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THE IMPACT OF MOTHERS' HEALTH EDUCATION ON THE PREVALENCE OF ACUTE RESPIRATORY INFECTIONS IN CHILDREN*

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SUMMARY: Günay O, Öztürk A, Öztürk Y. (Department of Public Health, Erciyes University Faculty of Medicine, Kayseri, Turkey). The impact of mothers' health education on the prevalence of acute respiratory infections in children. Turk J Pediatr 1994; 36: 1-5.

In this study, the effects of educating mothers on acute respiratory infections were investigated in Hacılar district of Kayseri, a province in Central Anatolia.

The intervention group included 69 children and the control group 57 children between the ages of 0 and 4 years. The children in both groups were checked for symptoms of acute respiratory infections (ARI) in January 1990 and 1991, before and after intervention. The intervention consisted of 30 minutes of face-to-face education of mothers regarding ARI prevention and treatment. In addition, the numbers of clinic visits by children for acute respiratory infections before and after intervention were compared.

The prevalence of acute respiratory infections decreased from 49.3% to 27.5% in the intervention group and from 43.9% to 38.6% in the control group. The decrease in the prevalence of acute respiratory infections in the intervention group differed significantly, from that of the control group. On the other hand, clinic visits by the intervention group for acute respiratory infections increased significantly. *Key words: acute respiratory infections, mother's education.*

Acute respiratory infections (ARI) are one of the most important causes of child mortality in developing countries. ARIs are responsible for the deaths of approximately four million children in the world every year. The great majority of these deaths are in developing countries and in children under five years of age[1-7].

Although the incidence of ARI in developing and developed countries is comparable, mortality of ARI in developing countries is 30-70 times higher than in developed countries. At least one-fourth of total child mortality in developing countries is due to ARI[3,5,7].

The causes and localizations of ARI vary widely[3,6,7]; however, the predisposing factors are almost the same worldwide. For this reason, there are important similarities between various types of ARI in terms of preventive measures and

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basic principles of case management. The general incidence of ARI can be decreased through timely immunization of children against diphtheria, pertussis, measles and tuberculosis, prevention of low birth-weight, breast-feeding, adequate and balanced nutrition, and distancing children from cigarette smoke[3,6,7].

Better case management strategies are needed in developing countries in order to reduce the ARI mortality and case fatality rates. It is known that the treatment of ARI is generally quite inexpensive and easy. The continuing education of community health workers and parents, especially mothers, is very important in order to be successful in controlling ARI[3,6,8]. Community health workers and mothers should know which cases should be seen by health personnel and which cases must be referred to the hospital. This study was performed in order to determine the effects of educating mothers on ARI in children.

Material and Methods

This investigation was done in Hacılar district of Kayseri, a province in Central Anatolia, between January 1990 and March 1991. Hacılar district is 10 km from the provincial center, and its population is approximately 11,000. In the center of Hacılar there is a local health center staffed by three practitioners and eight auxiliary health personnel.

At the time of the investigation, there were 710 children between the ages of 0 and 4 years in the area. One hundred and fifty of these children were randomly selected. All of the children who were selected were visited in their homes in January 1990 and were checked for symptoms of ARI. At the same time, a questionnaire was given to the mothers. The questionnaire contained 20 questions pertaining to certain characteristics of the children and their families.

The children were then divided randomly into two groups. One group was chosen to be the intervention group, and the other the control group. The mothers of the children in the intervention group were visited again in November 1990. They were educated about prevention and treatment of ARI in children and were each given a booklet about ARI. The mothers were educated face-to-face for approximately 30 minutes in their homes by the health center's doctor. The booklet given to the mothers described principles for prevention and treatment of ARI in children.

The children in both groups were visited for the final time in January 1991 and were again checked for symptoms of ARI. In addition, the records in the local health center were examined and the charts of children who suffered from ARI were evaluated. The practitioner who made the final visit and the person who examined the medical records were unaware of whether the children were in the intervention or the control group.

Twenty-four children were excluded from the study: nine of them left the reseach area in 1990, and 15 children could not be found at home in January 1991 in three attempted visits. For these reasons, 69 children in the intervention group and 57 in the control group were evaluated. Khi square test and student's t test were used to compare the groups.

In January 1991, the prevalence of acute lower respiratory infections was found to be 2.9% in the intervention group and 3.5% in the control group. Acute upper respiratory infections formed nearly 90% of total ARI cases in the both groups.

Discussion

As shown in Table I, there was no significant difference between the study groups in terms of characteristics which may affect ARI. The ages shown in the table were the children's ages in January 1990. It was found that in both groups, families were generally large and annual family incomes rather low.

In Table II, ARI prevalences in January 1990 and January 1991 and decreases in ARI prevalences in the study groups are shown. In both groups, ARI prevalence in January 1991 is lower than in January 1990. The decrease in the control group may be a result of the children's growth in one year. ARI is known to be more prevalent in children under two years of age[4]. The prevalence of ARI in the intervention group decreased by 21.8%, whereas the decrease in the control group was only 5.3%, yielding a statistically significant difference between groups ($p < 0.05$).

Table I: Selected Characteristics of The Study Groups

Characteristics	Intervention Group (n = 69)	Control Group (n = 57)	P
Age (Months) (Mean ± SEM)	22.3 ± 1.8	25.7 ± 1.9	> 0.05
Sex of Children			
Male (%)	44.4	43.9	> 0.05
Female (%)	55.6	56.1	> 0.05
Mothers' Age (Mean ± SEM)	27.7 ± 0.6	28.2 ± 0.6	> 0.05
Fathers' Age (Mean ± SEM)	30.7 ± 0.7	30.6 ± 0.7	> 0.05
Mothers' Literacy (%)	76.8	73.7	> 0.05
Fathers' Literacy (%)	100.0	100.0	> 0.05
Smokers at Home (%)	75.4	70.2	> 0.05
Family Size (Mean ± SEM)	5.50 ± 0.15	5.47 ± 0.17	> 0.05
Annual Family Income ($ US) (Mean ± SEM)	2484 ± 180	2352 ± 168	> 0.05

Table II: ARI Prevalence in Study Groups Before and After Intervention

Study Groups	n	ARI Prevalence (%) Before Intervention (January 1990)	ARI Prevalence (%) After Intervention (January 1991)	Decrease in Prevalence (%)
Intervention	69	49.3	27.5	21.8
Control	57	43.9	38.6	5.3
Total	126	46.8	32.5	14.3

$t = 2.63$
$p < 0.05$

In Table III, the number of clinic visits by the children because of ARI and increases in clinic visits in both groups are shown. In both groups the number of clinic visits in 1991 was higher than in 1990. The effects of mass media and educational activities of health personnel may have caused some increases in clinic visits. It is meaningful that while clinic visits increased, ARI prevalence decreased. Clinic visits increased 23.2% in the intervention group and only 7.1% in the control group. The difference between the two groups was statistically significant ($p < 0.05$).

The results of this study indicate that mothers should be educated in order to decrease the prevalence of ARI in children between the ages of 0 and 4 years. In addition, ARI cases may be treated more effectively and ARI mortality may be reduced. Better case management strategies have been given priority in the control of ARI because it is more difficult to prevent ARI cases. However ARI incidence can be also reduced through adequate education of families.

Table III: Applications to The Health Center Because of ARI in the Study Groups Before and After Intervention

Study Groups	n	Application to The Health Center: Before Intervention (January-February 1990) No	%	After Intervention (January-February 1991) No	%	Increase in Application %
Intervention	69	24	34.8	40	58.0	23.2
Control	57	19	33.3	23	40.4	7.1
Total	126	43	34.1	63	50.0	15.9

$t = 2.46$
$p < 0.05$

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EFFECT OF EXCHANGE TRANSFUSION ON ELIMINATION OF ANTIBIOTICS IN PREMATURE INFANTS*

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SUMMARY: Özkan H, Çevik N. (Department of Pediatrics, Dokuz Eylül University Faculty of Medicine, İzmir, Turkey). Effect of exchange transfusion on elimination of antibiotics in premature infants. Turk J Pediatr 1994; 36: 7-10.

Although the use of exchange transfusion has become routine in intensive care nurseries, little information is available on drug loss resulting from exchange transfusion. The aim of this study was to review the effect of exchange transfusion on the elimination of some antibiotics in premature infants according to the recent pharmacokinetic data. A pharmacokinetic equation was used to estimate drug loss from the body by exchange transfusion. Our data suggest that exchange transfusion can significantly decrease the serum concentrations of antibiotics with smaller volumes of distribution, but the drug loss of antibiotics with larger volumes of distribution can be acceptable. *Key words: exchange transfusion, antibiotics, premature infants.*

Exchange transfusion is commonly used in neonatal intensive care units in the management of certain newborn disorders such as hyperbilirubinemia, neonatal sepsis and disseminated intravascular coagulation[1]. Ill neonates undergoing exchange transfusion frequently receive concomitant antibiotic therapy. Because drugs are removed by exchange transfusion, the need to replace removed antibiotics or alter the dosage regimen is generally questioned. There are very few reports about the effect of exchange transfusion on serum antibiotic concentrations[2-6]. Although a pharmacokinetic equation for predicting drug loss has been described and hypothetical drug loss by exchange transfusion has been calculated[7], there is no information in the literature about recently used antibiotics in regard to exchange transfusion.

The aim of this study was to determine the effect of exchange transfusion on elimination of some antibiotics in premature infants according to recent pharmacokinetic data.

Material and Methods

In the present report, a one-compartment pharmacokinetic model with first-order elimination was used to calculate the hypothetical drug loss by two-volume

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exchange transfusion. The relationships of volume of distribution, elimination rate constant, and time after dosing on the fraction of the dose eliminated in the blood exchange were developed on the basis of a one-compartment body model. Drug loss from the body by two-volume exchange transfusion was calculated using a pharmacokinetic equation:

$$1 - e^{V / Vd}$$

Where V: plasma volume exchanged (determined from post-transfusion hematocrit) (liters) and Vd: apparent volume of drug distribution (liters).

In this model, the mean gestational age of the study group was 31.34 ± 4.45 weeks, mean birthweight was 1717.2 ± 875.1 grams, and mean postnatal age was 4.19 ± 4.20 days. All patients underwent two-volume exchange transfusion at a dose of 200 ml / kg for hyperbilirubinemia. At the time of exchange, the patients were receiving concomitant antibiotic therapy. Post-transfusion hematocrit of these premature infants was 0.416 ± 0.050. All data were derived from a recent report[8] and used for V in the equation.

For Vd, mean volumes of distribution of antibiotics according to recent reports in the literature were used (Table I). The reported values of Vd in these studies were derived from pharmacokinetic studies performed in newborn infants with normal rates of drug metabolism and elimination.

The hypothetical drug loss by two-volume exchange transfusion was calculated using the above-mentioned pharmacokinetic equation.

Table I: Mean Volumes of Distribution and Hypothetical Drug Loss by Two Volume Exchange Transfusion in Preterm Babies

Drug	Vd (L / kg)	Percent Loss
Amikacin[9]	0.57	18.5
Aztreonam[10]	0.29	33.5
Cefotaxime[11,12]	0.45*	23.0
Gentamicin[13-16]	0.54*	19.4
Netilmicin[17]	1.19	9.3
Ticarcilline/[18]	0.34	29.0
Clavulanate	0.41	25.0
Vancomycin[19-21]	0.55*	19.1

* An average value according to the reported mean Vd (L / kg) values in these studies.

Results

Drug loss for each antibiotic by exchange transfusion in preterm infants was calculated (Table I). As can be seen in the table, drug loss by exchange transfusion for most of the antibiotics evaluated was negligible. However, considerable loss of aztreonam and ticarcilline was calculated.

Discussion

As can be seen in Table I, considerable loss of aztreonam and ticarcilline was calculated. The reported percentages of gentamicin lost by exchange transfusion are similar to the percentage estimated in this calculation[5,6]. Hypothetical drug loss by exchange transfusion for amikacin, gentamicin and vancomycin in the study was found to be greater than that predicted by Lackner[7]. The difference can be explained by the higher blood and plasma volumes[22] and lower post-transfusion hematocrit values of premature infants[8]. The hematocrit value of 0.54 used by Lackner[7] is a remarkably high post-transfusion hematocrit value for preterm infants in comparison to the value mentioned above[8]. As expected from the equation, both of these factors increase drug loss by exchange transfusion. No information is available in the literature on measured or calculated drug losses of aztreonam, cefotaxime, netilmicin and ticarcilline / clavulanate resulting from exchange transfusion. Our data suggest that unless exchange transfusions are repeated and performed during the distribution phase rather than elimination phase, the drug loss of antibiotics with larger volumes of distribution can be acceptable. On the other hand, exchange transfusions can significantly decrease the serum concentrations of antibiotics with smaller volumes of distribution, and an alteration in dose may be necessary in critically ill premature neonates.

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EPIDEMIOLOGY IN PEDIATRIC ANESTHESIA
A Computerized Survey of 10,000 Anesthetics*

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SUMMARY: Esener Z, Üstün E. (Department of Anesthesiology, Ondokuz Mayıs University Faculty of Medicine, Samsun, Turkey). Epidemiology in pediatric anesthesia. Turk J Pediatr 1994; 36: 11-19.

The practice of anesthesia in 10,000 children was analysed and evaluated with the aid of Epi-Info, Version 5. There were 545 newborns, 1573 infants, 3147 children between the ages of 1 and 5 years, and 4735 children between the ages of 6 and 15 years. Female: male ratio was 1:1.9. In 92% anesthesia was provided for surgical and in 8% for diagnostic procedures. The most common sites of surgery were head and neck (19%), eye (12%), genitalia (9%) and inguinal region (8%). The type of admission was elective in 76%, emergency in 16% and outpatient in 8% of patients. The distribution within the ASA classes was 92% in I, 4% in II, 2.7% in III and 1.1% in IV + V. Premedication was given to 66% of cases. 98.5% had a general anesthetic and the remaining were given regional blocks. Induction was carried out with intravenous agents in 59% and maintenance with inhalational agents in 92%. The use of muscle relaxants was 82%, mainly succinylcholine followed by vecuronium. Endotracheal intubation was done in 86% of cases, with serious difficulties in 1.3%. 91% of the newborn babies were intubated, 2.8% with difficulty. 9.2% had blood transfusions. There were serious complications in 4.4% and 28 cardiac arrests, of which 20 were successfully resuscitated. Epi-Info, Version 5 was found satisfactory for epidemiological analysis and evaluation in anesthesia, and the information obtained with its aid was discussed in light of published data. *Key words: pediatric anesthesia, epidemiology, computer programs, Epi-Info.*

The practice of pediatric anesthesia and its autcome in 10,000 children were evaluated with the aid of Epi-Info, Version 5, a general-purpose computer program designed to facilitate the management and analysis of epidemiological data[1,2]. Various computer-based schemes especially for record-keeping as well as retrieval and analysis of information from large and multi-centre series have been used[3-7]. Epi-Info, the program utilized in this study, contains modules for: defining data entry screens; setting data entry validation checks; performing data entry and update; and producing summary analyses. There are five versions in this family, of which Version 5 was used in this survey.

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Material and Methods

A set-up based on Epi-Info, Version 5 was prepared for obtaining a suitable set of statements to describe the patient's history and anesthetic management. Forty-three parameters (Table I) obtained from the anesthetic records of 10,000 children betwen the ages of 0 and 15 years, given anesthetic over a 10 year period (1981-1991), were fed into 11 entry screens and analysed. Entry of each record took three minutes. Results of the analysis and evaluation of information so obtained were presented and discussed in light of published data.

Table I: Parameters Arranged in 11 Entry Screens and Fed Into Epi-Info for Each Patient

1. Date
2. Name
3. Surname
4. Protocol no
5. Sex
6. Weight
7. Diagnosis
8. Surgical Department
9. Type of surgery
10. Site of surgery
11. Type of admission (E, EM, OP)
12. ASA classification
13. Presence of CED
14. Type of CED
15. Blood group
16. Premedication
17. Anesthetic technique
18. Gas conduit (tube, mask, tracheostomy)
19. Type of intubation
20. No of endotracheal tube
21. Difficulty in intubating
22. Cause of difficulty
23. Type of induction
24. MR at induction
25. MR for maintenance
26. Inhalational agent
27. iv anesth for maintenance
28. iv analgesics for maintenance
29. Type of regional block
30. Local anesthetic used
31. iv fluids
32. Amount of blood transfused
33. Methods of monitorization
34. Type of CVS complication
35. Type of R complication
36. Other complications
37. Complication at recovery
38. Duration of anesthesia
39. Surgical position
40. Anesthetist (supervising)
41. Anesthetist (junior)
42. Notes

E : Co-existing disease.
EM : Elective.
OP : Emergency.
CED : Outpatient
MR : Muscle relaxant.
CVS : Cardiovascular.
R : Respiratory.

Results

The annual number of operations increased as the provision of surgical and anesthetic services increased in our hospital. The overall percentage of children in the total number of patients given anesthesia was 30.6.

Distribution of Age and Sex : There were 545 (5.5%) newborns, 1573 (15.7%) infants, 3147 (31.5%) children between the ages of 1 and 5 years, and 4735 (47.3%) children between the ages of 6 and 15 years. The overall female to male ratio was 1:1.9 (3469 vs 6531).

Types and Sites of Procedures : In 92% of the children, anesthesia was provided for surgical interventions, and in 8% for diagnostic procedures such as examinations, radiological or endoscopic investigations. The common sites of surgery are shown in Fig. 1. The majority of the operations were carried out by the Pediatric Surgery, Ear, Nose and Throat, Ophthalmology and Orthopedics Departments. The distribution of elective, emergency and outpatient cases was 76%, 16% and 8%, respectively.

Preoperative Clinical Status : Patients were classified according to their general conditions based on the classification of the American Society of Anesthesiologists (ASA)[8] as follows; (I) A normal healthy patient; (II) A patient with a mild systemic disease; (III) A patient with a severe systemic disease that limits activity but is not incapacitating; (IV) A patient with an incapacitating disease that is a

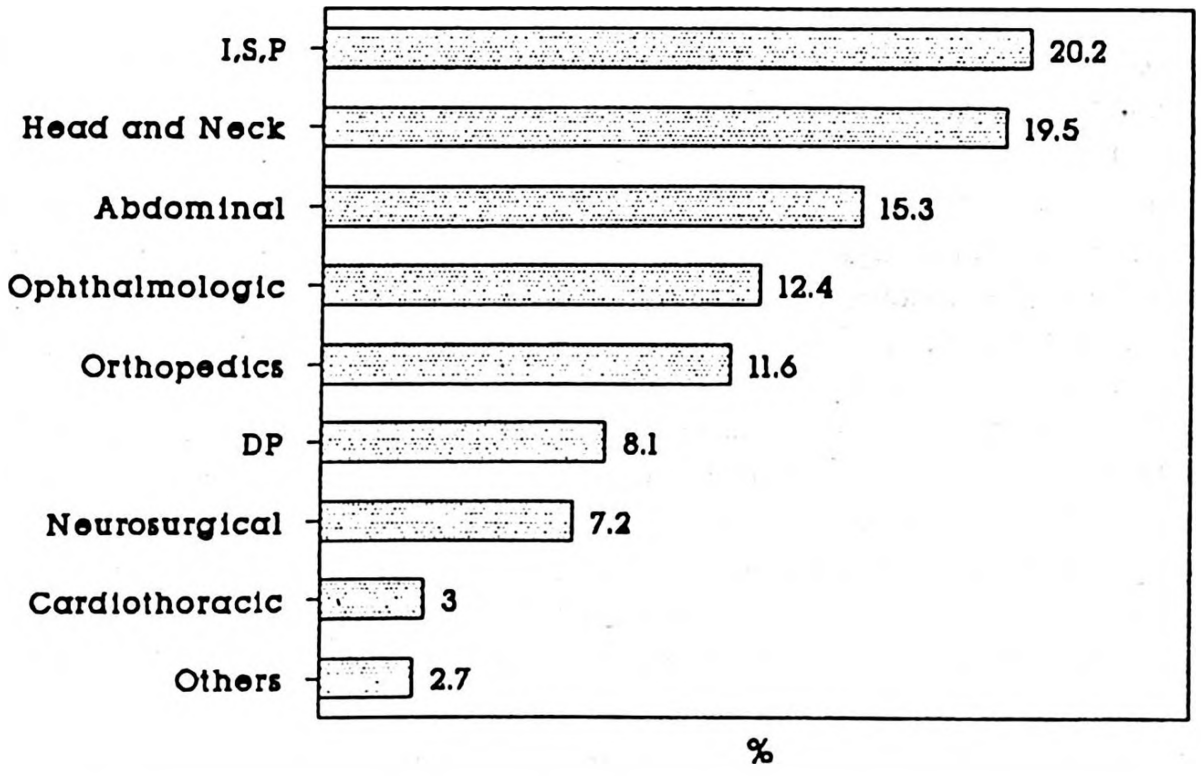

Fig. 1: Sites of surgery (I,S,P inguinal, scrotal and perineal, DP diagnostic procedure).

constant threat to life; and (V) A moribund patient not expected to survive 24 hours with or without an operation. ASA classes were recorded in 9418 patients. The distribution of these patients to the ASA classes were 92% in I, 4% in II, 2.7% in III and 1.1% in IV + V. Table II shows the distribution of ASA classes by age. In 7% of the children, co-existing diseases involving major systems were present.

Table II: Distribution (%) of ASA Classes by Age (ASA Class was Recorded on The Anesthetic Chart in 9418 Patients Out of 10,000)

ASA Class	Newborn	Infant	1-5 Yr	6-15 Yr	Total	
I	89.7	92.0	92.0	92.2	92.1	(8671)
II	6.2	4.3	4.2	3.7	4.1	(386)
III	2.9	1.8	2.5	3.0	2.7	(252)
IV-V	1.2	1.0	1.3	1.1	1.1	(109)

Premedication : 66% of the children were premedicated with various agents. In these children, overall use of atropine was 67%, decreasing to 33% in 1991, and there has been a substantial increase in the use of sedative and anxiolytic drugs over the years.

