in epileptic cases was questioned equal number of participants gave affirmative (n=8: 50%), and negative (n=8.50%) answers 8 and the difference was not found to be statistically significant (p=0.000). In our study, 10 subjects (62.5%) answered "yes" and 6 (37.5%) answered "no" to the question about bringing child to hodja to pray for him/her for any reason. The data were considered statistically significant (p=0.000). The risk factors of epilepsy cases are shown in the Table 4.

In our study, no statistically significant difference was found when socio-demographic findings of epileptics and non-epileptics are compared as shown in Table 5 (p>0.05).

When the cases participating in the study were examined in terms of drug use due to possible epilepsy (active or inactive epilepsy) or febrile convulsion, it was determined that the patients used valproic acid (VPA) (n=12:2.1%), carbamazepine (CBZ) (n= 5: 0.9%), VPA + levetiracetam (n=2: 0.4%), oxcarbazepine (n=1: 0.2%), phenobarbital (n= 1: 0.2%), levetiracetam ((n= 1: 0.2%) (0.2%) rectal diazepam (n=1: 0.2%), and CBZ + topiramate (n=1: 0.2%). The distribution of drugs used by patients with epilepsy was valproic acid in 6, carbamazepine in 4, phenobarbital in 1, levetiracetam in 1, oxcarbamezepine in 1, VPA + levotiracetam in 2, and CBZ + topiramate in 1 student. EEG was performed in 55 of 563 students included in the study. The results are shown in the Table 6.

Thirteen (81.2%) students with possible epilepsy had undergone Computed Brain Tomography and/or Magnetic Resonance Imaging which demonstrated normal anatomy (n=10: 76.9%), cystic lesions in the right temporal (n=1: 7.69%), astrocytoma (n=1: 7.69%) and encephalomalastic area (n=1: 7.69%).

According to the questionnaire results, the distribution of epilepsy prevalence by gender was 2.6/1000 in females, 4.5/1000 in males and 3.5/1000 in total as it is shown in Table 7.

In cases where the study population is insufficient to reflect the general population, the age-adjusted prevalence of epilepsy can be used to evaluate the study results more reliably. In this study, the age-adjusted prevalence rate was determined using the age- and gender-specific cumulative prevalence rate based on the population in the age group of 7-17 years (Table 8). This situation ensured that the calculated prevalence better reflected the prevalence of the entire target population rather than the sample. The cases were separated into three age groups to calculate the age-adjusted prevalence of epilepsy (Table 8).

DISCUSSION

Epidemiological studies relevant to epilepsy provide information about the risk factors that cause epilepsy, the natural course of the disease, and its economic and cultural aspects. Many studies have been conducted to determine the prevalence of epilepsy in the world. However, studies conducted in our country are far from revealing its prevalence. Prevalence studies conducted in developed countries are satisfactory. Prevalence provides important information about the etiology of the disease, reveals the natural history of the event and helps to guide allocation of health resources. The prevalence of epilepsy in developed countries is generally reported to be 6-8/1000. (USA, 6.8/1000; Italy, 6.2/1000; Iceland, 7.7/1000; Estonia, 3.6/1000; Japan, 9/1000; India 22.2/1000,and Turkey 8/1000.[7-12] In our study, the prevalence of clustered epilepsy was found as 3/1000 in females, 5/1000 in males, and 4/1000 for the sum of both groups. Epidemiological studies on the prevalence of epilepsy in certain age groups are scarce in our country.

In our study, a similar prevalence rate (5.6/1000) was found in a study conducted by Aydın et al in the same age group in İzmir.[13] This prevalence rate was lower than the prevalence rate (10.2/1000) in the study conducted by Karaağaç et al., which was performed in different age groups using similar methods.[6] Again in the same age group and using similar methods, the prevalence rate was 8/1000 in the study by Canpolat et al. conducted in Kayseri.[14] The prevalence rate was found as 8.6/1000 in a study conducted by Çan G et al. in 4288 cases aged 0-17 years in Trabzon.[15] Hüseyinolu et al. screened 17,345 patients in Kars between the ages of 6 and 14 and calculated the prevalence rate to be 8.6/1000[16]. In a 1980 study conducted in rural Ankara by Y. Bilgin, the prevalence rate was determined to be 7.39/1000. Seizure classifications, however, were not clear in this research.[17]

Although the different results of the studies depend on genetic, age, and geographical reasons, hiding diseases also emerges as an important problem in studies based on questionnaires.