Type of Anesthetic : 98.5% of the patients had general anesthetic only. The remaining had regional blocks, mainly caudal combined with general anesthesia or sedation. Mean duration of anesthesia was 80 ± 62 minutes.

Induction and Maintenance of Anesthesia : Induction was carried out with various intravenous agents in the majority of children (59%), mainly with thiopental (50%) followed by ketamine (7%). Use of inhalational anesthetics, mainly halothane (40%), for induction decreased with age, whereas maintenance was carried out mainly with inhalational agents (92%). Overall distribution of the use of halothane, isoflurane and enflurane for maintenance were 90.7%, 5.1% and 2.8%, respectively. Unless a contraindication was present, nitrous oxide was used routinely in these patients.

Muscle Relaxants : The overall use of muscle relaxants was 82%, mainly succinylcholine followed by vecuronium. Succinylcholine was used in 94% (n = 7607) of these children to aid endotracheal intubation and in 35% (n = 3392) during maintenance.

Endotracheal Intubation : was done in 86% of children, orally in 99.6% of cases. In the remaining patients, gas conduit was provided by a mask, a tracheostomy

tube or a bronchoscope. Forty of the 545 (7.3%) newborns were intubated awake. In 108 (1.3%) children, serious difficulties were encountered during laryngoscopy and intubation. Ninetyone percent of the newborn babies were intubated, 2.8% with difficulty. Causes of difficulty and their distribution by age are shown in Fig. 2. Four major causes of difficulty in order of appearance were epiglot obtructing the view (25%), soft tissue tumors or injuries (13.4%), restricted movement of jaw and neck (9%) and short, thick neck (5.4%).

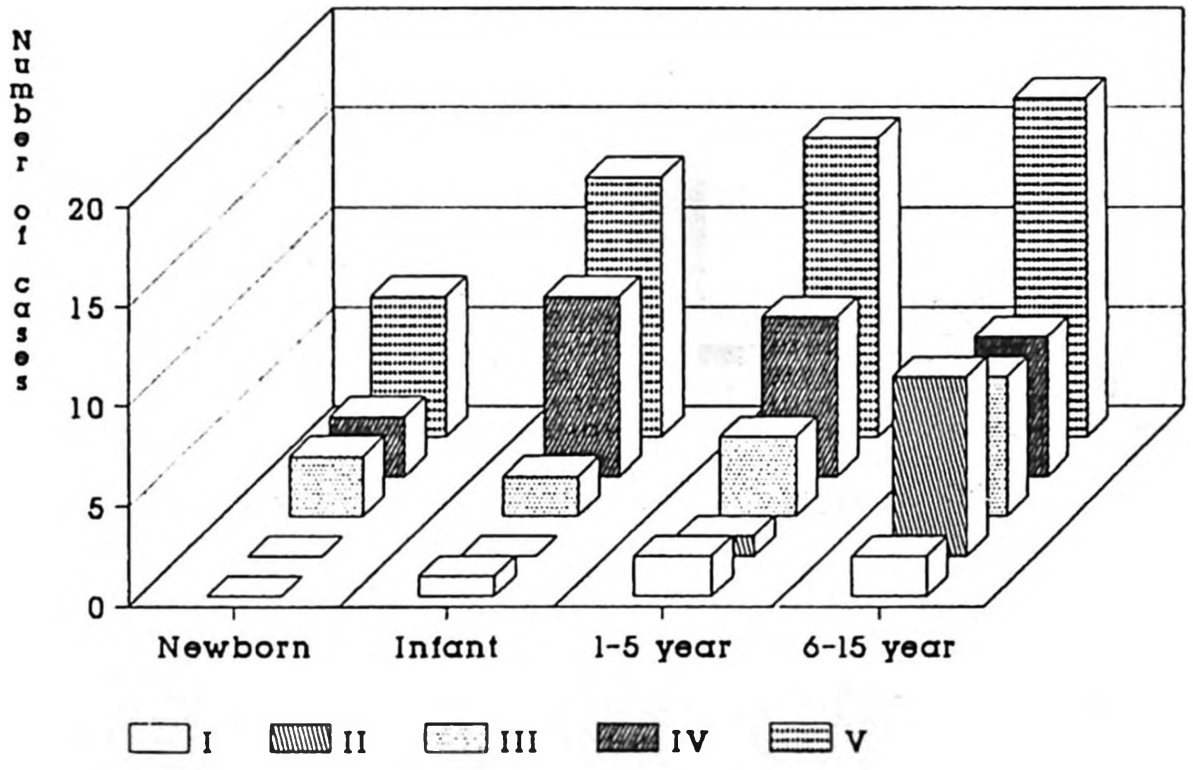

Fig. 2: Distribution of the causes of difficulty in intubating. I. Short, thick neck, II. Soft tissue tumors or injuries, III. restricted movement of jaw and neck, IV. problems arising from epiglot, V. others or unspecified.

Intravenous Fluids and Blood Transfusion : All the patients had an IV drip either before or after induction of anesthesia, and 9.2% of the patients had an intra-operative blood transfusion.

Complications and Mortality During Anesthesia : In 4.4% of the cases there were serious complications, mainly circulatory (66%) followed by respiratory problems (14%). In 7% (n = 32) of these children, anaphylactoid or allergic reactions were observed (Fig. 3). During anesthesia there were 28 cardiac arrests, of which 20 were successfully resuscitated. All of the 8 peri-operative deaths (two newborns, one infant, and five in the 1-5 year age-group) occurred in ASA class III or higher, and operations performed on these patients were major (intracranial in four,

abdominal in one and cardiac in three). The incidence of perioperative mortality and complications in our series was also higher among emergency procedures (0.184%) compared to elective and outpatient cases (0,066%) (Fig. 4).

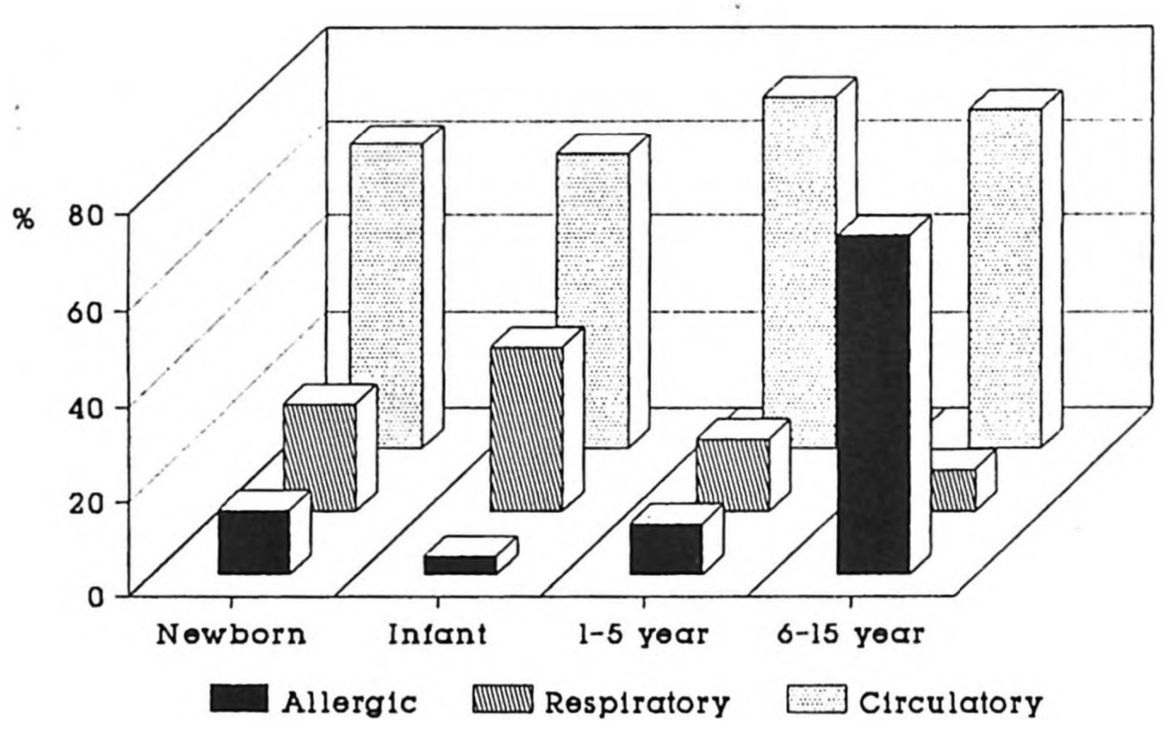

Fig. 3: Distribution of complications by age.

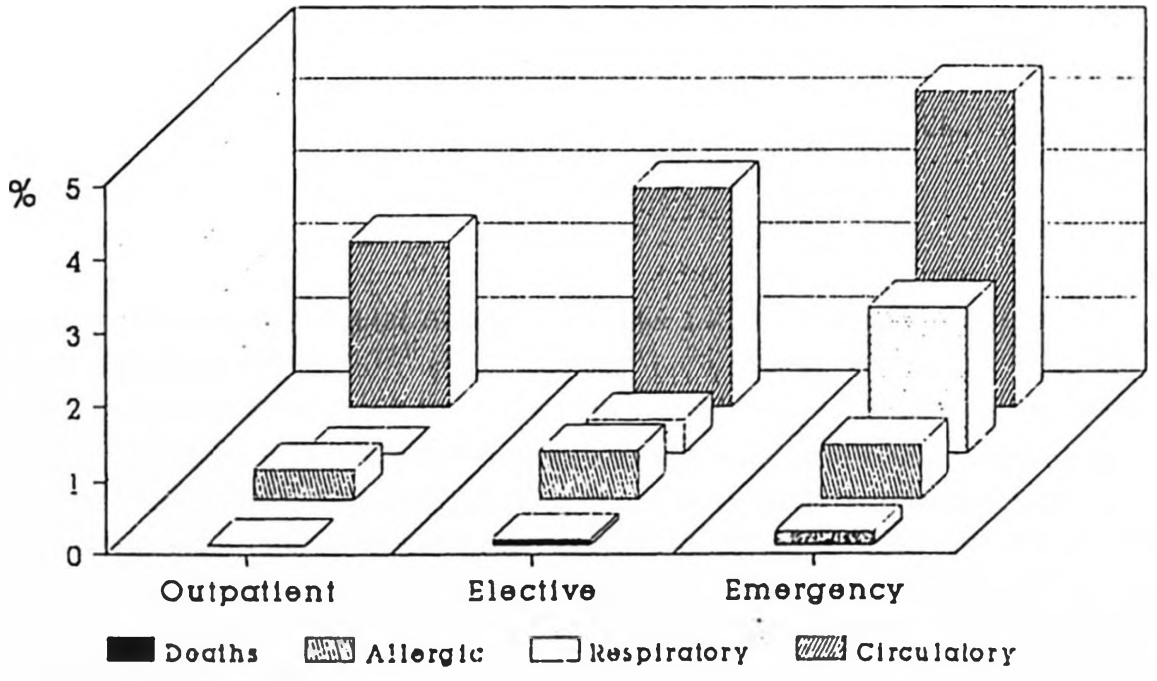

Fig. 4: Distribution of deaths and complications by the type of admission.

Discussion

Although various computer-based schemes for record keeping as well as retrieval and analysis of information from large and multi-centre series have been used, Epi-Info program, set up to meet our record-keeping standards was found to be easy, fast and satisfactory for data retrieval and analysis. Apart from containing modules for defining data entry screens, performing validation checks, facilitating data entry and update, and producing summary analyses, Epi-Info can also convert its files to other data file formats including dBase III, Lotus 1-2-3, Statistical Analysis System, and Statistical Package for Social Sciences PC formats or vice versa. There are five versions in this family, and the programs are in the public domain and may be copied freely. In order for any decision-making process to be computer-assisted, it is necessary for the information to be encodable in some way so that the computer can manipulate the data using logical operations. In this study, the information used to generate an anesthetic regimen included 43 parameters arranged in 11 entry screens for obtaining a suitable set of statements to describe the patient's history and anesthetic management. This set-up can be arranged to suit the needs and the protocol of any anesthetic department.

In our series, children comprised more than 30% of the patients. This may be due to the early establishment of the Pediatric Surgical Department in our newly founded Medical School.

The practice of premedication has changed over the years. Routine use of atropine, seen in 67% of cases in the total sample, was reduced to 33% of the children during the last year. There was a substantial increase in the use of sedatives and anxiolytics such as the butyrophenone and benzodiazepine drugs.

The choice of anesthetic technique was general anesthesia in the majority of patients. But the use of regional blocks combined with sedation or light general anesthesia is increasing. In our series, regional block was utilized in 1.5% of the children. Tiret et al[9] also reported 0.5% regional anesthesia in this age-group. The majority of the children had an intravenous agent for induction and an inhalational agent for maintenance. Although the use of halothane for maintenance was still approximately 90%, this percentage has decreased with the availability enflurane and isoflurane. Overall use of muscle relaxants was 82%, mainly succinylcholine followed by vecuronium. Succinylcholine was used in 94% of these children to aid endotracheal intubation and in 35% during maintenance. Due to concerns about its side effects and the availability of newer, fast-acting, medium-duration, non-depolarizing agents, use of succinylcholine has decreased considerably during recent years. The endotracheal intubation rate was higher in the newborn group (91% compared to 86% in the total pediatric population) and was associated with a higher incidence of difficulty (1.3% vs 2.8%). Unfortunately in nearly half of the cases, the cause of the difficulty was not noted. Although 7.3%

of the newborn babies were intubated awake, during recent years this practice has been limited to babies in very poor condition or to times when the anesthetist is not confident that intubation can be achieved without hypoxia.

Accidents were traditionally considered more common in children than in adults, but anesthetic morbidity and mortality in children have been lowered dramatically in recent decades. However, it is difficult to make comparisons between the series due to the differences in definitions, especially of "anesthetic death". The rate of anesthetic mortality in children has been reported to be 0.2 in 10,000[10], 0.7-1.3 in 10,000[11], and 1 in 40,000[9]. But the patients in these series were predominantly ASA class I and II. Other studies have reported overall anesthetic death rates in children as 12.8 per 10,000 operations, and one for every 300 children in ASA class III-V[12], whereas Hickey et al[13] report no anesthetic-related deaths in 500 children, the majority of whom were in ASA III-V. In our series the frequency of complications and deaths was closely related to the ASA grades and co-existing diseases. All of the perioperative deaths occurred in children with ASA class III or higher undergoing major surgery. The incidences of perioperative mortality and morbidity in our series were also higher in emergency procedures compared to elective cases.

Conclusion : The records and computer programs used in this study were found satisfactory for epidemiological research and capable of many more applications, and the data so obtained were found to be in accordance with current literature in pediatric anesthesia.

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CONGENITAL NASOLACRIMAL DUCT OBSTRUCTION IN KAYSERİ, TURKEY*

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SUMMARY: Ekinciler ÖF, Doğan H, Tatlışen N, Karaküçük S. (Department of Ophthalmology, Erciyes University Faculty of Medicine, Kayseri, Turkey). Congenital nasolacrimal duct obtruction in Kayseri, Turkey. Turk J Pediatr 1994; 36: 21-33.

Congenital nasolacrimal duct obstruction was diagnosed in 170 patients between 1982 and 1991 in Kayseri, Turkey, and 111 patients were treated with massage plus topical antibiotics (MBC), pressure irrigation (PI), probing (PRB) or infracturing of the inferior turbinate (INF). The ages of the patients ranged from one week to 15 years. The obstruction was bilateral in 38 patients.

Among the 149 obstructed lacrimal drainage systems of 111 patients, 101 were cleared by MBC (67.8%), 30 by PI (20.1%), eight by PRB (5.3%) and two by INF (1.3%). Eight cases were unsuccessful (5.3%), and the overall success rate was 94.6%.

The efficacy of four interventions was correlated to the patients' ages and to the presenting pathology. MBC carried out at the serofibrinous stage and at 7-13 months was more effective than other interventions, with a statistical significance ($p < 0.01$).

The effectiveness of four interventions is discussed, with an emphasis on the importance of early MBC. The importance of fluoroscopy during PI or PRB is also emphasized. *Key words: nasolacrimal duct, neonatal dacryocytitis, pressure irrigation, probing, fluoroscopy.*

Early inflammation of the lacrimal sac and congenital nasolacrimal duct obstruction (CNLDO) is a common disorder encountered by ophthalmologists and pediatricians. Although it is generally agreed that the canalization of the lower end of the nasolacrimal duct (NLD) is completed by the 8th or 9th month of intrauterine life, some authors have suggested that this happens just before birth[1]. If the nasal orifice of the NLD is obstructed by a membranous process called the valve of Hasner, epiphora and dacryocystitis can develop. If this obstruction is not cleared, fibrosis of the duct, mucocele, pericystitis, fistula or even orbital cellulitis can occur. The incidence of CNLDO is the subject of some conflict, reported as 1.75-6%[2,3], 5-15%[4] or 20%[5] by different authors. Cassady[6], in a study of stillbirths, found that 13 of 15 NLDs were obstructed. Nordlaw and Vennerholm[7], in an investigation of 100 patients with CNLDO, found that the failure originated

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from the punctum and canaliculi in 12, from the duct and canaliculi in 21, and from the NLD in 67. Abnormalities within the nasal passages, such as the impaction of the inferior turbinate on the opening of the NLD, may also contribute to the obstruction of the duct[8].

Clinically, infants with CNLDO usually present with epiphora or discharge of various types in their eyes. The initial serous discharge becomes fibrinous and later on, purulant. At this stage, copious mucopurulent secretion emerges when the lacrimal sac is compressed[9].

There is much controversy as to the appropriate management of CNLDO. It is stated that massage applied to the sac plus topical antibiotics is highly successful in relieving the obstruction. Price[10] found that the cure rate by this approach was 94.6% by the age of 2 years in a study of 203 patients.

Guerry and Kendig[3] stated that this approach was highly successful in their series. Nucci et al[11] also obtained a cure rate of 93% for children aged 1-12 months, and 79% for those aged 1-2 years with this conservative approach.

If massage and / or topical treatment (MBC) proves ineffective, pressure irrigation (PI), probe application (PRB), infracturing of the inferior turbinate (INF) or silicone intubation[12] may be performed as further procedures of choice. One of the standard dacryocystorhinostomy techniques may be performed as the last procedure, should all other procedures fail.

The purpose of this study was to discuss the effectiveness of MBC, PI, PRB or INF in the treatment of CNLDO. The effectiveness of various forms of therapy was also correlated to different age groups as well as to the presenting pathology (serofibrinous or purulant) of the obstruction.

The importance of early conservative treatment at the serofibrinous stage is also emphasized. A novel technique of probing carried out essentially under fluoroscopy, with a potential of more satisfactory results and less complications, is also discussed.

Material and Methods

One hundred and seventy patients with CNLDO were evaluated in this study. The patients were referred to the ophthalmology clinic of Erciyes University Hospital between 1982 and 1991. Fifty-nine of these patients failed to come to the clinic for follow-up and thus were eliminated from this study.

Of the remaining 111 patients, 65 were male (58.6%) and 46 female (41.4%). The ages of the patients ranged from one month to 15 years. Obstruction was bilateral in 38 patients (34.2%). Hence, 149 lacrimal drainage systems were evaluated. In an attempt to evaluate the effectiveness of treatment in different age groups, five

groups were formed. The distribution of the lacrimal drainage systems to five age groups were as follows:

0 - 6 months: 36 systems (24.2%)
7 - 13 months: 36 systems (24.2%)
14 - 18 months: 13 systems (8.7%)
19 - 24 months: 21 systems (14.1%)
24 + months: 43 systems (28.9%)

The secretion was serofibrinous in 98 systems (65.8%) and purulent in 51 (34.2%). Regardless of the age of the patients or the presenting pathology, the regimen was started without delay. The treatment consisted of four consecutive procedures designed such that only those who did not benefit from the previous procedure were referred to the next.

As an initial step, conservative treatment which consisted of massage together with administration of 7% sodium biborate eye solution and 10% chloramphenicol eye drops (MBC) was applied to all patients for three weeks.

Massage instruction was given as follows: The lower punctum was occluded and the sac compressed by the index finger, which stroked downwards along the path of the NLD. This maneuver was repeated 15 to 20 times a day. With the help of this maneuver, the hydraulic pressure within the sac was increased and the likelihood that the obstruction would be cleared was increased[13]. The treatment was continued for another three to four weeks regardless of the outcome of the therapy. Those who did not benefit from MBC after six or eight weeks were referred to the operating room for PI under general anesthesia. PI was performed by inserting a nasolacrimal cannula via the upper punctum, occluding the lower punctum with forceps to increase the hydraulic pressure inside the sac. Dacryocystograms were obtained before and after PI in order to visualize the nasolacrimal system.

Probing via the upper punctum was performed with a Bowman probe if the PI failed to clear the obstruction. An image intensifier fluoroscope (WHA - Shimadzu) was used in the operating room and probing performed under its guidance; in addition, photographs were obtained from the fluoroscopy screen (Canon AE - 1 camera, f: 35 / 105 mm; OrWo Black White 80 ASA film, processed for color printing with Fujicolor paper).

A careful intranasal examination was done in all cases. If the inferior turbinate seemed to be impacted on opening of the NLD, it was pushed medially and cracked in an upward rotation with a periosteal elevator. The probe was then inserted from the upper punctum and passed into the inferior meatus. Irrigation was repeated thereafter to confirm the patency of the passage.

During this procedure, patients, doctors and technicians were protected by lead

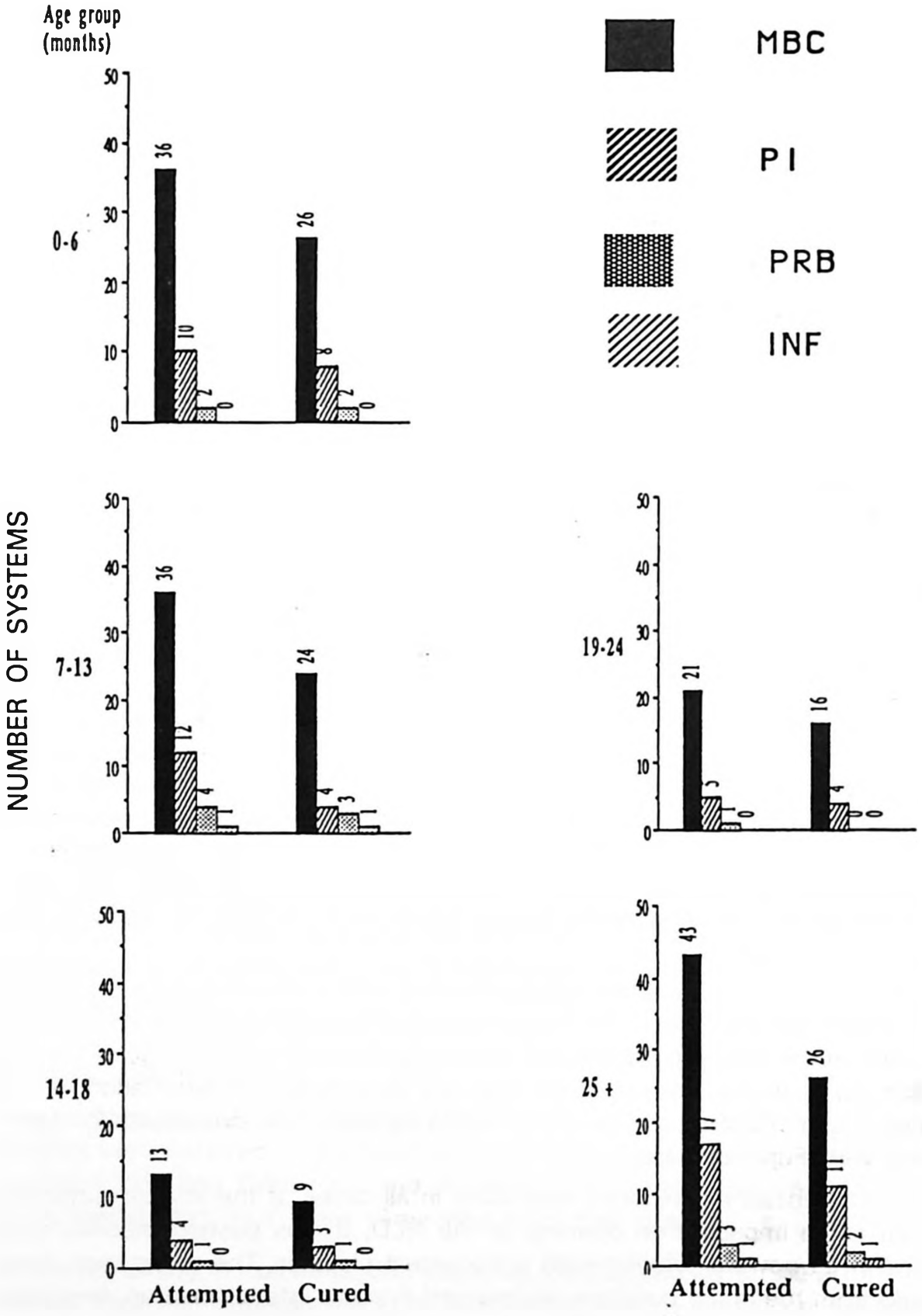

Fig. 1: Results of massage + biborate + chloramphenicol (MBC), Pressure irrigation (PI), probing (PRB) or infracturing of the inferior turbinate (INF) correlated to age. The difference is not statistically significant ($p > 0.05$).

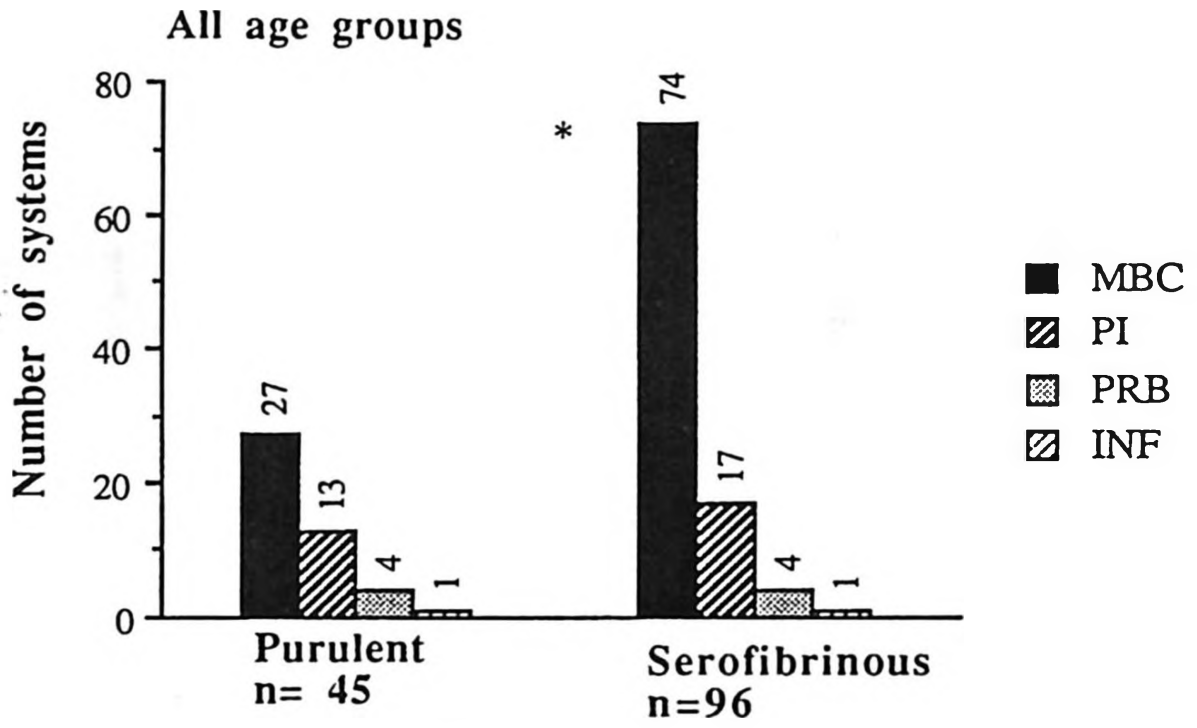

Fig. 2: Successful results (141 nasolacrimal systems) correlated to presenting pathology. MBC carried out at serofibrinous stage is more effective than that carried out at purulant stage (* $p < 0.01$).

aprons or gonadal shields from possible harmful effects of radiation. The procedure lasted approximately 2.5 minutes at 90 kVp, 2 mA, and the estimated radiation dose received by the patient was calculated as 10 rad. During dacryocystography, the dose received by the skull was estimated to be approximately 500 mrad[14]. Dacryocystograms (DCG) were performed before and after PI (Figs. 4, 5, 6) and fluoroscopic pictures obtained (Fig. 7).

Follow-up time for the patients was at least one year after the final procedure, with an average of 4.9 years (range: 1-8 years). Patients were seen regularly at one week, two weeks, and one month after the last procedure, and once or twice per year thereafter according to their symptoms. The treatment was regarded as successful when tearing and discharge ceased. Families of the patients were advised to return to the clinic should symptoms persist.

Results

One hundred and forty-nine obstructed lacrimal drainage systems of 111 patients were analyzed; 101 systems were cleared by MBC alone (67.8%). Among the remaining 48 that did not benefit from MBC, relief was obtained in 30 by PI (20.1%). Of the remaining 18 systems where PI was ineffective, eight benefitted from PRB (5.3%) and two from INF (1.3%). Eight cases were unsuccessful (5.3%), whereas 141 obstructed systems of the total of 149 were cleared by one or more interventions producing an overall success rate of 94.6%.

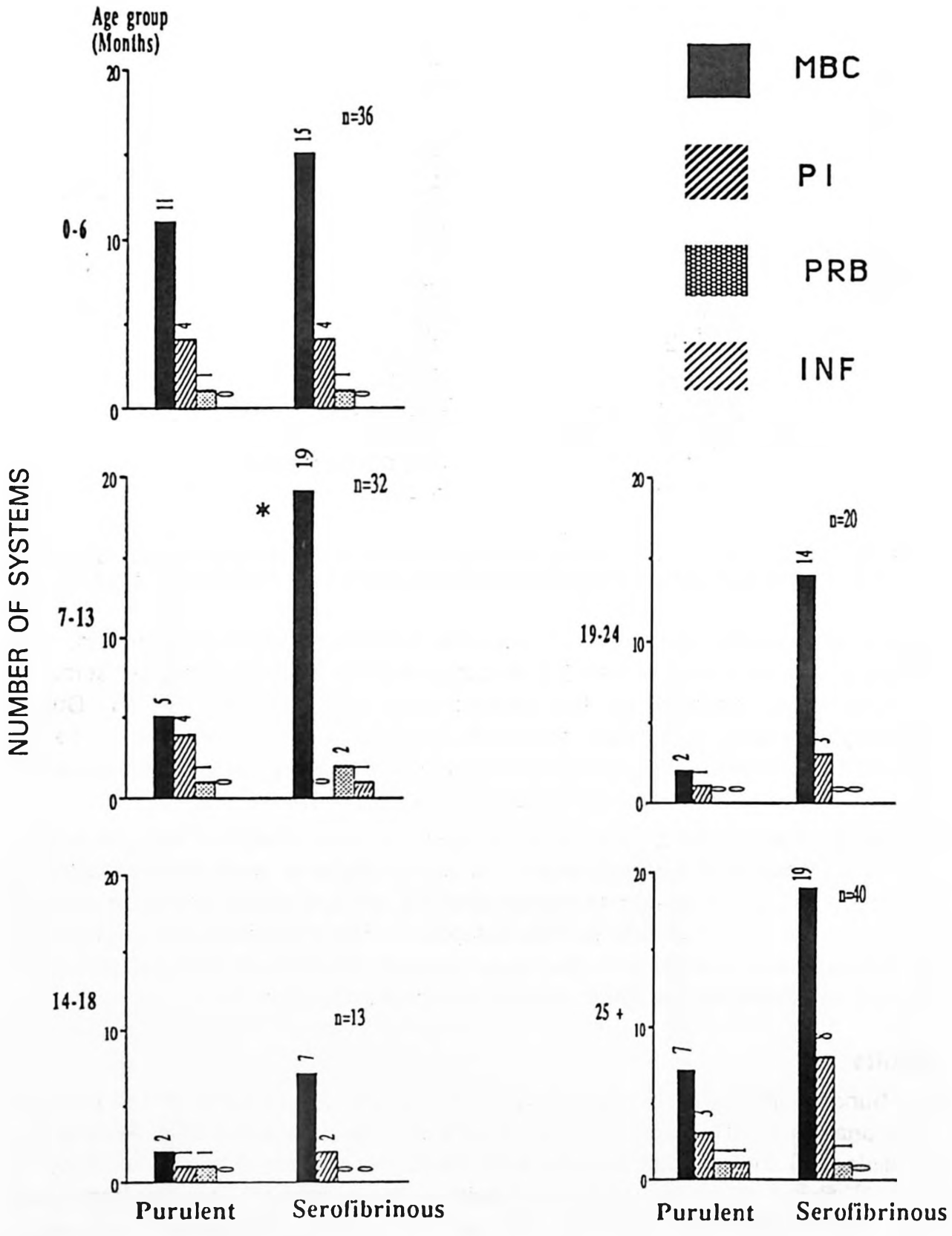

Fig. 3: Successful results (141 nasolacrimal systems) correlated to presenting pathology and to age. MBC caried out at 7-13 months at serofibrinous stage is more effective than that carried out at other age groups or at purulent stage (* $p < 0.01$).

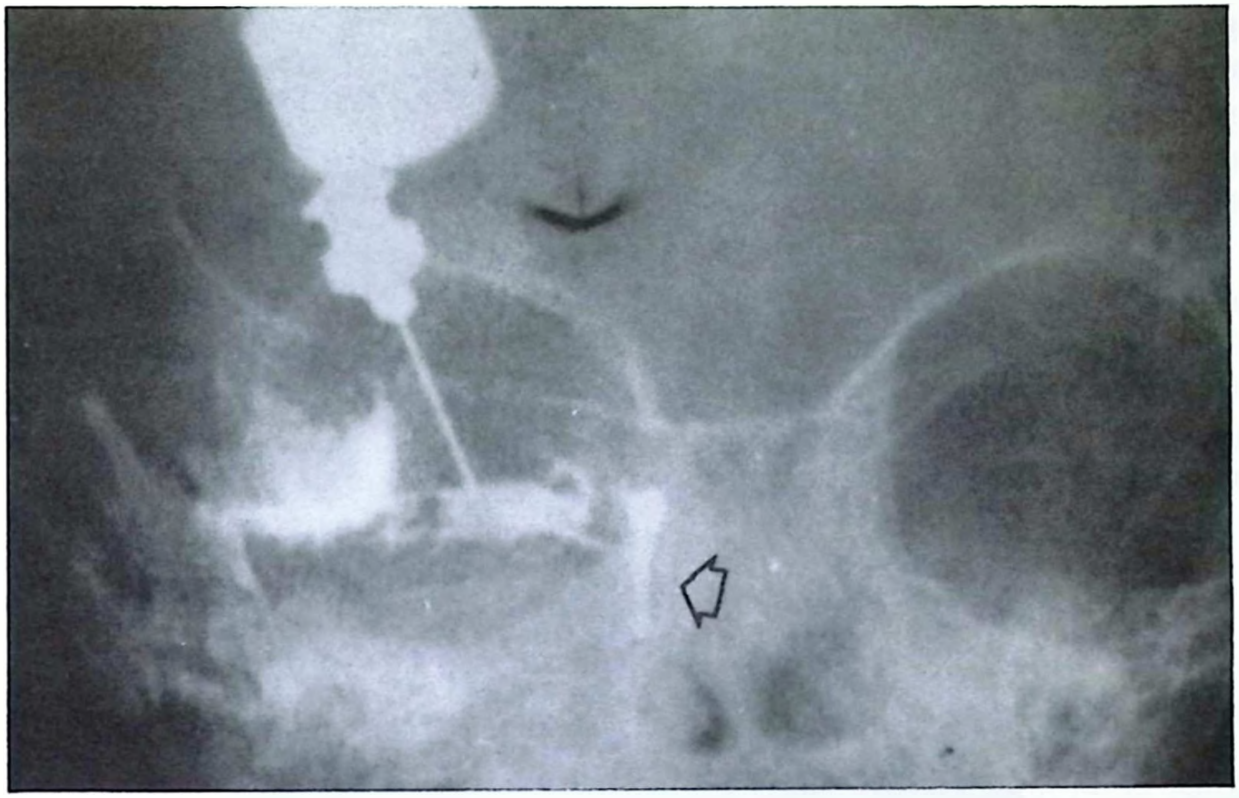

Fig. 4: Dacryocystogram before pressure irrigation. An obstructed duct is shown; the duct is straight (arrow).

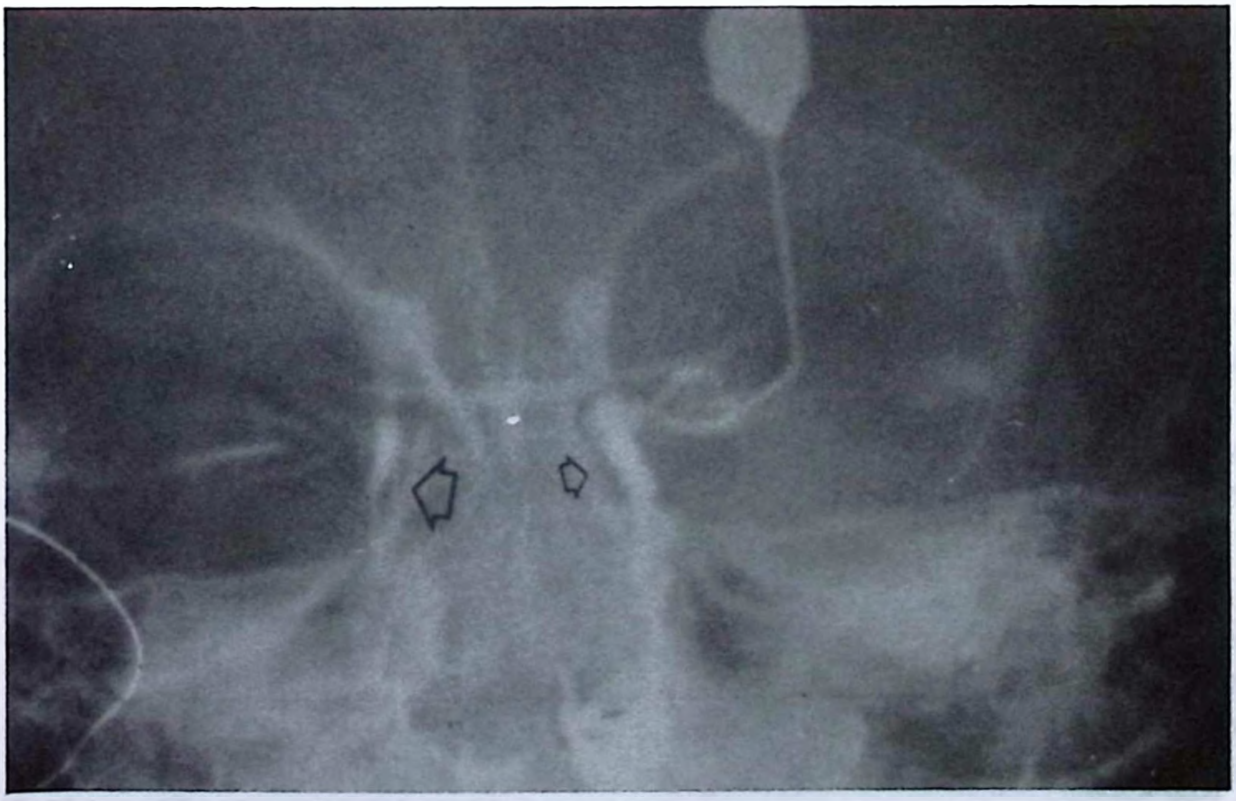

Fig. 5: Dacryocystogram after the pressure irrigation. Same patient as Fig. 4. Passage is demonstrated (large arrow). Patent nasolacrimal duct is seen on the other side (small arrow).

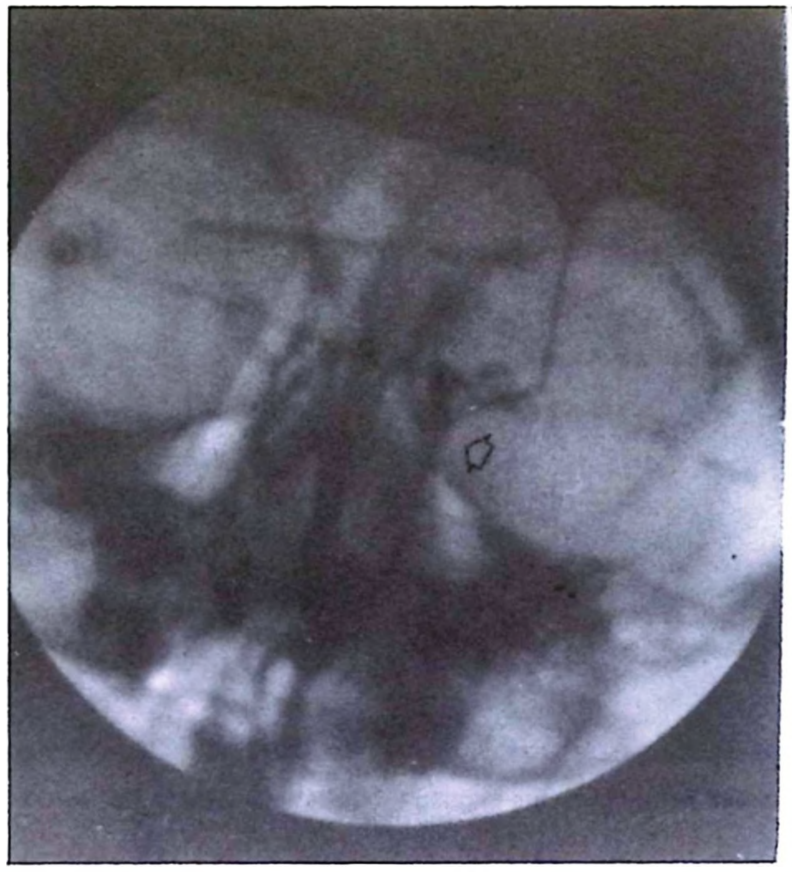

Fig. 6: Dacryocystogram after the pressure irrigation. Blockage is cleared (arrow).