The prevalence of epilepsy in developing countries varies between 3/1000-42/1000, and the mean prevalence range rate has been found to be 18.5/1000 in population-based studies using the WHO protocol.[18] Prevalence rates have been determined as follows: Guatemala, 5.8/1000; Tanzania, 10.2/1000; Kashmir, 2.4/1000; native population in Panama, 57/1000, and Nigeria, 37/1000.[19-23] In our study, the prevalence rate was found to be lower. The prevalence rate determined in our study is close to the prevalence rates of developed countries.

The prevalence rates of epilepsy in developed and developing countries vary widely between 3-22.2/1000 worldwide. Prevalence rates differ in studies performed due to many important factors as the use of different methodologies, materials, terminology, and diverse patient groups. In a pilot study in which prevalence was investigated with the ICBERG protocol, the prevalence has been indicated as 8/1000, while the prevalence has been reported as 18.5/1000 in the evaluation made with the WHO protocol for the same region.[24,25] Reporting high prevalence rates in the studies conducted in central and south America where the WHO protocol was used, makes us think the prevalence rates differ according to the methods applied. Therefore, the ICBERG protocol has been developed recently and the results of the studies based on the ICBERG protocol are more selective and specific, reflecting the prevalence rates with a more unbiased and accurate probability. The study population is limited to a specific region in all studies conducted in Turkey and in most studies conducted worldwide. Serdarolu et al. in Ankara conducted the most common study on this topic in Turkey.[30] Only one age group was

examined in our research, and this age group is critical in reflecting the general prevalence in Turkey. Since we determined the age-adjusted prevalence rate of epilepsy in our study, the determined prevalence demonstrates the prevalence of the entire target population rather than the sample.

Comparison of socio-demographic findings of epileptics and non-epileptics in our study, have demonstrated that they did not differ significantly between both groups similar to the studies of Karaağaç et al[6] which was considered statistically significant. In their study conducted in Honduras, Medina et al. have found that 67% of epilepsy cases had a family history.[26] This rate has been found to be 22% in the study by Tekle-Haimanot et al.[27] In the study conducted by Al Rajeh et al. in Arabia, it has been found that there was at least one epileptic relative in the family in 24% of epilepsy cases.[28] Studies have shown that the incidence of epilepsy in families of epileptic people is 2.5 times higher than in normal healthy population. Studies have shown that children with epileptic mothers carry a higher risk than children of epileptic fathers. However, in our study, 2.8% of fathers were found to have a positive history of epilepsy, which was not considered significant. In a study conducted by Yaman et al., in familial epilepsies, first, and second degree consanguinities have been found with prevalence rates of 10.3%, and 5.9%, respectively This indicates the importance of environmental factors as well as genetics in the emergence of epilepsy.[29]

Comparison of the prevalence rates of active epilepsy found in our study with the study of Karaağaç et al. performed in Silivri (10/1000, 10.3/1000, 10.2/1000) showed lower prevalence rates[6]. When compared with the study conducted by Aydın et al (4.5 / 1000, 7/1000, 5.6 / 1000), similar prevalence rates were found.[13] Compared to the study conducted by Canpolat et al. (7/1000, 4/1000, 6/1000), lower prevalence rates were obtained.[14] Our study data were found to be similar to the study conducted by Aydın et al. In our study, the prevalence rate of active epilepsy was found to be higher in males compared to females (4/1000 and 2/1000). We thought that this may be due to the fact that exposure to risk factors later in life such as head trauma are more common in males and that males participate more actively in social life.