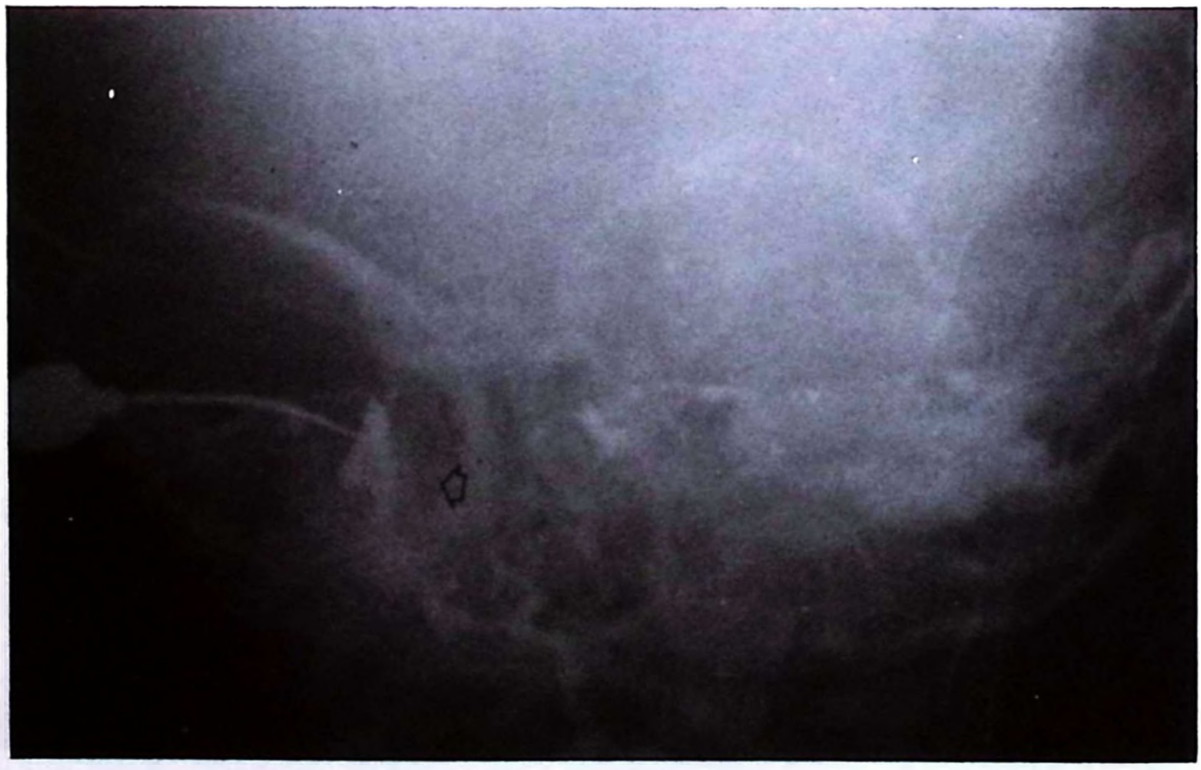

Fig. 7: Contrast filled nasolacrimal duct as seen on the fluoroscoopy screen. Blockage is cleared after probing (arrow).

The results were analyzed statistically with the chi-square test; Fisher's Exact chi-square test was used when applicable. The efficacy of four interventions (MBC, PI, PRB, INF) was related to age groups and the presenting pathology, and the correlation analysis was done. The difference between the results of various forms of treatment when correlated to age was not statistically significant ($p > 0.05$; Fig. 1).

Overall results of treatment when correlated to presenting pathology revealed that MBC carried out at the serofibrinous stage was more effective than that at the purulent stage ($x^2 = 6.825$, $p < 0.01$). When this finding was correlated to the five age groups, MBC carried out at the serofibrinous stage at 7 - 13 months was found to be more effective than that in other age groups (Fisher's Exact Chi - square test; $p = 0.0025$, < 0.01).

Discussion

This study represents the results of four interventions, namely MBC, PI, PRB or INF on 149 eyes of 111 patients with CNLDO. The overall success rate was 94.6%. The age range of the patients on admission was different from that of other studies, and some of the patients were much older than in other papers addressing same problem.

All the patients received MBC as the initial treatment, since the authors of the present study believe that any initial approach should be simple, cost - effective and non - invasive for the benefit of the patient. One hundred and one systems benefitted fully from MBC alone (67.8%). Fifty - nine patients were not included in this study since they failed to come to their follow - up visits. It is highly probable that these patients benefitted from their initial treatments and neglected to come to the clinic for follow - up. This suggests that the success rate of MBC is actually higher.

Busse et al[8] evaluated NLDs in cadavers radiologically and histologically, and found that NLDs displayed great anatomical variations. They proposed that the duct followed a curved path instead of a straight one, and the success rate of probing should be lower accordingly. In an attempt to test this hypothesis, we performed DCG on all patients before and after PI. Contrary to Busse's proposal and apart from irregularities in just a few systems, we found no evidence to support this concept (Fig. 4).

Kushner[15] demonstrated that irrigation is more effective with pressure than without it. We performed PI on those whose obstruction was not cleared with MBC, and this was usually performed when the patients were suitable for general anesthesia, regardless of age. Busse et al[8] and Bahçecioğlu[16] suggested probing with Bangerter probe and irrigating the system with pressure. Although PI was suggested as the initial form of therapy in classical texts, early probing was

alternatively suggested[17]. It is interesting that very few investigators have advocated the use of PI; we wish to emphasize its importance as an effective and less invasive procedure before one attempts PRB.

Guerry and Kendig[3] suggested probing under general anesthesia. However, Jones and Wobrig[17] and Koke[18] suggested this procedure be carried out on an outpatient basis under the age of one. We performed probing under general anesthesia regardless of age since we had an experienced pediatric anesthesia staff. This way, manipulation became much easier and less risky, and the quality of diagnostic X-rays was improved. It is stated that the risk of complicated anesthesia is minimal after six months of age[19]. We did not encounter a serious complication related to anesthesia except for one patient who developed minimal respiratory distress. Probing was not performed, and she was scheduled for probing in the near future.

The initial timing of probing has been controversial. While some authors believe that conservative treatment should be carried out for up to 12 or 13 months and PRB performed thereafter[5], others suggest PRB be performed during the first few months of life. Katowitz and Welsh[20] stated that the success rate of PRB performed under the age of 13 months was 97%, rapidly falling after that age. Lemke and Della Rocca[21] give similar cure rates for PRB. Nucci et al[11] advise PRB when conservative management fails after a three-months trial. Flanagan[22] advises treating the patients conservatively for nine months and performing PRB thereafter. Petersen and Robb[23], in a study which included 65 affected eyes of 50 patients, found out that while spontaneous relief was obtained in 58 eyes with massage alone, PRB was necessary in seven, and stated that PRB be delayed until the patient is eight months old. We performed PRB when necessary on eight patients regardless of age, when previous therapeutic forms failed. However, the small number of PRB in our series is hardly enough to make any statistical analysis possible, although the results are favorable in terms of clearance of the blockage.

Robb[4] stated that the success rate was 90% after first probing and 6% after the second. We performed second probing in two systems which belonged to separate patients. Both had their initial probing elsewhere, and during the second probing, a careful intranasal examination revealed inferior turbinate impaction which was successfully infractured, leading to relief of symptoms. Various authors stated that infracturing the inferior turbinate increased the success rate[24-27].

It is interesting that in our study, despite careful pre-operative nasal examination performed usually with an experienced otorhinolaryngologist, only two patients were found to have impacted inferior turbinates over the NLD and they underwent INF with relief. This number is not sufficient to make any statistical analysis possible. However, we recommend careful nasal examination on all

patients prior to surgery, since overlooking the presence of an impacted turbinate will eventually result in failure.

We strongly recommend PRB under fluoroscopy in the management of CNLDO. With the help of this procedure, the nasolacrimal system can be visualized with contrast material, and probing performed under observation. In doing so, the location of the probe in the duct and the inferior meatus can be confirmed and misdirection problems solved, particularly in the presence of anatomic variations. In our series, an ectopic sac, which could have been probed and damaged if not realized, was visualized with fluoroscopy and the probing was discontinued.

Meticulous effort was spent to visualize the systems during probing, since we believe that following and respecting the anatomic pathway as much as possible may increase the chance for permanent relief throughout the patient's life. Reported failure of probing in the literature[17] could be due to underestimating this fact, and the success rate should be increased accordingly.

The dose of radiation received by the skull during 2.5 minutes of fluoroscopy at 90 kVp, 2 mA is estimated to be 10 rad. During each dacryocystography, the dose received by the patient is approximately 500 mrad. Doses more than 1000 rad with a minimum dose of 200 rad per day are regarded as capable of producing serious side-effects such as formation of cataract[14]. Higher doses may result in retinal damage or even optic atrophy[28,29]. Since the total dose received by our patients was much lower than the potentially hazardous doses, the radiation received by our patients is justifiable.

Eight cases were unsuccessful in our series. One of these patients had complicated anesthesia, therefore probing was not attempted and she was scheduled for another probing in the near future. One patient had an ectopic sac demonstrated by fluoroscopy and probing was not performed. One patient had abnormal lower punctum and canaliculus; although obstruction was cleared following a successful PI from the upper punctum, some complaints continued. The families of four patients did not permit probing. In one patient, a successfully probed NLD was re-obstructed due to hypertrophied nasal mucosa. This patient did not have impacted inferior turbinate over the opening of the NLD, and he was scheduled for a second probing. However, the contact was lost since he moved to another part of the country.

The main treatment regimen is designed such that except for the MBC, other treated groups actually received more than one form of therapy. For instance, the PI group had also received MBC previously; the PRB group had received MBC and PI, and so on. However, an attempt was made to correlate the efficacy of the intervention to the age groups, and it was found out that MBC seemed to be more effective than other interventions, although this finding was not statistically significant ($p > 0.05$, Fig. 1).

However, when the overall treatment was correlated to the presenting pathology, MBC was found to be more effective if performed at the serofibrinous stage, and this finding was statistically significant ($p < 0.01$, Fig. 2). When this finding was correlated to the age groups, it was found out that MBC performed at the serofibrinous stage and at 7-13 months was more effective than that performed at other ages ($p > 0.01$, Fig. 3). This emphasizes the importance of early conservative treatment while the inflammation is still at the serofibrinous stage.

In conclusion, CNLDO should be managed with an initial conservative treatment started without delay and continued for up to two months. If the blockage is not cleared at the end of this period, the patient must be referred to the operating room for PI, PRB or INF. PI should be attempted before PRB in all patients, and PRB must be performed under fluoroscopy to minimize the risks of misdirection. This enhances safety and reduces the risk to the lacrimal passages. When these crucial points are remembered, CNLDO can be managed more successfully.

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OCULAR INVOLVEMENT IN CHILDHOOD LEUKEMIAS*

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SUMMARY: Soylu M, Tanyeli A, Özdemir N, Eroğlu A, Ersöz TR. (Departments of Ophthalmology and Pediatrics, Çukurova University Faculty of Medicine, Adana, Turkey). Ocular involvement in childhood leukemias. Turk J Pediatr 1994; 36: 35-41.

Ocular involvement was detected in 36 of 84 children suffering from acute leukemia. The major manifestation of leukemic ophthalmopathy was retinal hemorrhage. Neither platelet counts nor hematocrit values correlated with the occurrence of hemorrhages. As the eye is a pharmacologic sanctuary, it is emphasized that full ophthalmologic evaluation of leukemic patients is a critical part of their follow-up and will guide the choice of therapeutic regimen. *Key words: childhood leukemias, ocular involvement, retinal hemorrhages, optic nerve involvement, local radiotherapy.*

Leukemias are a heterogenous group of neoplasms characterized by malignant transformation of hemopoietic cells. Ophthalmopathy is commonly seen in leukemic patients. Ocular involvement such as retinal hemorrhages, exudation and / or papilledema may not require specific treatment. However, direct leukemic infiltration does require specific therapy[1-5].

Ocular involvement in leukemias is relatively constant. The incidence of leukemic ophthalmopathy was found to be 23-80 percent in autopsy series, and 9-62 percent in clinical studies[1,2,6,7].

In the present study, ophthalmoscopic examinations were performed in children with leukemia to evaluate the factors affecting leukemic ophthalmopathy, and the findings were recorded and analyzed retrospectively.

Material and Methods

The study group consisted of 84 patients with leukemia who were followed in the Pediatric Hematology and Ophthalmology Clinics at Çukurova University Medical Faculty between 1987 and 1992. There were 54 (64.3%) boys and 30 (35.7%) girls between the ages of 6 months and 15 years (mean age 8.36 ± 3.84 years).

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The patients were followed for one month to five years. Seventy-three (87%) of the patients were diagnosed with acute lymphoblastic leukemia (ALL), and 11 (13%) with acute myeloblastic leukemia (AML).

In all patients, visual acuity testing, and biomicroscopic, direct and indirect ophthalmoscopic evaluations were done. Fundus photographs were taken if the patients were cooperative. The type of leukemia, date of initial diagnosis, hematological and systemic manifestations were recorded, and a statistical analysis was done using Fisher's exact test.

Results

Ocular involvement occurred in 36 patients (43%). Thirty-three (45.2%) cases with ALL and three (27.2%) with AML showed leukemic ophthalmopathy.

Anterior segment involvement in one of the patients with AML, a mass was detected on the upper eyelid, and another patient had a subconjunctival hemorrhage. In the ALL group, there were subconjunctival and / or subcutaneous hemorrhage in three, mixed ciliary injection and tyndallization in one, and posterior subcapsular catarct[5] in two cases. The catarcts developed three and 36 months after initial diagnoses (Table I).

Table I: Types of Ocular Involvement in Leukemic Children

Type of Ocular Involvement	Type of Leukemia	
	ALL (n)	AML (n)
Anterior segment involvement		
infiltration	–	1
hemorrhages	3	1
keratitis	2	–
uveitis	1	–
cataract	2	–
Posterior segment involvement		
infiltration	6	2
hemorrhages	16	3
exudate	4	1
vascular dilatation	4	1

Table II: Relationship Between Some Hematological Parameters and Retinal Hemorrhages

Hematological Parameter	Retinal Hemorrhages	
	n	%
Thrombocyte count (/ mm^3)		
< 30.000	8	42.1
30.000-100.000	4	21
> 100.000	7	36.8
Hematocrit (%)		
< 30	15	79
30-35	3	15.8
> 35	1	5.2

Table III: Nerve Involvement

Type of Leukemia	Papilledema	Optic Atrophy	Cranial Palsy
ALL	9	10	3 Facial, 1 Abducent
AML	1	–	–

Table IV: Relationship Between Ocular Involvement and Duration of Leukemia

Type of Lesions n (%)	0-2 Months	3-10 Months	11 Months-4 Years
Retinal hemorrhages	13 (68.5%)	4 (21%)	2 (10.0%)
Papilledema	3 (30%)	4 (40%)	3 (3%)
Optic atrophy	3 (37%)	4 (50%)	1 (13%)
Retinal exudate	–	–	1

* Figures in paranthesis indicate percentages.

Discussion

Ophthalmopathy is commonly seen in leukemias, usually when the disease is clinically and hematologically active. In our study, no significant difference in ocular involvement was found in patients with ALL and AML. The incidence of leukemic ophthalmopathy is known to be higher in acute leukemias than in

chronic leukemias, but no data are available regarding the differences among the types of acute leukemias[3].

Infiltration of the anterior segment by leukemic cells is uncommon. Involvement of the orbit and adnexa, nodular infiltration in the limbus, conjunctival and corneal infiltration, hyphema, uveitis, glaucoma and cataracts can all be seen in leukemias[2,3,8,9]. In our study, no significant difference was found between anterior segment involvement and the type of leukemia ($p = 0.849$). Anterior uveitis was detected in one of our patients with ALL. In clinicopathologic studies, it was found that in uveitis, the cells in the anterior chamber are leukemic cells[2]. Posterior subcapsular cataracts were detected in two cases with ALL. Although the mechanism of cataract development is not well known, it is postulated that lens opacities result from the toxic effect of various therapeutic agents on the lens[8].

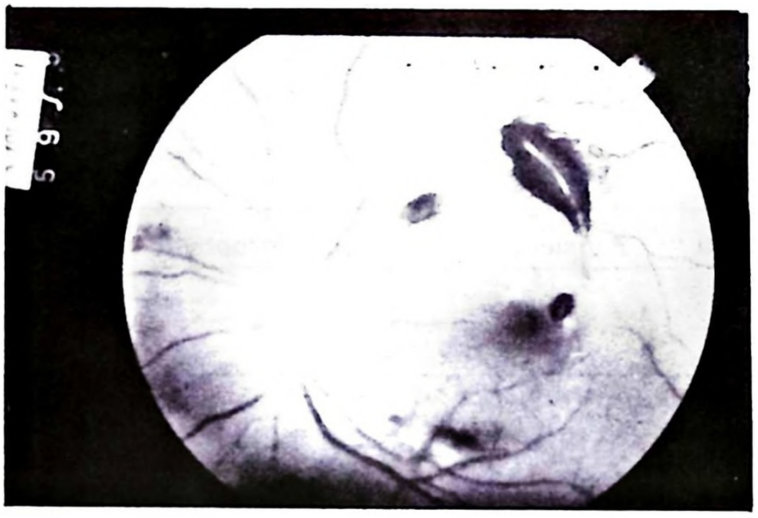

Fig. 1: Intraretinal and white centered hemorrhages in a patient with ALL.

Fig. 2: Papilledema and retinal hemorrhages in a patient with ALL who had CNS involvement.

No statistically significant difference in retinal involvement was found between patients with ALL and those with AML ($p = 0.366$). Retinal hemorrhages are significant features of leukemic ophthalmopathy. Although they have been attributed to anemia and thrombocytopenia the exact mechanism of hemorrhages is not well known. No significant correlation has been found between hematologic status and hemorrhages. In our study group, neither platelet counts nor hematocrit values were correlated with retinal hemorrhages.

There are at least three mechanisms by which the optic nerve and retina may be involved in leukemia. There may be: 1. papilledema secondary to increased intracranial pressure; 2. direct infiltration of the retina by leukemic cells; or 3. the presence of neoplastic cells in the optic nerve without retinal involvement[2,4]. Papilledema, usually bilateral, is a common sign of increased intracranial pressure in patients in whom malignant cells have proliferated in the subarachnoid space. These cells produce mechanical or ischemic effects on the optic nerve, axoplasmic transport is obstructed, and as a result papilledema occurs[1,2]. Except in one case, all cases with papilledema in our study group exhibited central nervous system (CNS) involvement, and intrathecal chemotherapy and radiotherapy were started.

Although most descriptions of leukemic infiltration of the retina and optic nerve are based on appearances at necropsy, the diagnosis may be made during life, as the ophthalmoscopic appearance of leukemic involvement of the optic nerve is characteristic. Typically there are areas of opaque swelling, and these may develop asymmetrically and involve one eye before the other[4]. Also, magnetic resonance imaging (MRI) facilitates early recognition of optic nerve involvement[11]. In one of our cases with ALL, there was typical optic nerve involvement (Fig. 3). In this patient's other eye, there was optic atrophy. After the patient was treated with intrathecal chemotherapy and local radiotherapy, optic

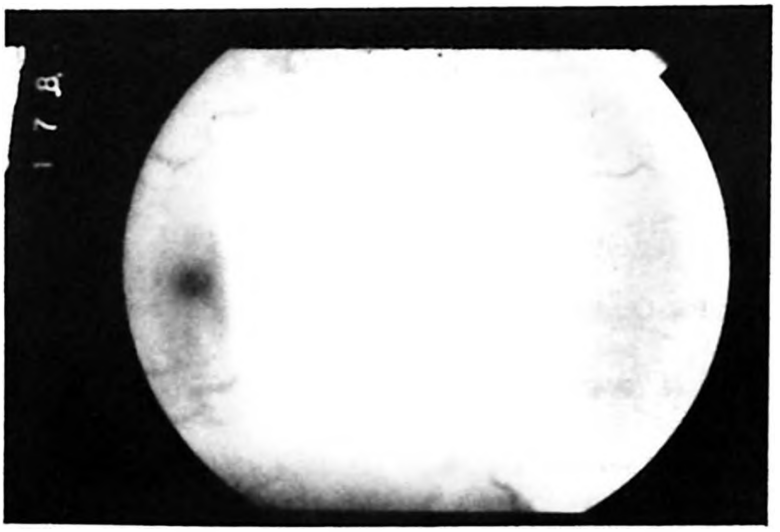

Fig. 3: Optic nerve involvement before treatment.

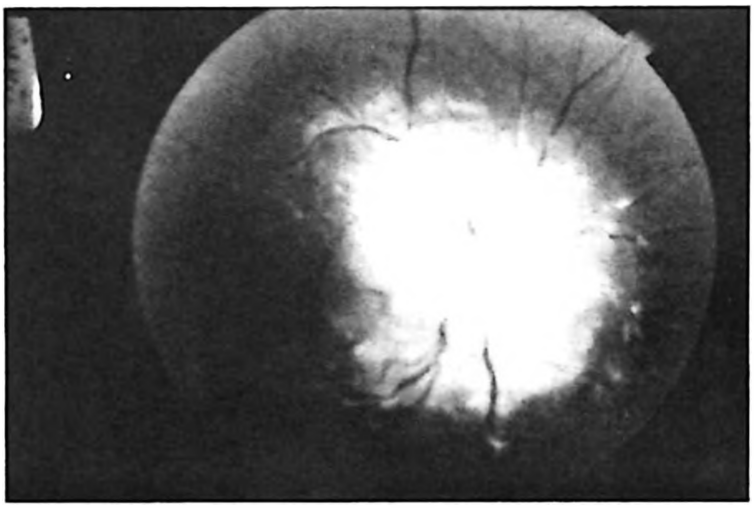

Fig. 4: After local radiotherapy, optic atrophy developed.

nerve involvement regressed and optic atrophy developed (Fig. 4). Although meningeal leukemia is sometimes treated with intrathecal cytotoxic drugs and cranial radiotherapy, such an approach to leukemic ophthalmopathy is not effective because the subarachnoid space ends just posterior to the globe. Thus, patients with optic nerve involvement need to be treated with local radiotherapy[4].

In our study group hemorrhages were detected mostly in the first months of diagnosis. Hemorrhages occur when the disease is active. It can be postulated that in time, chemotherapy leads to remission and hemorrhages dissappear[1,2].

It can be postulated that although leukemic ophthalmopathy is not an indicator for prognosis and mortality of leukemia, ophthalmoscopic evaluation should be performed in all patients. Ophthalmoscopic features play an important role, especially for the diagnosis of CNS and optic nerve involvement. Leukemic ophthalmopathy should be treated locally, as the eye is a pharmacologic sanctuary for leukemic cells. As a result, combined use of intrathecal cytotoxic drugs with local radiotherapy seems to provide the best chance of controlling or curing leukemic involvement of the eye.

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LONG – TERM USE OF ANTI – D IN CHRONIC IDIOPATHIC THROMBOCYTOPENIC PURPURA*

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SUMMARY: Yaprak I, Çağlayan S, Kansoy S, Özdoğru E, Bakiler AR, Aydınlıoğlu H. (Department of Pediatrics, SSK Tepecik Teaching Hospital, Yenişehir, İzmir, Turkey). Long-term use of anti-D in chronic idiopathic thrombocytopenic purpura. Turk J Pediatr 1994; 36: 43-47.

Chronic idiopathic thrombocytopenic purpura is an autoimmune disease characterized by antibody-mediated destruction of platelets. To maintain the platelets above the symptomatic level, we administered anti-D (100 µg for 5 consecutive days) in 19 children with idiopathic thrombocytopenic purpura (ITP). Four patients did not respond to treatment. Fifteen responded with an increase in the average platelet number to 76,000 / µL on the 7th postinjection day. Within 45 days, however, platelets dropped to 27,000 / µL. Three months after this study, two patients from the study group were re-administered anti-D in daily injections for 5 consecutive days, as was done previously. Monthly administration of anti-D in two patients maintained platelets above 30,000 / µL for periods of five and six months.

We concluded that monthly administration of anti-D after five consecutive daily injections can maintain platelet levels above the symptomatic level and may provide a corticosteroid-free safe interval of nearly five months. *Key words: chronic idiopathic thrombocytopenic purpura, anti-D.*

Childhood immune thrombocytopenic purpura (ITP) is an autoimmune disorder resulting from the formation of autoantibodies to platelets, and leading to platelet destruction in the accessory cell system[1]. Rapid decrease of platelets to levels below 20,000 / µL may result in mucosal, skin and, less frequently, central nervous system bleeding. For the emergency treatment of these situations, either platelet transfusion or some other treatment modalities such as intravenous immunoglobulin (IVIg), intravenous methyl prednisolone and splenectomy have been advised. To achieve a long-term complete remission (platelets consistently greater than 100,000 / µL) or partial remission (platelets between 30,000 and 100,000 / µL) without clinical symptoms, other therapeutic protocols have been proposed. Corticosteroids have been the drugs of choice for long-term therapy for

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many years. High-dose methyl prednisolone[2,3], cytostatics[4,5], IVIg[6,7], danazol[8] colchicine[9] and ascorbic acid[10] have also been used.

Anti-D is an alternative drug for chronic ITP. It has been used in varying doses and in varying protocols[11-13]. In this report we present our results of long-term use of anti-D in chronic ITP and discuss the potential benefit of its use in reducing the steroid requirement to maintain the platelets above the critical level.

Material and Methods

Nineteen children, age 15 or less, with chronic ITP and platelet levels lower than 30,000 / μL, (coulter counter, coulter electronics) were enrolled in the study. All patients had been treated previously with oral corticosteroids, and some had also been given either high-dose intravenous methyl prednisolone or intravenous immunoglobin (Table I). The occurrence of thrombocytopenia resistant to other therapeutic modalities for more than six months was accepted as the criterion for ITP chronicity. Antiplatelet antibodies were not measured. All patients were injected with 100 μg of anti-D using a 25-gauge disposable needle for five consecutive days, and were then followed until the platelet level dropped to 30,000 / μL or less.

Table I: Therapeutic Regimens Previously Used in Patients

Regimen	Patients*
Prednisolone (Oral)	19
IVIg**	4
HDMP	16
Anti-D	19

* All of the patients were given at least two treatment protocols.

** IVIg, intravenous immunoglobulin. HDMP, high-dose methyl prednisolone.

Two of the 19 patients were then enrolled in another study protocol after an interval of three months after the above-mentioned anti-D therapy. Both patients were given the some dose of anti-D for five days, followed by repeat injections on days 15, 30 and every 30 days thereafter until their platelet levels dropped below 30,000 / μL. In both studies, hemoglobin (Hb), reticulocyte and lactic dehydrogenase (LDH) levels and direct Coombs tests were checked at regular intervals, but haptoglobulin levels were not determined.

Results

Of the 19 patients, four were male and 15 female (M / F ratio 1 / 4). Four patients (2M, 2F) did not respond to therapy at all, and their platelet levels did not rise above 30,000 / µL during the therapy. Injections caused no bleeding problems in patients. Table II displays the changes in platelet levels in the 15 responding patients. The average initial platelet level of 18,000 / µL increased to 50,000 on the 3rd and to 76,000 on the 7th day. On day 15, the average level was 63,000, then dropping to 35,000 on the 30th, and to 27,000 on the 45th day.

Table II: Average Platelet Values of 15 Responsive Patients

	Postinjection Days				
	3	7	15	30	45
Platelets (10^3 / µL)	50	72	63	35	27

During monthly administration of anti-D to two patients, the platelet levels remained above 30,000 / µL for five and six months, although a gradual decrease in platelet levels was observed after two months of therapy (Fig. 1). Changes in LDH and Hb values were not significant. Direct Coombs tests became weakly positive in some patients, still with no changes in Hb values.

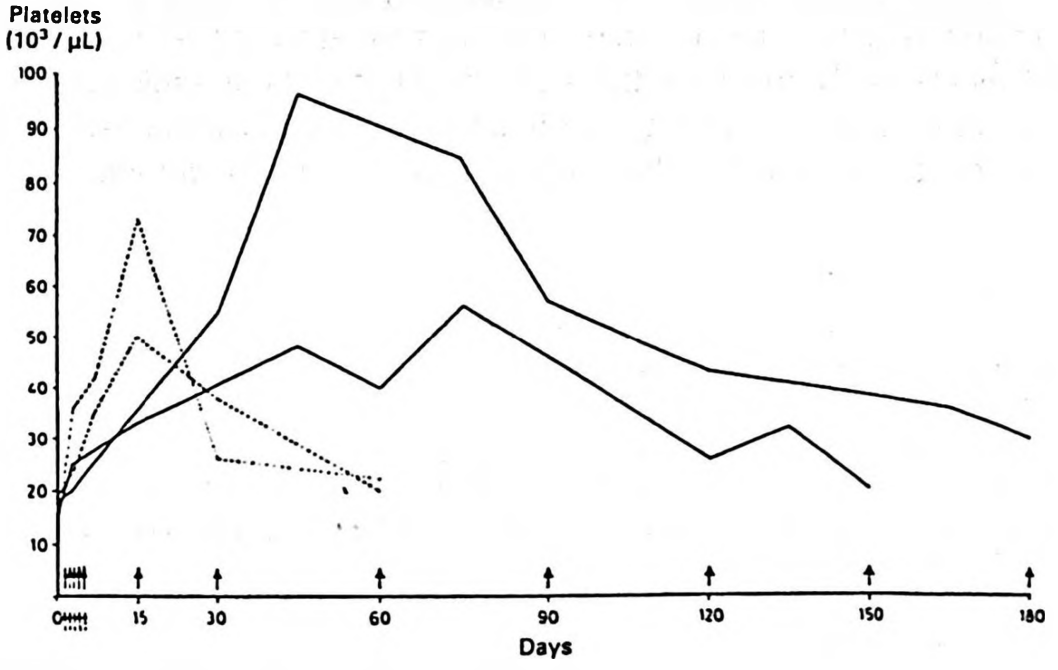

Fig. 1: Platelet levels of two patients after two different anti-D administration. Broken lines: Platelet levels after five days of anti-D. Solid lines: Platelet levels after repetitive use of anti-D.

Discussion

For the treatment of chronic ITP, several treatment modalities have been suggested. In addition to classical oral prednisolone therapy, high-dose methyl prednisolone[2,3], IVIg[6,7], antineoplastic agents[4,5] and recently anti-D[11-13] have been found to be useful with varying success. Anti-D was found to be effective in increasing the platelet counts in 79% of our patients. The highest platelet level of 76,000 / μL was reached between 10 and 15 days after anti-D, then dropping to 35,000 on the 30th postinjection day.

The platelet counts of two patients who were given repeated anti-D were maintained above 30,000 / μL for five and six months. This is an important point, because the platelets of the same patients had dropped below 30,000 within 30 days of the previous anti-D protocol (100 μg for five consecutive days). In accordance with a previous report[14], we could not find any direct relationship between the clearance of red blood cells and direct antiglobulin test positivity, because there was no significant change in Hb and LDH values despite weak antiglobulin test positivity and a slight increase in the reticulocyte count.

A suggested mechanism of action of anti-D is that IgG-coated red blood cells induce a diminution of the Fc-dependent clearing capacity of the accessory cell system. Whatever the mechanism of action, anti-D may be a viable alternative to corticosteroids, because long-term use of corticosteroids is usually limited, due either to resistance or to side effects. In these situations, repeated anti-D injections can provide a safe platelet level for at least five months. After this period, corticosteroids or another alternative drug can be reused.

In summary, anti-D can be an alternative agent in the treatment of chronic ITP. It can maintain the platelet level within safe limits for at least five months if used in repeated injections. To minimize the side effects of corticosteroids and to reduce unresponsiveness to either corticosteroids or to anti-D, rotational use of both drugs can be considered for the long-term treatment of chronic ITP.

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VIOLENCE: A GROWING DANGER TO CHILDREN THE AMERICAN CASE

*James W. Sayre MD**

The world we live in is full of violence. There is recurring and persistent fighting in Northern Ireland, the former Yugoslavia, Russia, the Middle East. These are conflicts between differing religious groups, civil wars, wars of a political nature. I'm alarmed and ashamed to say that in our land we have our own issues of violence. These are not religious, civil or political but of a different kind. There are no warring factions; there will never be a winner or loser, for this is becoming what I think you can call a lifestyle. It strikes us suddenly, unexpectedly and usually unpredictably. Worse yet, these episodes of violence have become more frequent lately.

In June of this year we had four gunshot injuries in patients of our inner city office. This is where I do my pediatric practice. In the month of July in our city of Rochester, with a population of around 300 thousand, there were 14 homicides. There were recorded 50 homicides in the first eight months of this year, as many as occurred in all of 1992.

In the U.S. we count over 60 homicides per day, equivalent to 23,000 per year. By comparison, the U.S. military lost 46,000 men in all the eight years of the Vietnam war.

Homicides by handguns among all ages in 1990 have been compared in seven countries:

Australia	10
Sweden	13
Great Britain	22
Canada	68
Japan	87
Switzerland	91
United States	10,567

Our numbers are more than 100 times higher than the next highest country.

Furthermore, there has been a marked increase in homicides in children recently. In the age range 15-19, a 100% increase was noted between 1985 and 1991.' Judging by preliminary figures for 1993, that will be much greater this year.

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As of this time we have no way of counting violence-related injuries as compared to mortalities, since hospitals and doctors do not report to a central agency. The likelihood of a permanent injury to the brain or spinal cord is great. We've had three that I've been personally involved with in the past two years. For a young person, this is a hard life to face.

How Does This Happen ?

While one might think that most such episodes of violence occur during house robberies, hold-ups in shops or on the street, to motor car occupants, this is simply not the case. The Federal Bureau of Investigation reports only 6% of such violence being related to drug use or drug dealing. Alcohol use is surely a factor, greater than drugs.

Demographics

The demographics are striking. Males predominate, in the 15-25 age range. Black, inner-city residents are four times more at risk than other males, and far more than females. Poverty, broken families, and unemployment loom large. The assailant and victim are frequently related, are commonly acquaintances and live near one another. The incidents occur in any location where children go: at home, on the street, on playgrounds, and increasingly in the schools.

Guns are Everywhere

In the United States, guns are easily available. The size and power is appalling. It is estimated that there are at least 200 million guns in non-military hands, of which about 60 million are hand-guns.

Studies repeatedly tell us that most people keep their guns at home, "at ready," loaded, easily available in a drawer, under the bed or pillow. We know that few of these guns have any kind of safety device. Many larger guns are loaded, in the closet, behind the door. Young children are, of course, fascinated by guns, have toy guns of their own for play. The real gun of father's is, of course, much more interesting, and we hear the story so often that a youngster was showing the gun to a neighbor child when it went off. One of my own patients, a two-year-old visiting his mother down in North Carolina, found a pistol and shot himself in the abdomen.

A Legal Right

We have a Constitutional amendment that specifies that to maintain a militia (a citizen's reserve), the right to own guns is protected under our Constitution. A very powerful group of gun enthusiasts, the National Rifle Association (the N.R.A.), resists any and all attempts to restrict ownership, importation, and

manufacture of any and all forms of guns, including so-called assault weapons, which are used for one purpose only, to kill. The N.R.A. rewards financially our legislative representatives to see that they do not allow any measures to be passed that would restrict gun activity in any way. On any occasion when our county legislature considers any measure that would restrict gun use or require safety devices, a massive turnout of N.R.A. members fills the room and noisily defends their views.

A Population Afraid

This epidemic of violence, stabbings and shootings has produced a state of great fear in our communities. People feel they are no longer safe, not just on the streets, but in the home, at work or in the car, even in hospitals. As a result, many people purchase guns for self-protection, carrying them at all times. There is a fallacy in this, however. A study just published shows clearly that gun ownership increases threefold the risk of death to the one possessing the gun. More police protection has developed, leading to more arrests, more jail sentences, more crowding of prisons. Meanwhile, in spite of this, homicides increase.

Why Does This Happen?

Examining the apparent reasons why these shootings occur among our younger population, we find that there is often little or no justification for these shootings. We learn that there was an argument, that someone insulted someone else's mother, sister or girlfriend. Someone stole or even just used another's sneakers, jacket or bicycle. Someone is insulted by another on one day. The next day, to "get even," a gun is produced and used. Here's another example: Just a year ago, in Baton Rouge, Louisiana, two teenagers were dressed up for a holiday party. One was a Japanese exchange student. They were looking for a party they were to attend. Mistakenly, they went to the wrong house. The Japanese student asked in broken English if this was the house of the party. The housewife who answered the door became frightened, called her husband, who came with gun, was also frightened, and shot the student dead on the spot. The citizens of Japan were so incensed they have collected two million signatures on a petition expressing their grave concerns, which will be presented to our President Clinton next month on the anniversary of the day President Kennedy was shot thirty years ago.

There's another major cause of these deaths: suicide. Depression in the young is a common phenomenon, and suicide attempts are often contemplated. The availability of a gun right in the house makes this easy to do at almost any time. The only son of a close friend and former pediatrician partner of mine took his own life along with that of a close friend in a double-suicide.

Contributing Factors

Looking more closely at the background of many of the young group from the "inner city" population, there appear to be some strongly contributing factors from family life. Our poverty and near-poverty population commonly live in very much disrupted homes where there is a pattern of aggression and ongoing daily conflict between parents, relatives, boyfriends. Young children copy these behaviors. More than half of black children are born to single-parent families lacking a father. A persistent high unemployment rate for all males can have a marked effect on their self-esteem. Such fathers feel useless, are unable to support their families. They often move from woman to woman, fathering more children. Children raised without a father's presence lack very necessary attention and control. The lack of a father figure in the home is particularly bad for boys. Having no father to pattern their lives after, they seek substitutes such as older boys, whom they see as strong, brave and daring. Many gain this identity and behavior from male TV stars whom they see doing dangerous things: fighting, crashing cars and shooting assailants. Even very young children in such families see and copy aggressive behavior. Their mothers, often barely grown out of childhood themselves, do not teach them to mind by using kindly words. Instead they holler, scream and spank them, demonstrating to them an aggressive style of personal interactions. Such children at an early age use loud, noisy and unpleasant language with their siblings and playmates. They learn to talk back to their parents. This style of interaction then gets carried along to the school setting where they annoy and challenge teachers. We know that behaviors are always established through early life experiences and are carried along, often for the rest of life.

What Can Be Done?

Society must respond to these incidents. We think immediately of the need for more police protection. But the police response is always *after* the incident, after the damage has been done. Suspects are apprehended, often arrested. There then follows the court of law; people are imprisoned. Our prisons are overcrowded; we build more. Should young children be sent to prison? The prison scene is not a good one either. There is no treatment, no counseling in prison. And, as you may have seen from the Los Angeles police beating episode of Rodney King, the interaction of police with our black population is not a satisfactory one, producing building and lasting resentments. Schools have now begun to inspect children with metal detectors at the door. Some have a police officer in the school walking the corridors.

Limiting Gun Use

Restraints on guns is another attempt at a solution. The so-called "Brady Bill,"

presented for several years to Congress, would invoke a waiting period of five days in gun purchases to allow a police check on the purchaser. Yet the N.R.A. has repeatedly caused rejection of this. President Bush, an N.R.A. member himself, imposed a restriction on the import of assault weapons for a short time. Production in the U.S. could be stopped. One of our states, Connecticut, has been trying to limit production of assault weapons in the state, but fails to get support in the legislature. A group of us pediatricians in Rochester has campaigned for two years to persuade parents to store their guns safely and to use locks on the gun trigger to prevent childhood accidents. We developed a poster which we have given to doctors to display in their examination rooms. While waiting to see the doctor, people can read it over. This promotes discussion with parents on the importance of gun safety. Ten states now have laws that make the parent guilty in any incident where a child of theirs commits such an act.

Medicine's Response

Over 30 years ago we began efforts to deal with a form of family violence called child abuse, declaring that medicine, particularly pediatrics, has a major responsibility to search carefully for children injured by this means. We have met that challenge by a whole system of reporting and protecting children so exposed. By the pure weight of numbers and risks, we physicians should be even more alarmed by this issue. However, little has happened so far. Medicine's response has been largely limited to a "sew `em up," admit to hospital, approach. Since the major treatment is surgical, we practitioners often do not even learn that an injury has occurred to our patient. When we are informed, we console the family, often making referrals to mental health counselors.

A Pediatric Responsibility

As pediatricians we have told ourselves that we are in a unique position to examine and understand the functioning of the family, their lifestyle, some of their interactions, their family supports. Nowhere does this seem easier than in the first several years of a child's life, when families come for frequent well-child visits. The interactions of parent and child and even child with siblings can be examined and discussed. Since many minor disputes between parent and child occur in my office under my direct observation and often provoke parents to be harsh and noisy in attempting to control their behavior, I find I can intervene right then and discuss better means of control.

Responses of the child in school to the teacher's authority is another touchpoint of adversive behavior. Teachers often call us and look to us for help. In our offices we can discuss the matters of picking the right friends, goals for the future, interests, habits, hobbies and sports. How to settle conflicting views without

arousing intense anger is another important subject. Some extra time is necessary for these discussions-time I consider to be well spent.

School Programs

A number of schools have developed programs that take up these issues of conflict with the children in classroom groups. Curricula have been developed for this type of discussion. There are now a few pediatricians who make themselves available to conduct just such school discussions. Ingenious "mediation" and "peacemaker" programs have begun to develop. From these come some students who become just such "peacemakers" themselves.

Action in Neighborhoods

We have begun to see action on a very local level where neighborhoods pull together to change their own environment: cleaning up, clearing out drug "pushers," patrolling the streets, watching out for each other's children. In the middle of Harlem, New York City, where gun and knife injuries are a daily occurrence in the Harlem Hospital, a pediatric surgeon, Dr. Barbara Barlow, pushed the community and the city to clean up the parks, start sports programs for children. Parents began to take pride in their new parks and clean streets, chased out the drug pushers. Vegetable and flower gardens appeared in the parks. The hospital had an unoccupied floor. Barlow used the floor to start classes in dance and gymnastics for the girls. A striking result of these efforts was a 25% reduction in traumatic injuries treated in Harlem Hospital.

In an area of Newark, New Jersey, which was destroyed in the riots of the 1960s, a group of inhabitants worked together to rebuild their own neighborhood, doing construction, developing their own shops and stores, parks and sports fields, small industries, health care facilities, churches—a whole new community. All this with a very small amount of outside capital. There is no violence. The people themselves see to that.

The Role of Television

It is time for prople to speak out about another part of the violence problem: TELEVISION! The television industry can CLEARLY be held responsible for adding much fire to this bad situation. America produces phenomenal amounts of violence and explicit, traumatic sex for programs directed at all ages. Efforts have been made to change this. Thus far, not much has happened on a voluntary basis, largely because the public seems to enjoy this kind of entertainment and the advertising industry thrives on popularity "ratings." There appears to be a slowly growing sentiment for more effective action through legislation, but that will probably be very slow in taking place.

Summary

A frightening, growing epidemic of senseless, irrational and inexcusable violence has seized the United States. While it involves all ages and localities, the occurrences are predominantly in areas of poverty, poor housing and unemployment. Children, particularly the adolescent and young adult male black population, are at greatest risk. There are recognized many contributing forces such as low self-esteem, family disruption and single parenting. Country-wide there is easy access to guns and lack of gun safety guards. Violent television sets an example for our youth and lends an air of adventure and excitement to their lives. The solution to this enormous problem is clearly not an easy one and must be through a combination of many social and legal changes. This is most assuredly a medical problem and demands thought and active participation by physicians. There are a number of strategies for physicians, especially pediatricians. We must look carefully at family interactions, attempting to promote more kindly behaviors, enhance self-esteem. School-age children can be helped through office discussions and collaboration with teachers. "Leave the knives and guns at home, avoid noisy arguments, use more kindly words." "Television is not real life; the actors do not die." These are our people. Their needs are great. We must help.

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SUBACUTE NECROTIZING ENCEPHALOPATHY (LEIGH SYNDROME): REPORT OF TWO JUVENILE CASES WITH FATAL OUTCOME*

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SUMMARY: Göğüş S, Yalaz K, Güçsavaş M, Akçören Z. (Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Subacute necrotizing encephalopathy (Leigh syndrome): report of two juvenile cases with fatal outcome. Turk J Pediatr 1994; 36: 57-65.