When comparing the age-adjusted prevalence rates of epilepsy in our study, the study of Aydın et al. found 9.2/1000 for the age group 7-10 years, 12.1/1000 for the age group 11-14 years, and 13.4/1000 for the age group 15-17 years for males, females, and the total population, respectively. It was found to be 15.2/1000, 10.0/1000, 12.6/1000, respectively[13]. On the other hand, Serdaroğlu et al. reported a prevalence rate of 7/1000 at age 7-10 years, 8/1000 at age 11-14 years, and 7/1000 at age 15-17 years.[30] In the study by Canpolat et al. reported 8/1000 at age 7-10 years, 9/1000 at age 11-14 years and 6/1000 at 15-17 years.[14]

When comparing the prevalence of gender-specific epilepsy with the study of Aydın et al. and Canpolat et al., they obtained similar results as in this study.[13,14] In many studies, the prevalence rates of epilepsy in males have been found to be 1.1-1.4 times higher than females. According to the results of the study conducted in our country, the prevalence rates of the male gender are generally higher than the female gender. Except for the study performed by Serdaroğlu et al., there is no statistically significant difference between genders ($p>0.05$). In a study by Tellez-Zenteno et al in Canada, the researchers have found that the prevalence rate of epilepsy was significantly higher in families with low monthly income, low education, and unemployment problems compared to others.[31] In the study of Hesdorffer et al, it has been shown that low socioeconomic level in the adult age group increased the prevalence rate of epilepsy.[32] The fact that there was no statistically significant difference as for the economic level of participants in our study is attributed to the low number of active epilepsy cases and the families may have avoided answering questions about their economic levels.

In a Swedish research on the prevalence of epilepsy, Forsgren et al. reported that an etiologic cause could only be found in 17-57 % of the cases.[33] In the study conducted by Aydın et al., a history of Central Nervous System (CNS) infection has been found in 6 persons (18%).[13] Similar rates were also found in our study, and the risk of developing epilepsy after CNS infection was found to be similar to that reported in the literature.

Many studies have been conducted on the increased risk of developing epilepsy after febrile convulsion. In our study, a history of febrile convulsion was found in 50% of epilepsy patients. History of febrile convulsion was found to be statistically significant in epileptic cases (p=0.000). Different prevalence rates of febrile convulsion which increased the risk of epilepsy have been reported in various studies: (Aydın et al., 25.5%; Cansu et al. 19%; Çalışır et al., 30%; Hüseyinoğlu et al., 7%, and Canpolat et al. 40%).[13,14,16,34] Higher rates were found in our study. It is thought that this is due to the geographical differences of the regions where the studies were conducted. In a study conducted in Rochester Minnesota, USA between 1935-1979, the incidence of clustered epilepsy after febrile convulsion has been found to be 6%.[18] This incidence has been found to be 2.5% after simple febrile convulsion and between 6% and 50% after complicated febrile convulsion.[18] However, in our study, febrile convulsion was not differentiated as simple and complicated febrile convulsion.

Most of the epidemiological studies conducted in Turkey are based on prevalence studies. Moreover, most of these prevalence studies are local surveys. Incidence studies are challenging to perform due to the lack of accurate and regular records. As a result of this study, we concluded that a more comprehensive organization is needed to obtain optimal prevalence rates.

CONCLUSION

When all these study data are evaluated together, epilepsy continues to be an important health problem in our region. As a conclusion, preventable risk factors, especially febrile convulsion, are important as the risk factors for epilepsy, and that the factors causing epilepsy and their prevalence rates should be determined in different socio-economic layers of our country and the actual prevalence should be determined. However, incidence and long-term cohort studies are needed to better determine the etiology of epilepsy.

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Case Report

Herpetic Whitlow: A Case Complicated with Candidemia

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ABSTRACT

Herpetic whitlow is a herpes simplex virus infection of fingers affecting the distal phalanx. The disease is often misdiagnosed as a bacterial infection which leads to inappropriate treatments. In this paper, we reported a case of herpetic whitlow in a 10-month-old girl who is misdiagnosed as bacterial paronychia and treated with surgical intervention and broad-spectrum antibiotics, as a result, she had invasive candidiasis which has a high mortality rate. Physicians should be aware of this entity for correct initial diagnosis and accurate management.

INTRODUCTION

Herpetic whitlow is herpes simplex virus type-1 and type-2 (HSV-1 and HSV-2) infection of fingers characterized by painful, nonpurulent, and erythematous lesions usually affecting the distal phalanx. Herpetic whitlow is rare and its' incidence is 2.4/100000.[1,2] It occurs with inoculation of impaired skin with HSV-1 and HSV-2.[3-6] Because of its rarity, it may be misdiagnosed as bacterial infection, cause inappropriate treatments and complications.[6]

The clinical features of herpetic whitlow should be known by physicians, especially pediatricians, for accurate diagnosis and appropriate treatment. In this paper, a ten-month-old girl who developed candidiasis because of misdiagnosis and inappropriate treatment was described, and the current literature was reviewed.