The clinical and pathological findings of two children diagnosed on autopsy with subacute necrotizing encephalopathy (SNE) are presented. One of the patients was a previously healthy 12-year-old boy with a rapid clinical course and fatal outcome. The second case was a mentally retarded 13-year-old girl with a positive family history of neurological disease and progressive deterioration.

Brain edema, bilaterally symmetric gray-brown areas of spongy degeneration and cavity formation were present in the basal ganglia in both cases. A small cavity was noted in the right inferior olive in Case 2. Mamillary bodies were spared in both cases macroscopically and microscopically.

Microscopic sections of the involved areas and the periaqueductal region in Case 2 exhibited variable degrees of necrosis, spongiosis with a striking proliferation, and dilatation of the capillaries. Similar changes were noted in the cerebral cortex of Case 1. Microglial and astrocytic proliferation with some loss of myelin were also noted. The neurons, although reduced in number, were frequently preserved within the lesions.

To our knowledge, only three patients over two years old have been reported in the literature with an acute clinical course and a fatal outcome. Case 1 is the fourth such case. *Key words: subacute necrotizing encephalo (myelo) pathy, Leigh syndrome, mitochondrial cytopathy.*

Subacute necrotizing encephalopathy or encephalomyelopathy (SNE) or Leigh syndrome is a rare degenerative disease of the central nervous system (CNS) associated with various biochemical defects and considerable clinical variability[1-6].

An autosomal recessive mode of inheritance has been suggested, and the onset is usually during infancy or early childhood[1-7]. However, in the sporadic or X-linked form, juvenile and adult cases have also been reported[2,6-13]. Recently, maternally inherited Leigh syndrome in two siblings was presented by Ciafaloni et al[14]. The

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clinical course is variable; although the affected patients usually die in the first few years after diagnosis, a rapidly fatal course, spontaneous remission, chronic evolution, a relapsing form and survival beyond three decades have also been documented[4,8,9,15,16].

Clinical manifestations at the onset include, in order of frequency: feeding problems; motor retardation; hypotonia; ocular signs and symptoms; mental retardation; seizures; respiratory problems; cerebellar, pyramidal and extrapyramidal signs; and coma[4].

The characteristic pathologic findings are necrotizing lesions most commonly found in the tegmentum of the midbrain, pons, medulla and basal ganglia with a symmetrical distribution. The lesions usually destroy both the gray and white matter, and gray-brown discolorations or cystic softenings can be observed on macroscopic examination. The histopathological changes consist of spongy necrosis with microglial and astrocytic reactions and prominent vascular proliferation[1,2,4-18].

Since the first description of this syndrome by Dennis Leigh[1] in 1951, more than 200 cases have been reported in the literature[4]. Although several defects of oxidative metabolism have been causally related to this entity, the definitive diagnosis still requires pathologic examination[3,4]. In a recent survey of the literature, van Erven et al[4] found 173 cases of pathologically proven Leigh syndrome.

We recently studied two children diagnosed on autopsy with lesions of the brain characteristic of this disease. These are the first cases seen in our Pediatric Pathology Department in the past twenty years. One patient was a previously healthy student with a sudden onset of the disease and a rapidly fatal outcome. To our knowledge, only three other patients over two years in age with an acute clinical course and fatal outcome are documented in the literature[6,8,9]. This report describes the clinical and pathological findings of the two cases seen in our department.

Case Reports

Case 1

A 12-year-old boy was admitted to a local hospital with a five-day history of constipation and difficulty urinating. After admission he became unable to walk and spoke incoherently. He was referred to Hacettepe Children's Hospital upon progressive obtundation. There was no history of exposure to drugs, chemical agents or animals. The developmental history was unremarkable. He was the sixth child of consanguineous parents. There was no family history of neurologic disease.

Physical examination on admission revealed a disoriented child. He cried intermittently and withdrew his lower extremities upon painful stimuli. Vital signs were normal; weight and height were in the tenth percentile. Pupils were bilaterally equal in size and reactive to light. The optic fundi were normal. Cranial nerve functions, muscle bulk and strength were intact. The lower extremities were spastic. Tendon reflexes were obtainable. There was sustained clonus of both ankles, and his Babinski sign was bilaterally positive. Meningeal signs were negative. The remainder of the physical examination was unremarkable.

Urinalysis, complete blood count, blood chemistry profile and pseudocholinesterase levels were within normal limits. Blood ammonia was 73 μg / dl (N: 70-120). Serum lactate was 4.5 mg / dl (N: 10-14) and pyruvate was 1 mg / dl (N: 0.5-1). Serologic tests for Salmonella and Brucella were negative. A lumbar puncture yielded clear, colorless, acellular cerebrospinal fluid (CSF) with normal glucose and protein contents; a culture yielded no microorganism. An X-ray film of the chest was normal. A cranial computed tomographic examination (CT) revealed bilateral radiolucent areas in the basal ganglia and scattered radiolucent regions in the frontal and parietal lobes. A second cranial CT scan performed five days after admission showed bilateral narrowing of the cortical sulci and ventricular systems. An electroencephalogram displayed irregular background activity with centroparietal focal slow waves.

The patient's condition rapidly deteriorated, and bilateral papilledema, anisocoria and bradycardia developed. Intravenous dexamethasone and mannitol were administered. Intravenous acyclovir was initiated for a tentative diagnosis of Herpes simplex encephalitis. Mechanical respiratory assistance was required for apnea and cyanosis. The patient died on the seventh day of admission despite intensive care. An autopsy was performed.

Case 2

A 13-year-old girl was brought to Hacettepe Children's Hospital with loss of consciousness. Generalized weakness and stupor of three days duration and vomiting following a minor head trauma one day prior to admission were noted.

She was the first child of distantly related parents. She was born at term after a complicated delivery. Her developmental milestones were delayed. A tentative diagnosis of choreathetoic cerebral palsy due to anoxic birth was made at nine years of age at Hacettepe University Pediatric Neurology Unit. Internal squint, rigidity of the extremities and right optic atrophy were noted at that time while serum and urinary amino acid levels and cranial CT were normal. She attended a special school for the mentally retarded. Degenerative CNS disease was considered at ten years of age. She was unable to walk without assistance, and her speech deteriorated.

Her 10-year-old brother was described as moderately mentally retarded. Several cousins of both the mother and father had histories of mental retardation, motor deterioration, and life expectancies of 25-30 years.

Physical examination on admission revealed a comatose child with irregular breathing who did not respond to painful stimuli. Cutis marmoratus and cyanosis were present. Pupils were slowly reactive to light; right optic atrophy and left papilledema were noted. Right facial nerve paresis was present. The extremities were spastic, and patellar tendon reflexes were unobtainable. Meningeal signs were negative.

The patient was resuscitated and mechanically ventilated in the Intensive Care Unit. However, she died within ten minutes of admission and laboratory investigations could not be done. An autopsy was performed.

Pathological Findings :

Both patients' major pathological findings present on autopsy were localized to the CNS. Brain edema and bilateral cerebellar tonsillar herniation were present in both cases.

Coronal sections of the cerebral hemispheres disclosed bilaterally symmetrical gray-brown areas of spongy degeneration with some cavity formation in the basal ganglia of both patients. The putamen and caudate nuclei were particularly affected (Fig. 1). Few small hemorrhagic discolorations were present in the gray matter of the cerebral cortex and rostral pontine in Case 1. A small cavity was noted in the right inferior olive in Case 2.

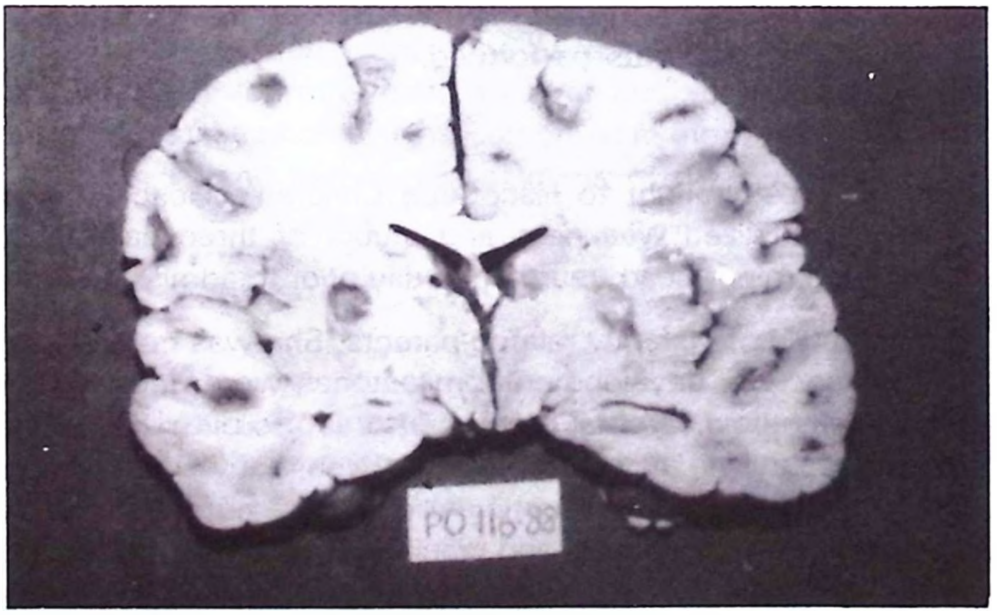

Fig. 1: Case 1: Coronal section of the cerebral hemisphere showing symmetrical spongy necrosis and cavity formation in the basal ganglia.

Microscopic Findings :

Case 1 : Sections of the basal ganglia exhibited varying degrees of necrosis, cystic degeneration and spongiosis with capillary proliferation (Fig. 2). In some sections of the cerebral cortex, spongiosis and proliferation of capillaries were also noted (Fig. 3). The hemorrhagic areas showed congested vessels surrounded by small recent hemorrhages. No changes were seen in the sections of the pons, medulla oblongata, periaqueductal region, mamillary bodies and spinal cord.

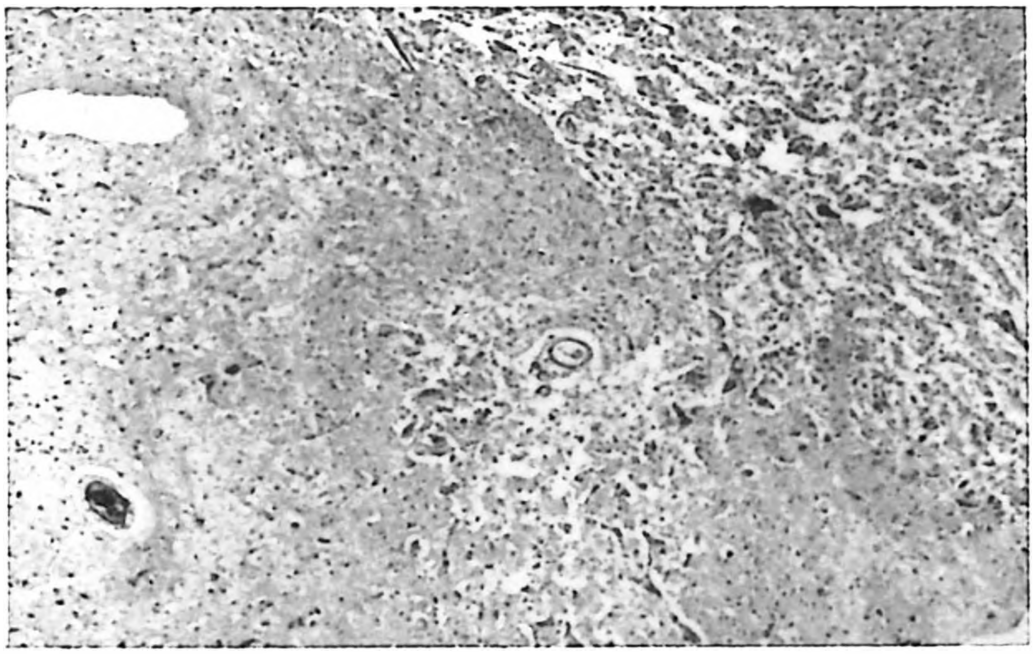

Fig. 2: Case 1: Necrotic areas in the basal ganglia. (HE, x 13).

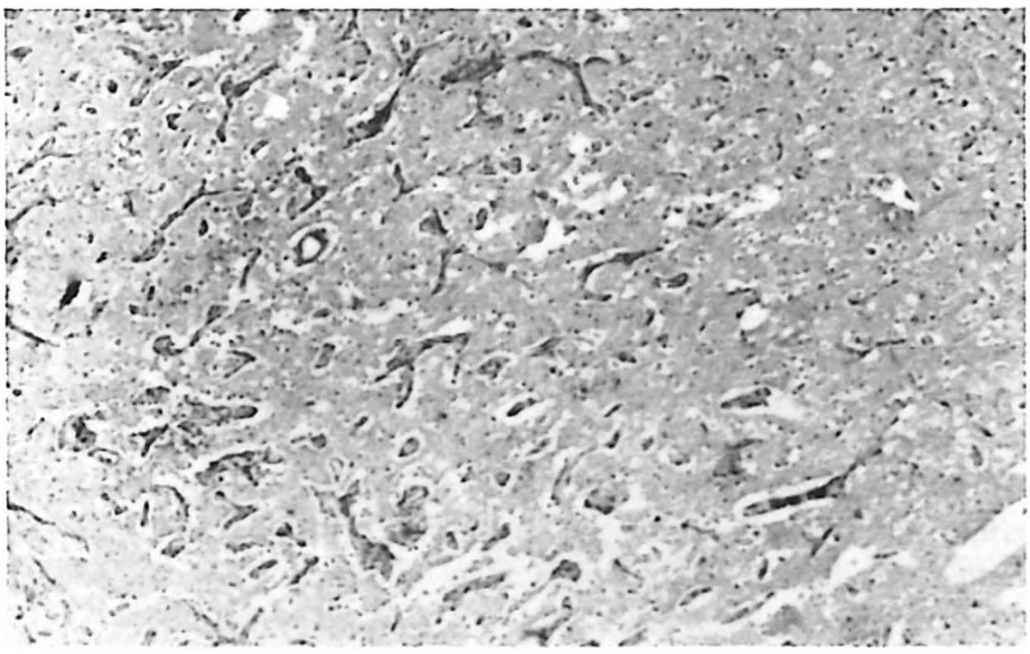

Fig. 3: Case 1: Cerebral cortex lesion showing marked proliferation of the capillaries and spongy degeneration. (HE, x 13).

Case 2 : Basal ganglia showed histopathological findings similar to those of Case 1. The lesions in the periaqueductal region were symmetrical and butterfly-like, and showed striking capillary proliferation and dilatation (Fig. 4). Rarefaction and cystic disintegration of the nervous parenchyma was detected in the right inferior olive. Brain edema was more prominent than in Case 1, and separations between the molecular and granular layers of both the cerebral and cerebellar cortex were noted. Slight vacuolization and loss of myelin was observed in the optic chiasma. No pathological changes were present in the spinal cord and mamillary bodies.

The neurons, although reduced in number, were frequently preserved within the lesions; microglial and astrocytic proliferation with some loss of myelin was also detected in both patients.

Fig. 4: Case 2: Periaqueductal lesion showing prominent vascular proliferation and dilatation. (HE, x 13).

Discussion

Subacute necrotizing encephalopathy (SNE) is a distinct pathological entity with variable clinical presentations[1-6]. Case 1 was a previously healthy child with an abrupt onset of neurological symptoms. Only three cases with an acute clinical course and rapid fatal outcome in children over two years of age have been reported in the literature[6,8,9]. Case 1 is the fourth such case. Case 2 presented with a history of developmental delay, psychomotor retardation and progressive deterioration. The family history was also suggestive of degenerative CNS disease.

The topography of the lesions within the brain tissue and the characteristic macroscopic and microscopic pathological findings of both children are consistent

with and supportive of the diagnosis of SNE. Case 1 had cerebral cortex and basal ganglia involvement. The cortical form of SNE has been reported in the literature[18]. Lesions can also occur in the spinal cord in 74% of patients; however, spinal cord involvement was not detected in our cases[4].

Because of the existence of hemorrhagic petechial areas in Case 1 and the resemblance of histopathological findings to SNE, a differential diagnosis was made with Wernicke's encephalopathy, a CNS disorder due to thiamine dificiency[2,19]. However, neither mamillary bodies nor hypothalamic involvement, most commonly seen in Wernicke's disease, was present[2,7,11]. In some cases of SNE, mamillary body involvement has been reported, and small hemorrhages have also been described[2,5,6,12,13,17].

Diverse biochemical causes have been proposed for the etiology of SNE[2-5]. In recent years, deficiency of pyruvate carboxylase (PC) or pyruvate dehydrogenase complex (PDHc), defective activation of PDHc and defects of the respiratory chain, such as cytochrome c oxidase complex I (reduced nicotinamide-adenine dinucleotide-coenzyme Q reductase) and succinate oxidation have been found to be associated with this disease[2-5]. These enzymes and the respiratory chain are located in the mitochondria, and their deficiencies cause a disturbance in energy metabolism. Thus, SNE is now accepted to be one of the mitochondrial cytopathies[4]. Recently, Ciafaloni et al[14] demonstrated a point mutation at nucleotide 8993 in the adenosinetriphosphatase-6, gene of mitochondrial DNA in the tissues of two half-sisters and their mother.

A disturbance of pyruvate metabolism or a deficiency of the respiratory chain often leads to elevated lactate and pyruvate levels in serum, CSF and urine. Determinations of the levels of lactate and pyruvate in body fluids are therefore of utmost importance in patients suspected of having SNE[4]. However, normal levels have also been described[7,15]. The serum lactate and pyruvate levels were normal in Case 1, while the CSF and urine levels of lactate and pyruvate were not determined. Unfortunately, no biochemical investigations could be done in Case 2.

A recent report by Baumgartner et al[5] of a child with laryngeal stridor, progressive neurologic deterioration, and death at 21 months of age has demonstrated biotinidase deficiency as a cause of SNE. The authors speculated that chronic lactate accumulation in the brain due to metabolic abnormalities may be responsible for the specific neuropathologic lesions in SNE. Lactate has been shown to be toxic to the brain and may be involved in neovascularization[20]. The specific and symmetrical distribution of the CNS lesions in the diencephalon and brain stem may be due to a selective local susceptibility of these structures to metabolic accumulation.

Hypertrophic cardiomyopathy associated with SNE has also been demonstrated on autopsy in some cases[21]; however, cardiomyopathy was not noted in our patients.

In a number of SNE patients, it is possible to demonstrate cerebral lesions on CT scan and magnetic resonance imaging (MRI). The most consistent findings are bilateral radiolucent or hypodense lesions in the basal ganglia, usually localized in the putamen[22]. Bilateral, symmetrical, low-density areas in the thalamus, throughout the midbrain, adjacent to the fourth ventricle and scattered throughout the cerebral cortex, have also been reported. retrospectively, the CT findings in Case 1 are consistent with these descriptions. Medina et al[23] recently reported MRI findings of nine patients with SNE, and emphasized a pattern of symmetrical hyperintense lesions on T2 weighted images involving the basal ganglia and brain stem with predominant involvement of the putamen as highly specific for SNE.

Despite all recent developments, the definitive diagnosis of SNE still rests on pathologic findings. However, specific attention to the signs and symptoms, genetic transmission, disturbances in energy metabolism and bilateral hypodense areas in the basal ganglia region on CT or MRI may lead to a clinical diagnosis in this syndrome.

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PERFORATED DUODENAL ULCER: AN UNUSUAL COMPLICATION OF MENINGITIS*

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SUMMARY: Tanzer F, Baskın E, İçli F, Toksoy H, Gökalp A. (Departments of Pediatrics and Pediatric Surgery, Cumhuriyet University Faculty of Medicine, Sivas, Turkey). Perforated duodenal ulcer: an unusual complication of meningitis. Turk J Pediatr 1994; 36: 67-70.

An 11-month-old boy was admitted to the hospital with fever, vomiting and seizures and was diagnosed with purulent meningitis. Two days later, an acute, perforated, duodenal ulcer was detected in the patient. Surgery was performed, and the patient made an uncomplicated recovery. Peptic ulceration is underdiagnosed in children and this leads to delay in diagnosis and appropriate management. Peptic ulceration may occur during severe illness or viral infections, but perforation is rare. *Key words: purulent meningitis, duodenal ulcer.*

Acute peptic ulcer is not rare in childhood but remains underdiagnosed. Despite this, it is not featured prominently in textbooks, where it is said to be an uncommon but well-recognized complication of many serious diseases as well as severe stress in childhood[1]. A child with an acute peptic ulcer usually presents with vomiting or gastrointestinal hemorrhage or both, or the ulcer may be an accidental finding at necropsy, with perforation a rare occurrence[2,3].

We report perforation of an acute duodenal ulcer in an 11-month-old boy who had purulent meningitis.

Case Report

An 11-month-old boy was admitted to the hospital with a seven day history of vomiting, fever and generalized seizures. On admission, the boy was spastic, and his weight was at the 25th percentile. He had a bulging anterior fontanel. Laboratory examination revealed a hemoglobin concentration of 10.8 g / dl, white blood cell count of 8800 / mm^3 with a differential count of 74% neutrophils, 6% band forms, 20% lymphocytes and a normal platelet count. Urinalysis and

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biochemical tests were normal. Cerebrospinal fluid was cloudy, polymorphonuclear leukocytes 500 / mm^3, protein 90 mg / dl, and the glucose level was below detectable limits. Diphtheroid bacilli grew in the cerebrospinal fluid culture. The patient was diagnosed with purulent meningitis and penicillin G, chloramphenicol and phenobarbital were administered for treatment.