CASE REPORT

A previously healthy 10-month-old girl presented with swelling, redness and discoloration at the distal end of the third finger of her left hand. One week previously her finger became red, vesicular rash appeared on her affected finger (Figure 1) and had a fever for one day. She was admitted to another hospital on the second day after onset of her symptoms, and hospitalized for four days and treated with intravenous antibiotic therapy and two surgical drainage for bacterial paronychia. Then she was referred to our hospital with a prediagnosis of necrosis because of bruising on her finger (Figure 2).

On clinical examination, there were necrotic and erythematous areas in the distal pulp and around the paronychial region of the third finger of the left hand, three vesicles on the lateral side and two incision scars due to the previous surgical drainage

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attempted in bilateral paronychial regions. No pus was observed. Distal pulses were normal. There were no vesiculer lesions in her mouth. Leukocytes: 5400/mcL, ANS: 2300/mcL, Hgb: 12 g/dL; Plt: 445000/mcL; CRP: 2.1 mg/L, and coagulation parameters were within normal limits. Thrombosis was ruled out due to the presence of vascular flow in both arteries and veins on the Doppler spectral examination of the hand. The X- ray radiogram of fingers was normal. Piperacillin tazobactam and teicoplanin were given with the suspicion of superimposing bacterial infection because of previous hospitalization and two surgical procedures. Intravenous acyclovir was given with suspicion of herpetic vesicles. The molecular tests of vesicle fluid revealed positive HSV-1 DNA. Herpetic whitlow was confirmed and antibiotics were discontinued. Acyclovir treatment was completed to 10 days.

On the eighth day of hospitalization, the patient had a fever. Physical examination did not reveal any focus of infection. Leukocytes: 6700/mcL, ANS: 2100/mcL; Hgb: 11.9 g/dL; Plt: 341000/mcL; CRP: 3.9 mg/L, and urinalysis was normal. Yeast growth was determined in her blood culture taken when she had fever and caspofungin (loading dose of 70 mg/m^2/day followed by 50 mg/m^2/day) was started.

Abdominal ultrasonography, echocardiography and ocular examination were normal in terms of candidal infection. During the follow-up, platelet count decreased 66000/mcL, liver transaminase levels elevated (maximum values were AST: 112 U/L, ALT: 75 U/L). Blood cultures obtained on the following days of antifungal treatment showed no growth. Fever disappeared on the second day of antifungal therapy. Yeast was typed as *C. parapsilosis* which was susceptible to caspofungin (MIC: 0.25 mcg/ml for caspofungin, 0.5 mcg/ml for fluconazole and 0.25 for liposomal amphotericin B, broth dilution method). Systemic antifungal treatment was continued for 21 days. Thrombocytopenia and elevated liver enzymes returned to normal levels during follow-up. Four weeks after the first herpetic whitlow, vesicular lesions developed in the lateral part of the fourth finger of the left hand which was evaluated as recurrence. Any treatment was not recommended, and the lesion disappeared spontaneously within 14 days without development of any additional complications. Since immunodeficiency was not considered in the patient's history, an examination for immunodeficiency was not requested.

DISCUSSION

Herpetic whitlow is an infection characterized by painful, multiple, erythematous non-purulent vesicles formed by HSV type-1 and 2.[4,7] It was first described by Adamson in 1909 in an adult.[8] It is characterized by local swelling, erythema and vesicular lesions following the pain and burning after 2-20 days of incubation. In infants, fever and malaise may be present.[9]

Unlike pus in bacterial infections, lesions have clear fluid. But one week later, a cloudy appearance in vesicle fluid may be present due to white blood cells.[9] In children, herpetic whitlow occurs frequently with autoinoculation or contact between family members if there is herpes stomatitis, herpes labialis, or herpes genitalis.[4,7] No relevant data were found in our patient's history. The diagnosis of whitlow is usually based on clinical suspicion. In the presence of HSV infection in the patient or close contacts, vesicular lesions on the fingers should suggest herpetic whitlow. The diagnosis should be confirmed by the Tzank test, polymerase chain reaction (PCR) and viral culture from the intravesicular fluid.[1,3,6,10] The sensitivity and specificity of the Tzank test is variable depending on the person evaluating it, because of this, recently this test is not preferred.[11] The diagnosis of our patient was confirmed by the detection of HSV- 1 by PCR from the vesicle fluid.

The clinical course of herpetic whitlow in children was described by Szinnai et al.[6] In this study, 42 children who were followed up for herpetic whitlow between 1970-2000, the age distribution of patients shows a peak (72% of all cases) particularly in the first 2 years of life and the most common etiologic agent in this age group is HSV-1 and 65% of cases were initially misdiagnosed as "bacterial paronychia".[6] Our case is also in this age group and HSV-1 positive, also bacterial infection was considered at first and incisional drainage was performed twice, like in reported cases. Recurrences were reported 23% of these children in 2-25 months.[6] Recurrence was observed in our case four weeks after the first

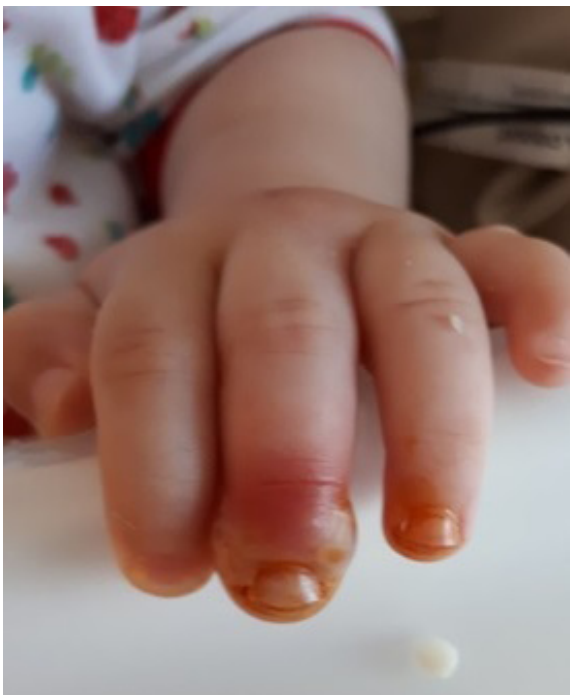

Figure 1. Turbid, yellow and purulent painful vesicles on an intensely ertyhematous base on 1 the medial and lateral side of the third finger

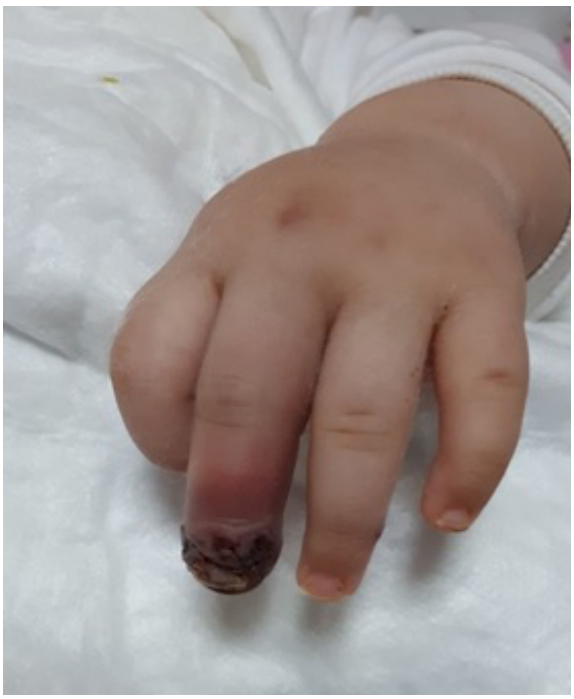

Figure 2. Necrotic areas on ertyhematous base after surgical intervention on the medial and 3 lateral side of the third finger on day 5 of illness