Two days later, vomiting recurred the patient's abdomen become mildly distended. On rectal examination, the feces were soft and normal in color. On radiographic examination, free air was detected under the diaphragm (Fig. 1). In surgery his abdomen was found to be extremely distended, and 300 ml of bile-stained fluid contaminated with food was evacuated. The stomach and duodenum were exposed, and a perforated acute duodenal ulcer 2 cm in diameter was found. Postoperatively, the patient recovered with no complication. Subsequent estimation of serum gastrin concentration was normal.

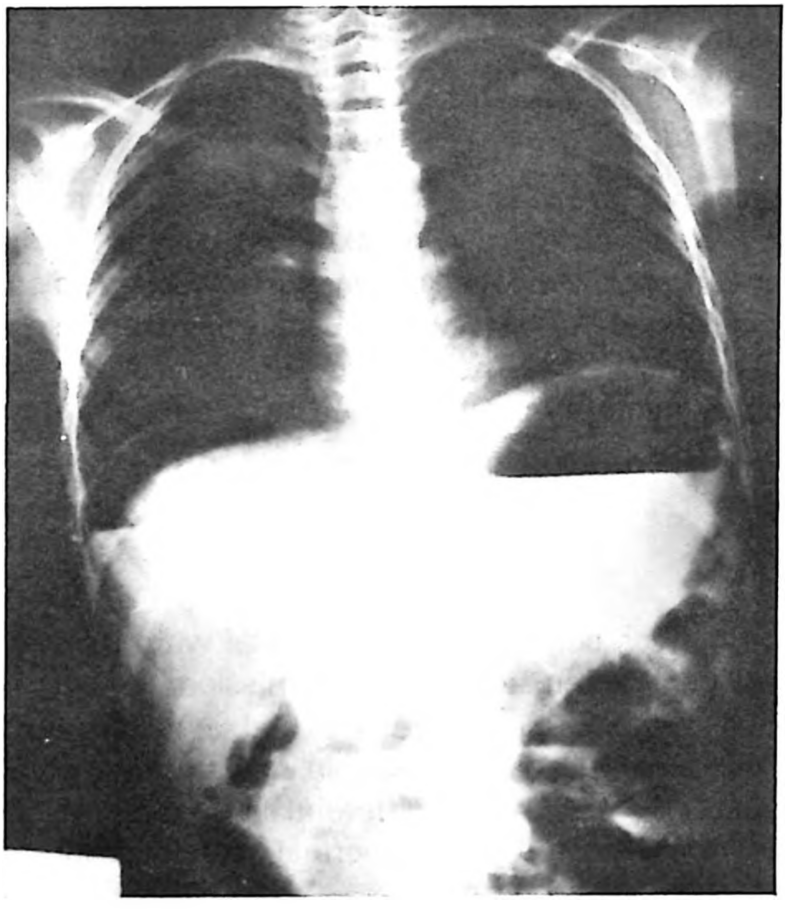

Fig. 1: Abdominal x-ray showing free air under the diaphragm.

Discussion

The occurrence of peptic ulceration in children has been recognized for many years, but the real incidence is unknown (3-4 / 10000-1 / 4700)[2,4]. Peptic ulcer

disease in children is generally described as being either primary or secondary. Primary ulcers occur in the absence of underlying systemic disease, and present at a mean age of eight years in the pediatric population. the male: female ratio is 4: 1. There is often a strong family history[4]. Secondary ulcers or stress ulcers account for at least 80 percent of peptic ulcer disease encountered during infancy and early childhood, but in older age groups the incidence drops to 20 percent. Stress ulcers are associated with shock, respiratory failure, sepsis, hypoglycemia, severe burns (Curling's ulcer) and intracranial lesions[5,6]. We believe that in our case, the stress ulcer occurred because of an intracranial lesion. Stress ulcer is generally an acute disorder. Males and females are affected equally. The distribution has been described as equal between the stomach and duodenum. Patients with stress ulcers generally present with hemorrhage. Perforation is quite rare, however the risk of perforation is higher in duodenal ulcer than gastric ulcer[7-10].

The incidence of perforated peptic ulcer is 6.9-8.7 / 100,000 overall, but the real incidence in children is unknown[11]. In 1826, a perforated gastric ulcer was reported in a 2-day-old child[12]. At the Hospital for Sick Children, Toronto, only six perforations were detected in 20 years[3], and at Montreal Children's Hospital there were eight in 11 years[2]. In a study of 54 children, only eight perforations were reported[13]. Acute duodenal ulceration was reported by Hsu in a study of 31 children and by Murphy in a study of 110 cases. None of these ulcers had perforated[14,15]. In 1990, Wilson presented a patient with a perforated duodenal ulcer as an unusual complication of gastroenteritis[1].

The presented case is interesting because of the development of perforated duodenal ulcer during the course of purulent meningitis. Acute duodenal ulcer may occur during severe illness or viral infections, but perforation is rare.

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The Turkish Journal of Pediatrics 36: 71-75, 1994

TRANSORBITAL STAB WOUND: A CASE REPORT*

*Yusuf Erşahin MD**, Saffet Mutluer MD***, Elif Güzelbağ MD*****

SUMMARY: Erşahin Y, Mutluer S, Güzelbağ E. (Division of Pediatric Neurosurgery, Aegean University Faculty of Medicine, Bornova, İzmir, Turkey). Transorbital stab wound: a case report. Turk J Pediatr 1994; 36: 71-75.

Stab wounds of the skull are uncommon. They are usually accidental in children. An apparently trivial wound may cause death due to vascular damage or infection. A 5-year-old boy presented with a nail in the left intraorbital region. He fell with a nail in his hand five hours prior to hospital admission. Computed tomographic scans displayed the nail penetrating the cranium through the left orbital roof and extending towards the left anterior clinoid process. The nail was removed under general anesthesia in the operating room. Meningitis developed two days after the removal of the penetrating object and responded well to antibiotics. The pertinent literature was reviewed. *Key words: stab wound, head injury, penetrating head injury.*

Penetrating stab wounds of the brain are uncommon. There is a male predominance and the injury is caused by combat in the majority of cases[1-6]. However, this type of injury is usually accidental in children. A 5-year-old boy with a transorbital stab wound is presented and the pertinent literature is reviewed.

Case Report

A 5-year-old boy presented with a nail in the left intra-orbital region (Fig. 1). He fell down with a nail in his hand while running, five hours before he was transferred to

Fig. 1: Photograph showing the penetrating object (nail) in situ.

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our division from an outlying hospital. He was alert and cooperative. His vision and pupillary reactivity were normal. The movements of the left eye to both sides were restricted. Plain x-ray films of the skull revealed a metallic object with intracranial penetration (Fig. 2). The nail, penetrating into the cranium through the left orbital roof and extending towards the left anterior clinoid process, was visible

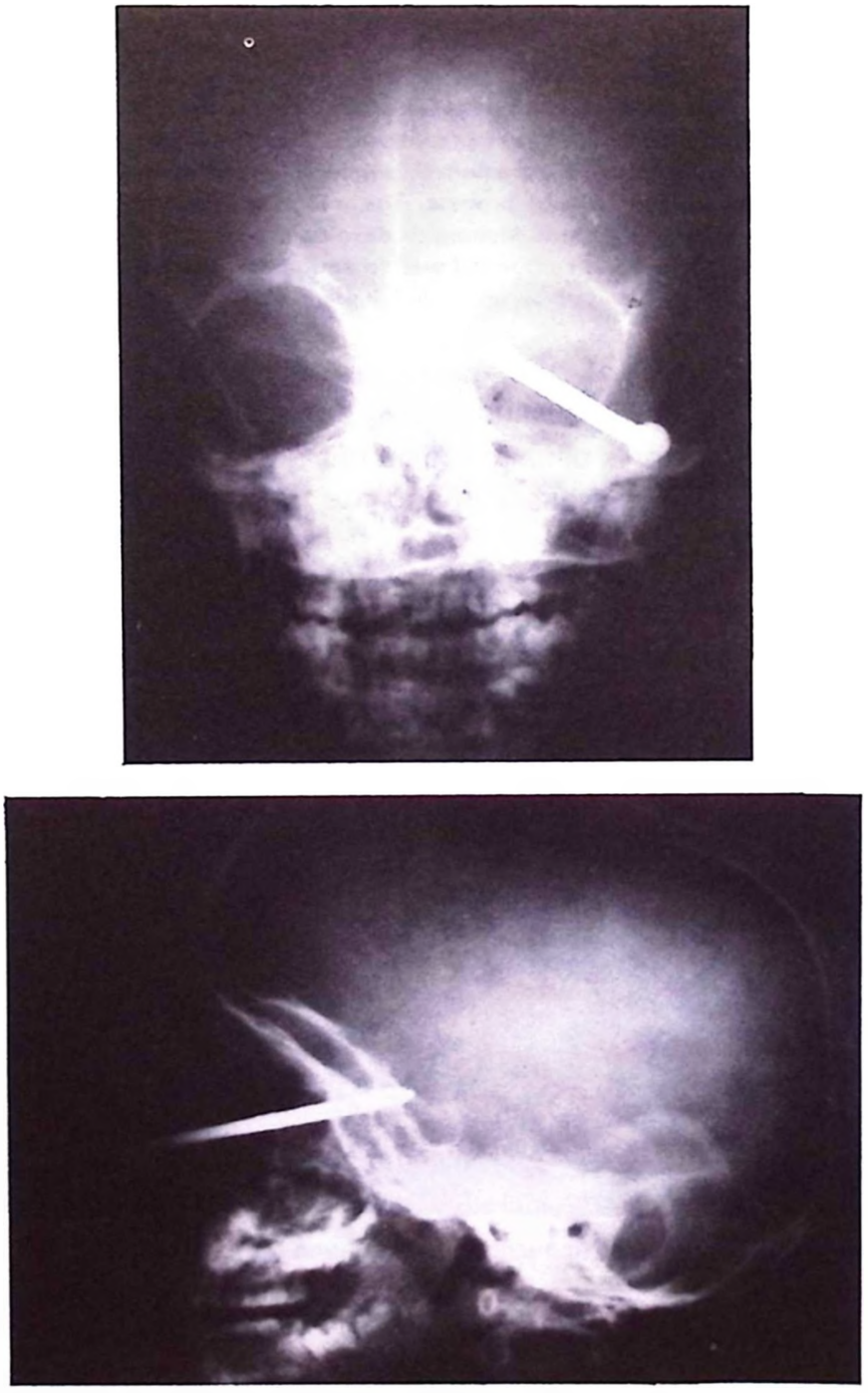

Fig. 2: Plain x-ray films of the skull: (a) anteroposterior and (b) lateral views showing intracranial extension of the penetrating object.

on the computed tomographic (CT) scans (Fig. 3). Tetanus prophylaxis was administered and intravenous antibiotics (mezlocillin, gentamicin and metradinazol) were started. The patient was taken to the operating room and prepared for an emergency craniotomy. The nail was removed under general anesthesia. Cerebrospinal fluid (CSF) came out of the opening for a few seconds after

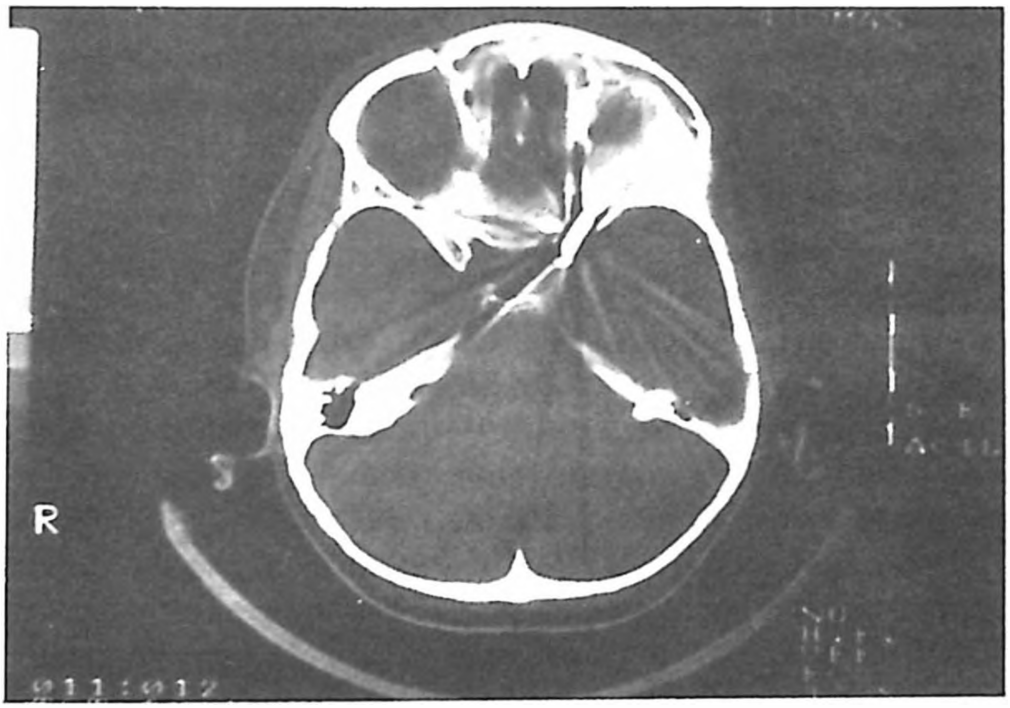

Fig. 3: CT scan showing penetration of the nail into the cranium through the left orbital roof.

removing the object. He awoke from the anesthesia and was taken to the intensive care unit where his consciousness could be closely monitored. Gaze restrictions of the left eye improved remarkably following removal of the penetrating object. Left periorbital edema developed on the following day. On the second postoperative day, he had complained of neck stiffness and he vomited a few times. Lumbar puncture was done and turbid CSF was obtained. Microscopic examination of the CSF revealed 1480 white blood cells / mm^3. He was transferred to the department of infectious disease. No organism grew in the CSF culture as he had been on antibiotics. His symptoms and signs improved, and CSF was normal when he was discharged from the hospital 10 days later. He is neurologically intact six months after injury.

Discussion

Penetrating stab wounds of the skull are uncommon[1,2,5-7]. This is typically an afflicton of the young adult male and usually related to interpersonal violence, assaults and gang warfare[1-7]. Only a small number of reported cases, particularly in children, resulted from accidental stabbing[5-8]. Knives are the objects most commonly used[1-7]; however, nails, spikes, iron rods, pencils, scissors, a fan blade

and screwdrivers have been reported as objects causing stab wounds[4,5,9]. Most stab wounds to the head occur on the left side, reflecting the predominant right-handedness of the assailants[1,2,4,6]. Stab wounds may be obvious and fatal, or a trivial wound may lead to death days or weeks later because of rupture of a traumatic intracranial aneurysm or infection[5].

The mechanism of injury in transcranial stab wounds differs from that of missile or gunshot injuries. There is no concentric zone of coagulative necrosis[10]. Unlike in motor vehicle accidents, brain damage is restricted to the wound tract[11]. In the absence of direct injury to the brain stem or laceration of a major intracranial vessel, the prognosis is good.

Although de Villiers and Sevel[7] mentioned that transorbital stab wounds causing intracranial complications occur more frequently in children than adults, and are reported more often in boys than girls, all of their cases were older than 20 years. The skull and orbital roof of a child can be exceedingly thin[12,13]. The orbit is a quadrangular pyramid on a posteromedial axis. Objects entering near the orbit tend to be funnelled toward the apex. The superior orbital fissure or thin superior orbital plate grants access to the intracranial contents. At the time of injury, the head is often thrown backwards by reflex, further exposing the superior orbital plate. The orbital depth is approximately 42 to 50 mm. Therefore, a pointed object can easily reach and penetrate the dura mater[14,15]. It has been suggested that the globe often escapes injury if a slender-pointed instrument is used. In low-velocity stabs, the eyeball can move into the space afforded by the copious orbital fatty tissue which surrounds the eye. However, the eye is frequently damaged by a large knife[7].

In our case, when the patient fell down, his head conceivably extended and the nail punctured the orbital roof. The globe was not damaged because it was a low-velocity injury. Infection is common in transorbital stab wounds[7,8], caused by either a contaminated penetrating object or communication with the paranasal sinuses. The contaminated and rusted nail caused meningitis in this patient, in our opinion. Birsch-Hirschfield[16] and Kjer[17] have reported 30 cases of tetanus caused by transorbital injury. Ventricular damage, pneumocephalus, subdural, intracerebral and intraventricular hemorrhages, damage to the cavernous sinus, carotid-cavernous fistulae, traumatic cerebral aneurysms, occlusion of the internal carotid artery and cerebral abscesses have been reported as cerebral complications of transorbital stab wounds[5,7,8].

Special views should be taken to demonstrate orbital fractures on the plain x-ray films. The presence of pneumocephalus indicates intracranial penetration or communication between the brain and paranasal sinuses[3,7]. CT scanning can detect intracranial damage or hematoma. But a considerable artifact may seriously impair the interpretation of the CT scan when the penetrating metal object is

embedded in the cranium[3]. Angiography should be performed whenever a vascular complication is suspected[5-7]. Kieck and de Villiers[5] found five cerebral aneurysms at the base of the brain in 20 cases following transorbital stab wounds. They advise repeated cerebral angiographies to detect vascular damage.

The penetrating object should be removed in the operating room. The patient should be prepared for a craniotomy. Antibiotic therapy should be started, and tetanus prophylaxis is mandatory. The patient should be closely followed for infection and vascular complications.

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The Turkish Journal of Pediatrics 36: 77-79, 1994

URETERAL INJURY DUE TO KIRSCHNER WIRE IN A FIVE – YEAR – OLD GIRL A CASE REPORT*

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SUMMARY: Altın MA, Gündoğdu ZH. (Department of Pediatric Surgery, Numune Hospital, Ankara, Turkey). Ureteral injury due to Kirschner wire in a five-year-old girl. A case report. Turk J Pediatr 1994; 36: 77-79.

Traumatic injury to the ureter in childhood is uncommon, and since it is not associated with hematuria may remain undiagnosed for a relatively long period of time. In this paper we reported the case of a five-year-old girl who had ureteral injury due to Kirschner wire application for hip dislocation. We drew attention to the fact that pelvic interventions may be complicated by ureteral injury, and intravenous pyelography to a useful tool to reach the final diagnosis. *Key words: ureteral injury, Kirschner wire.*

Ureteral injuries are uncommon in children, accounting for only 4 percent of all genitourinary trauma[1]. Lower ureteral injury may occur in conjunction with pelvic fractures[2]. Injuries from ureteral catheterization and stone basketing are of more concern in children than adults because of the relatively smaller diameter of the ureter[3]. However, to the best of our knowledge, no patient has previously been reported in the literature as having ureteral injury due to Kirschner wire application.

Case Report

A five-year-old girl was treated in our orthopedic department for bilateral congenital dislocation of the hip. A Kirschner wire was inserted, and she was discharged after immobilization with a pelvipedal cast (Fig. 1a, 1b). She was readmitted three months later with abdominal distension, vomiting and failure to pass stool, and the case was brought for consultation to our department.

Abdominal ultrasonography showed ascites as well as a cystic mass filled with fibrinoid material in the retroperitoneal region posterior to the bladder. The patient was diagnosed with a retroperitoneal pelvic abscess and underwent surgery.

During the operation, ascitic fluid, purulent material and fibrin were found posterior to the bladder, and abdominal ascites was noted. The region was explored and a retroperitoneal drain employed. Following surgical intervention,

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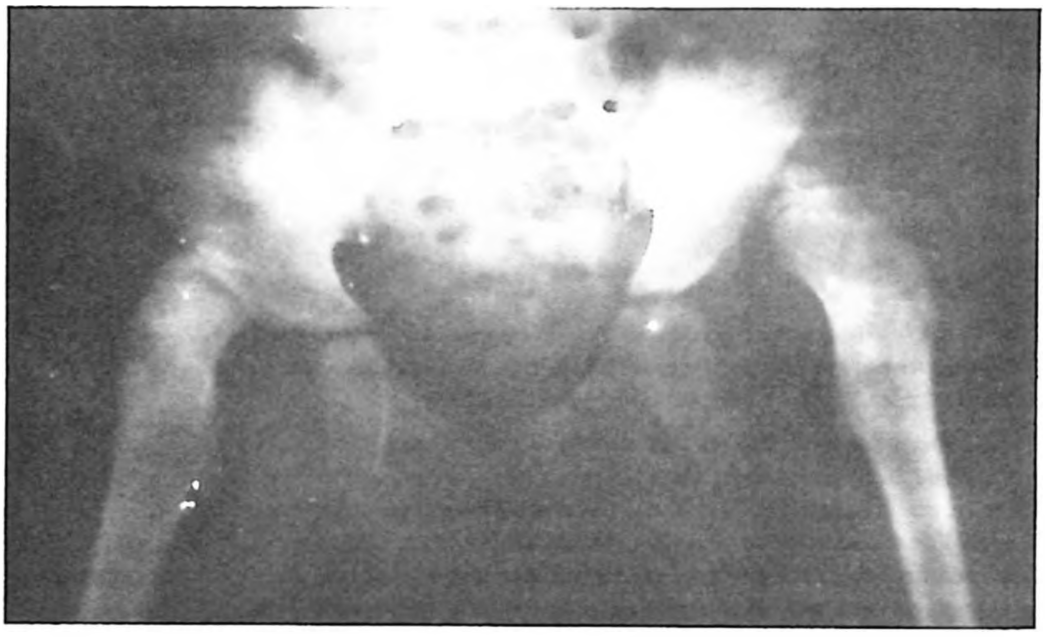

Fig. 1a: Direct pelvic graph of 5 year-old-girl with bilateral congenital dislocation of the hip.