episode. No treatment is necessary for healthy children, but some clinicians have reported that systemic treatment reduces the duration of herpetic whitlow.[6] But systemic acyclovir is indicated for immunosuppressive patients.[12] The initiation of antivirals within 48 hours of symptom onset results in better outcomes.[1] Treatment effectiveness of systemic acyclovir, famciclovir or valaciclovir has not been compared, there is no available data. Topical antiviral therapy is not effective.[1,13] Suppressive therapy with an antiviral agent may be useful for recurrent herpetic whitlow.[1] Antibiotics should be considered in patients with superimposing bacterial infection.[6] Surgery is contraindicated because it can lead to the spread of the infection and may result in secondary bacterial infection. The clinical differentiation of bacterial infection and herpetic whitlow is not always easy. Herpetic whitlow is characterized by less pain, clear vesicles at baseline, long and self-limiting clinical course, and non-responsiveness to antibiotics, with these findings it can be distinguished from bacterial infection. Misdiagnosis may lead to additional infections, serious diseases in immunosuppressed individuals, surgery may cause prolongation of recovery and pain, secondary infection and encephalitis.[6] In our case, due to misdiagnosing, surgical drainage was performed twice and broad-spectrum antibiotics were used because of a possibility of bacterial paronychia. As a result, candidemia developed due to this risk factor.

Candidemia is the fourth most common cause of bloodstream infections.[14] Colonization with Candida spp., prolonged antibiotic use, presence of central venous catheter, hyperalimentation, long-term hospitalization, previous surgery and intensive care are risk factors for candidemia.[15-17] In our patient, there was no risk factor other than broad-spectrum antibiotic use. Candidemia was treated with caspofungin successfully. Misdiagnosis and treatment with antibiotics lead to candidemia which has a high mortality rate. Unnecessary surgical drainage and antibiotic treatment due to misdiagnosis led to both hospitalization with increasing cost and life-threatening infection. In our knowledge, there was no case of candidemia in the herpetic whitlow course.

In summary, herpetic whitlow should be suspected upon manifestation of clinical signs and diagnosis can be made by PCR and viral culture. The disease is self-limited and surgical interventions should be avoided. Physicians should be aware of this entity for correct initial diagnosis and accurate management.

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Case Report

A Rare Location of Subgaleal Dermoid Cyst: Coronal Suture. A Propos of a Child

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ABSTRACT

Congenital dermoid cyst (CDC) is a benign, uncommon and, slow-growing lesion covered with normal skin. Its characteristic manifestation is seen at birth and the sole treatment modality is total excision. The coronal suture is a rare location for the CDCs. Herein, we report a 15-month-old female who had cranial subgaleal CDC located in the left coronal suture. The cyst was completely excised after correct radiological diagnosis with computed tomography and magnetic resonance imaging. The differential diagnosis of slow-growing lesions of the cranium and scalp should be considered in the differential diagnosis.

INTRODUCTION

Congenital dermoid cysts (CDCs) are rare lesions with an incidence of 0.1-0.5% of all tumors in the cranium.[1,2] Embryologically, the CDCs consist of the entrapment of ectoderm throughout the fusion lines.[3] Although CDSs are benign, slow-growing, soft swelling, and non-tender lesions, imaging with computed tomography (CT) and magnetic resonance imaging (MRI) should be performed for the correct diagnosis. The CDCs are usually seen in the midline structure of the brain, however, such lesions can rarely occur at various sites in the skull including coronal suture. There have been very few reports of CDCs arising in the coronal suture. Herein we report a case of completely removed cranial subgaleal CDC which is located in the left coronal suture.

CASE REPORT

A fifteen-month-old female patient was admitted with a history of swelling lesion in the left frontotemporal region of the scalp since birth. There was no history of fever or seizure and the swelling progressively increased in size. Physical examination demonstrated a firm, non-pulsatile, non-tender and non-compressible swelling overlying the left coronal suture. The remaining systemic and neurological examinations were normal. X-ray of the skull showed a radiolucent area in the left coronal suture (Figure 1A). CT demonstrated a cystic lesion within the left coronal suture without evidence of intracranial extension (Figure 1B). Non-contrast MRI showed an extradural lesion, 10x20 mm in diameter, with low-intensity on the T1-weighted images and a

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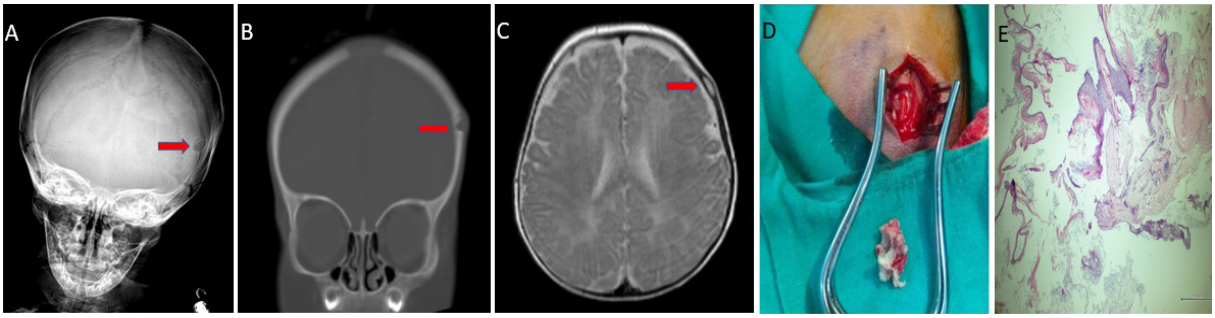

Figure 1. Preoperative X-ray (A), coronal CT bone window of the skull (B), and MRI T2 sequence axial view (C) showing a subgaleal cranial CDC, 10x20 mm in diameter, located in the left coronal suture. Intraoperative appearance of the surgical area and the excised material (D). H.E. × 40; Hematoxylin-Eosin-stained lesion showing keratinized multi-layer flat epithelium that forms the wall of the cystic cavity (E)

high-intensity on the T2-weighted images without apparent connection with the intracranial contents (Figure 1C). A complete excision of the lesion with clear contents was achieved without capsular rupture through scalp incision made over the swelling and the bone structure was carefully curated (Figure 1D). Histopathological examination of the lesion with hematoxylin-eosin staining showed multi-layer flat epithelium that forms the wall of the cystic cavity and the lesion was reported as "CDC" (Figure 1E). The postoperative course was uneventful. The patient was discharged two days after surgery without neurological impairment. Physical and neurological examinations were within normal limits seven months after the surgical intervention.

DISCUSSION

Anatomically, coronal suture is a rare location for subgaleal CDCs. Herein we report a rare case of completely removed subgaleal CDC which was located in the left coronal suture.

CDCs develop from primordial germ cells 3-5th weeks of embryonic life.[4,5] As non-pulsatile and fluctuant masses, they arise from the bones of the calvaria, in particular in cranial suture lines, at birth.[4-6] Histologically, these lesions include a clear fluid and surrounding capsule which is covered with squamous epithelium with various adnexal appendages such as hair follicles, sebaceous, and sweat glands.[7,8] Typically, they develop from inclusion material and produce a well-defined destruction area in the adjacent bone.[9] In the largest series to date, Khalid and Ruge described a total of 159 patients with CDCs; of these, only 14 patients (8.8%) had CDCs along the coronal suture.[10] Its differential diagnosis involves epidermoid cyst of the cranium, sebaceous cysts, lipomas, subgaleal hematoma, hemangiomas, lymphangioma, and abscess of the scalp.[11,12]

Radiologically, X-ray demonstrates the presence of cranial destruction with well-defined sclerotic margins.[4,5] The presence of scalloping involving the outer table of the cranium in X-ray examination is a diagnostic finding. However, CT scan and MRI can reveal the details of the lesion with the underlying anatomic structures.[13]

As a rule, the diagnosis of CDC of the skull has to be confirmed by histopathological examination. In our case, the histological analysis revealed the diagnosis of cranial CDC. Total excision of the CDC of the scalp provides both the correct diagnosis and treatment, as did in our case.[5] Both clinical findings and radiological studies such as CT or MRI may provide further information for differential diagnosis of these tumors from other congenital lesions of the bony skull and scalp macroscopically. Histopathological diagnosis is always required to confirm the diagnosis of CDC. Despite life-threatening complications in some complicated cases, the overall outcome is usually excellent.

In conclusion, CDC is a lesion located in the midline structures of the cranium. The location of coronal suture is rarely seen. Although imaging with CT and MRI, complete surgical excision ensures both exact diagnosis and curative treatment. Herein, we

presented a case of CDS with a very rare location that was treated with successful surgical intervention.

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