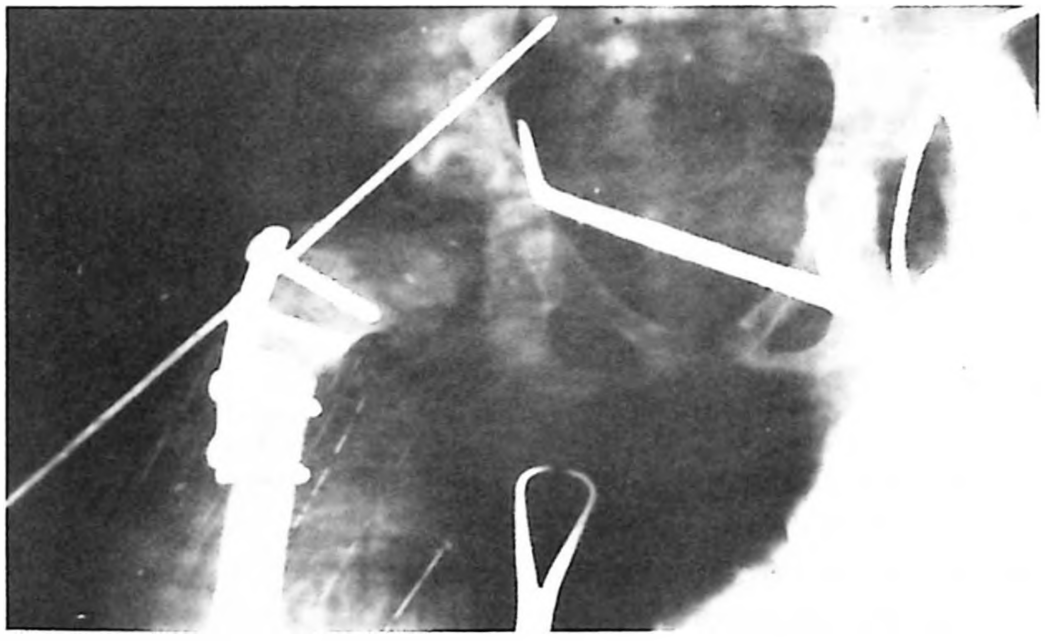

Fig. 1b: After Kirschner wire was inserted.

urine-like fluid was found draining from the operative site. Therefore an intravenous pyelograph (IVP) was done and revealed ureteral urine flowing into the abdominal cavity (Fig. 2). On exploratory surgery, the right ureter was seen to have been sectioned close to the bladder, and the proximal portion of the ureter was fixed to the posterior wall of the abdomen. The right kidney was mobilized downwards, both portions of the ureter were found and after removal of the devitalized ends, the ureter was repaired by end-to-end primary anastomosis. The patient was discharged without further complications and was symptom-free on follow-up.

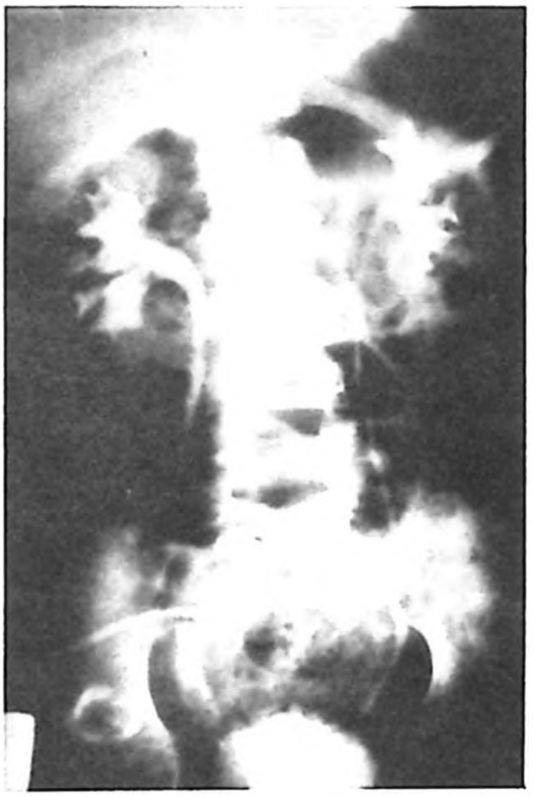

Fig. 2: IVP showing the ureteral extravasation in the pelvic region.

Discussion

Traumatic injury to the ureter in childhood is uncommon. Because children with this injury may not have hematuria, the condition may go unrecognized for a long period following the accident unless an excretory urogram is obtained routinely in cases of severe blunt abdominal trauma[4,5].

This case illustrated that ureteral injuries may occur following pelvic interventions. Our findings emphasize the point that intravenous pyelogram (IVP) sould be performed to avoid dangerous delays in accurate diagnosis.

Acknowledgements

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The Turkish Journal of Pediatrics 36: 81-85, 1994

MULTIPLE SCLEROSIS IN A SIX-YEAR-OLD BOY*
(CASE REPORT)

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*Meral Topçu MD*****, Barış Diren MD******, Aytekin Besim MD*******

SUMMARY: Olcay L, Renda Y, Bakkaloğlu A, Topçu M, Diren B, Besim A. (Departments of Pediatrics and Radiology, Hacettepe University Faculty of Medicine, Ankara, Turkey). Multiple sclerosis in a six-year-old boy. Turk J Pediatr 1994; 36: 81-85.

A 6-year-old boy with multiple sclerosis, youngest diagnosed in our hospital, is presented. In addition to the clinical findings, the diagnosis was supported by increased immunglobulin levels, positive IgG index and oligoclonal bands in the cerebrospinal fluid, normal cranial angiography, typical lesions on the cranial computed tomography and magnetic resonance imaging. *Key words: multiple sclerosis, childhood.*

Multiple sclerosis (MS) is a demyelinating disease which affects the white matter of the central nervous system (CNS). MS often occurs in the third decade of life, and is rare under the age of 15. Females are affected more than males. We present the youngest patient with MS ever encountered in our hospital.

Case Report

A six-year-old boy who was in good health until May 1989 was placed on antibiotic therapy with the diagnosis of pneumonia. Four days later he developed ataxic gait and tended to fall to the left.

The patient was a product of an uncomplicated pregnancy and delivery. His growth and development were normal.

On admission to our hospital, he was found to have an ataxic gait, bilateral dysmetria, dysdiadokokinesia, hyperactive deep tendon reflexes (DTR), and bilateral Babinski and clonus signs. He did not display nystagmus or dysarthria. Lumbar puncture revealed normal cerebrospinal fluid (CSF) pressure, 30 cells /

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mm^3, 11 of which were lymphocytes; a protein level of 48 mg / dl; a glucose level of 68 mg / dl; and negative cultures for microorganisms. Electroencephalogram showed a paroxysmal disturbance of electrical activity originating from the right posterior regions of the brain. Cranial computed tomography (CT) showed multiple hypodense areas in the cerebellum. The patient received sulbactam and ampicillin therapy 200 mg / kg qid, as well as dexamethasone 0.6 mg / kg qid orally for 15 days. CT taken on the sixth day of therapy showed that all of the former lesions had disappeared. His symptoms gradually resolved and ceased. He was readmitted eight months later with complaints of nausea, vomiting, gait ataxia, a tendency to fall to the left, holding his head to the left, and swaying to the left. On examination, he had gait ataxia, intentional tremor, uncoordinated movements, hyperactive DTR, bilateral Babinski and clonus signs, head tilt to the left, astenia, hypermetria, dysdiadokokinesia, asinergia and explosive dysarthria. He did not display nystagmus.

Complete blood cell count, urine analysis, hepatic and renal function tests, erythrocyte sedimentation rate, lactic acid, pyruvic acid, ammonia, urine and serum aminoacids were found to be normal; C-reactive protein (CRP), latex, antinuclear antibody (ANA), anti DNA, salmonella, brucella, Paul-Bunnell agglutination tests, vanylmandelic acid in urine were also negative. CSF pressure was normal, with slightly elevated protein (48 mg / dl) and normal glucose levels, with no cells. Bacterial cultures were negative. CT disclosed two hypodense lesions in the posterior fossa with no mass effect or edema. Magnetic resonance imaging (MRI) showed multiple hyperdense lesions of the white matter at T2 weighted imagings which were considered as plaques of multiple sclerosis in the centrum semiovale, pons, mesencephalon, pedunculus cerebelli, around the periventricular region and more often in the left cerebellar hemisphere. IgG in CSF was 7.8 mg / dl (normal range is 1.5 - 5.5 mg / dl). IgG index, which is obtained by measuring CSF IgG / albumin over serum IgG / albumin was 0.8 (ratio greater than 0.77 is generally considered abnormal). Oligoclonal bands in CSF were positive. Brainstem auditory-evoked responses (BAER) showed prolonged central conducting time, while visual-evoked potentials (VEP) were normal.

Dexamethasone therapy was started at a dose of 0.6 mg / kg / day qid, orally. By tapering down the dose, it was stopped within six weeks. On the fifth day of the treatment, cerebellar findings gradually resolved, then subsided.

Discussion

Multiple sclerosis (MS) often occurs in the third decade of life and is rare under the age of 15 and over the age of 50. The incidence of initial manifestations before 16 years of age is 2.7%[1], while the incidence before 10 years of age is 0.3%[2]. The youngest patient documented with MS is a 24-month-old girl[3]. Our case is the youngest MS case ever encountered in our hospital.

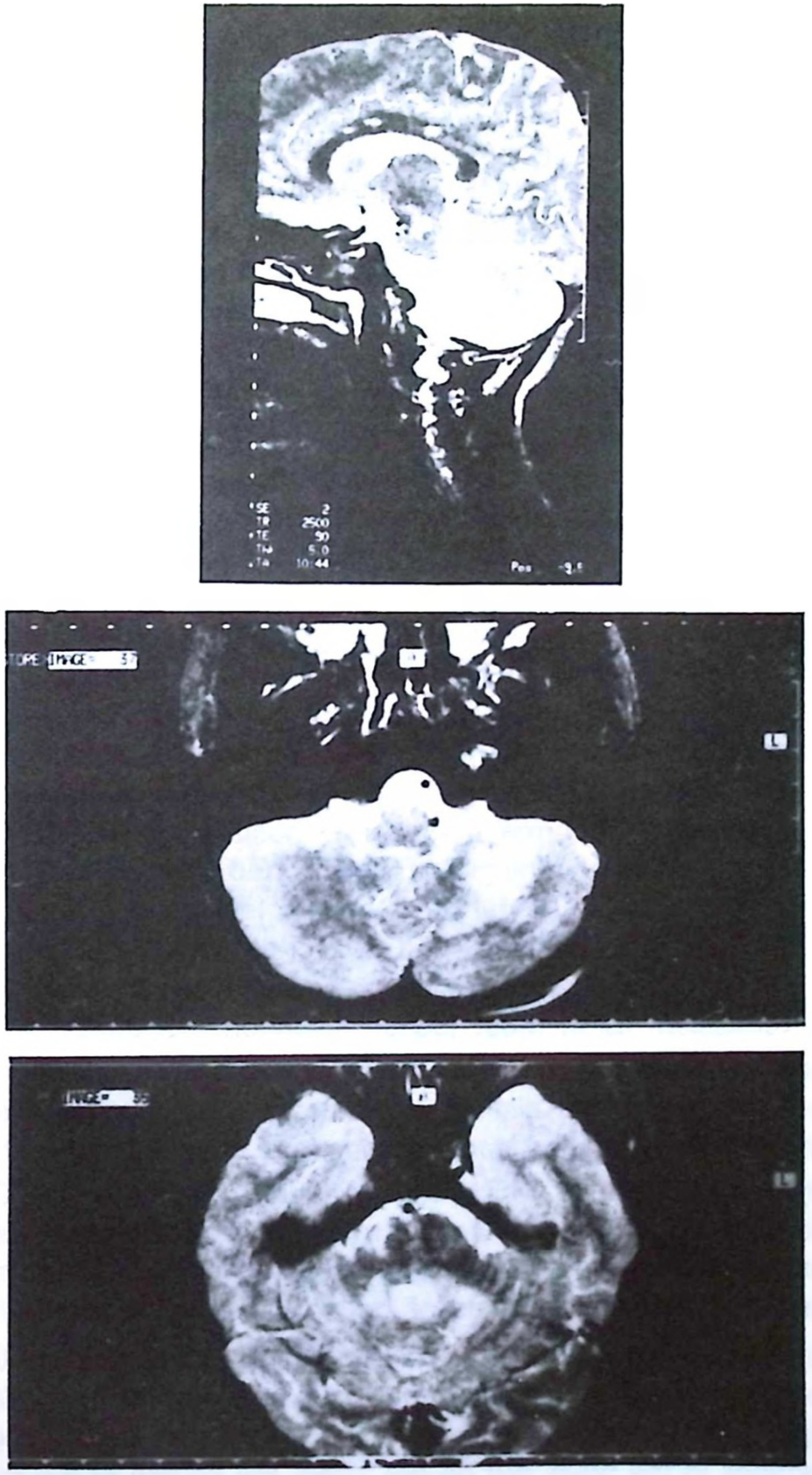

Fig. 1: T2 weighted segments (TR / TE: 2500 / 90 msec) sagittal (a) and transverse (b, c) images.
a) Hyperintense lesions in pons, mesencephalon, corpus callosum and cerebral white matter.
b) Hyperintense lesion in left cerebellar hemisphere.
c) Demyelinating plaque in pons and bilateral dentate nuclei are seen.

The female / male ratio is 2 / 1 in the total MS population and 3 / 1 in the childhood group[1]. On the other hand, a relative overpresentation of boys has been reported in the late-onset forms of MS with poor recovery and a progressive course[2]. Although our patient is male, the disease is neither a late-onset nor a progressive form of MS. This implies that our patient displays a relatively rare property of childhood MS. During both of his hospital admissions, the patient elicited signs of cerebellar dysfunction which denoted involvement of cerebellar hemispheres, partially paleocerebellum and perhaps vermis and / or fasciculus longitudinalis. As initial manifestations, the reported incidences of certain symptoms are as follows: gait problems and ataxia 5-50%, nystagmus 35-75%, dysarthria 6-50%[2,4,5].

Laboratory tests for MS are not specific but have supportive value. Mildly increased CSF protein, leukocyte count of up to 20 / mm^3, and elevation of gammaglobulin to greater than 12% of total protein without any corresponding increase in serum gammaglobulin are notable. IgG index is abnormal in up to 80-90% of patients with MS. Our patient's IgG index was 0.8. A ratio over 0.77 is generally considered abnormal[5]. IgG with an oligoclonal nature, denoting the presence of plasma cells in the plaques, is present at rates of 90% in definite and 30-40% in possible MS cases; nevertheless, it may also be seen in some other inflammatory diseases of the central nervous system (CNS)[5]. By using both BAER and VEP, subclinical lesions are detected in 71% of cases, and the addition of sensory-evoked potentials and blink reflexes contribute an additional 3% of cases[6,7]. Our patient's abnormal IgG index, positive oligoclonal bands, and prolonged central conduction time in BAER supported the diagnosis. Although CT is very helpful, MRI is more useful for detecting lesions in the posterior fossa which are poorly demonstrated by CT and also for detecting silent plaques except on the optic nerve[8,9]. The patient's clinical course was characterized by periods of relapse and remission, as in most (56%) childhood MS attacks.

By Poser's classification, our patient is consistent with a clinically definite MS, as there were two attacks and clinical evidence of two lesions. Those attacks occurred one month apart and each lasted more than 24 hours[10].

Other differential possibilities which cause multiple lesions of the CNS with a course of relapes and remissions include meningovascular syphilis, sarcoidosis, cerebellar abcesses, arteriovenous malformations and vasculitis. In our case these are all excluded on the basis of both clinical and laboratory data.

There is no definite therapy for MS. Adrenocorticotropine hormon (ACTH) and corticosteroids are used in the early phase, especially for the relapsing and remitting type. These medications shorten the duration of attacks and modulate immune reactions in the brain, but do not affect the course of the disease[11,12]. Azathioprine, cyclophosphamide, cyclosporin, lymphatic irradiation and plasmapheresis are being used as a trial[11]. Physical therapy and psychotherapy are also useful in the chronic phase.

We found that our patient's cerebellar findings gradually resolved from the beginning of the fifth day of the oral corticosteroid therapy, which was stopped within six weeks by gradual reduction. Since then the patient has been well and has not had any complaints.

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KOSTMANN'S SYNDROME WITH CHRONIC PNEUMONIA AND LYMPHOCYTOSIS: EFFECT OF RECOMBINANT HUMAN G – CSF*

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SUMMARY: Yetgin S, Özbek N, Tuncer M, Göçmen A, Özçelik U. (Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Kostmann's syndrome with chronic pneumonia and lymphocytosis: effect of recombinant human G-CSF. Turk J Pediatr 1994; 36: 87-91.

Kostmann's syndrome is a congenital disorder characterized by impairment of myeloid differentiation in bone marrow with severe absolute neutropenia. A 17-month-old girl was admitted to the hospital with complaints of recurrent skin infections since birth and severe pneumonia of the right lung which had been resistant to antibiotics since the patient was eight months old. Anemia, severe neutropenia and maturational arrest of granulocytes at the myelocyte stage in bone marrow were detected. At the age of 20 months, a right pneumonectomy was performed because of resistant cystic infection. Postoperatively, she was diagnosed with Kostmann's syndrome. Recombinant human granulocyte-colony-stimulating factor (rhG-CSF) was administered intravenously at a dose of 3 μg / kg / day, gradually increasing to 60 μg / kg / day in sequential seven-day courses to obtain a neutrophil count of more than 500 cells / mm^3. Absolute neutrophil counts increased to greater than 1000 cells / mm^3 at a dose of 60 μg / kg / day, and at that time bone marrow aspiration revealed an increase in neutrophilic granulocytic precursors beyond the myelocyte stage. In order to maintain the neutrophil response, a dose of 20 μg / kg / day rhG-CSF subcutaneously was continued successfully. The patient has tolerated rhG-CSF treatment without complications, and infectious attacks have significantly decreased. *Key words: congenital agranulocytosis, congenital neutropenia, Kostmann's syndrome, recombinant human granulocyte-colony-stimulating factor.*

Kostmann's syndrome is a congenital disorder usually detected in the first months of life. The syndrome is characterized by bone marrow morphology displaying maturational arrest of the development of neutrophil precursors with severe absolute neutropenia (500 neutrophils per microliter or less) and variable degrees of monocytosis, eosinophilia. thrombocytosis and hypergammaglobulinemia[1,2]. Children with this disorder suffer infections that may be either recurrent local infections or severe septicemia, thus accounting for the high morbidity and mortality associated with this syndrome.

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The etiology of the disease is not clearly understood. Anti-neutrophil antibodies and serum inhibitors have not been shown to be causative. Various approaches, including leukocyte transfusions or the administration of steroids, testosterone, lithium and vitamin B_6, have been used to stimulate neutrophil production[3-5]. Although bone marrow transplantation is the best treatment for this disease, several difficulties limit its successful application. Recent publications have described good results with the administration of granulocyte-colony stimulating factor (G-CSF)[6-9]. In this report, a patient with Kostmann's syndrome, who was diagnosed initially with tuberculosis because of chronic pneumonia and lymphocytosis, is presented along with the results of G-CSF treatment.

Case Report

A 17-month-old girl was admitted to the hospital with cough, weakness, and reported weight loss since the age of eight months, as well as recurrent skin infections since birth. At the age of nine months, she developed severe pneumonia which was resistant to antibiotics. At that time, the patient's immunoglobulin A,G,M levels were high. PPD test and acid fast bacterium staining of bronchial and gastric lavage specimens were negative. She was given antituberculous therapy because of the presence of consolidation in the upper part of her right lung as well as pleural effusion on chest radiograms, lymphocytosis in peripheral blood, and unsuccessful nonspecific antibiotic regimens.

On admission, her weight was 10.5 kg and height 80 cm. Physical examination revealed oral angular cellulitis, furuncles on the face, clubbing, and no breath sounds in the upper part of the right lung. Hematological findings were as follows; Hb 5.8 g / dl, WBC 8200 / mm^3, reticulocyte 3%; the peripheral blood smear revealed hypochrome microcytic red cell morphology with 3% neutrophils, 16% eosinophils, 17% monoytes, 64% lymphocytes and thrombocytosis. Red cell mean corpuscular volume (MCV) was found to be 56 fl, serum iron level 12 µg / dl and iron binding capacity 270 µg / dl. Bone marrow aspiration revealed maturational arrest at the myelocyte stage. Immunophenotyping of bone marrow monocytes revealed 3% CD-34, 8% CD-19, 2% CD2, 2% CALLA, and classification as null-cell type. Immunoglobulin levels were as follows: IgG 6660 mg / dl (N: 889 ± 223), IgM 353 mg / dl (N: 118 ± 24), IgA 496 mg / dl (N: 659 ± 159). Nitro blue-tetrazolium dye test was low but within normal limits. Liver and renal function tests and coagulation parameters (PT, PTT, fibrinogen and fibrin split products) were within normal limits, and RAST tests for cow's milk and egg were negative. Chest x-ray, tomography and bronchoscopy showed signs of chronic pneumonia. The patient was diagnosed with Kostmann's syndrome and chronic pneumonia. Tuberculosis was ruled out since the diagnostic tests for tuberculosis were negative and the antituberculosis treatment was unsuccessful.

At the age of 20 months, a right pneumonectomy was performed. Pathological examination showed pneumonia with abscess formation and reactive hilar lymphadenopathy.

Postoperatively, the patient was given rhG-CSF (Roche) initially at a dose of 3 µg / kg / day by intravenous infusion over 30 minutes. Thereafter the bolus doses were increased to 10, 30, and 60 µg / kg / day in sequential seven-day courses. A response to therapy was achieved at a dose of 60 µg / kg / day with an increase in the absolute neutrophil count to greater than 1000 cells per microliter. At that time, bone marrow aspiration revealed an increased number of neutrophilic granulocytic precursors beyond the mylocyte stage. One third of the maximum dose (amounting to 20 µg / kg / day) was continued daily by subcutaneous injections and was found to be sufficient to maintain the neutrophil response (Fig. 1, Table I).

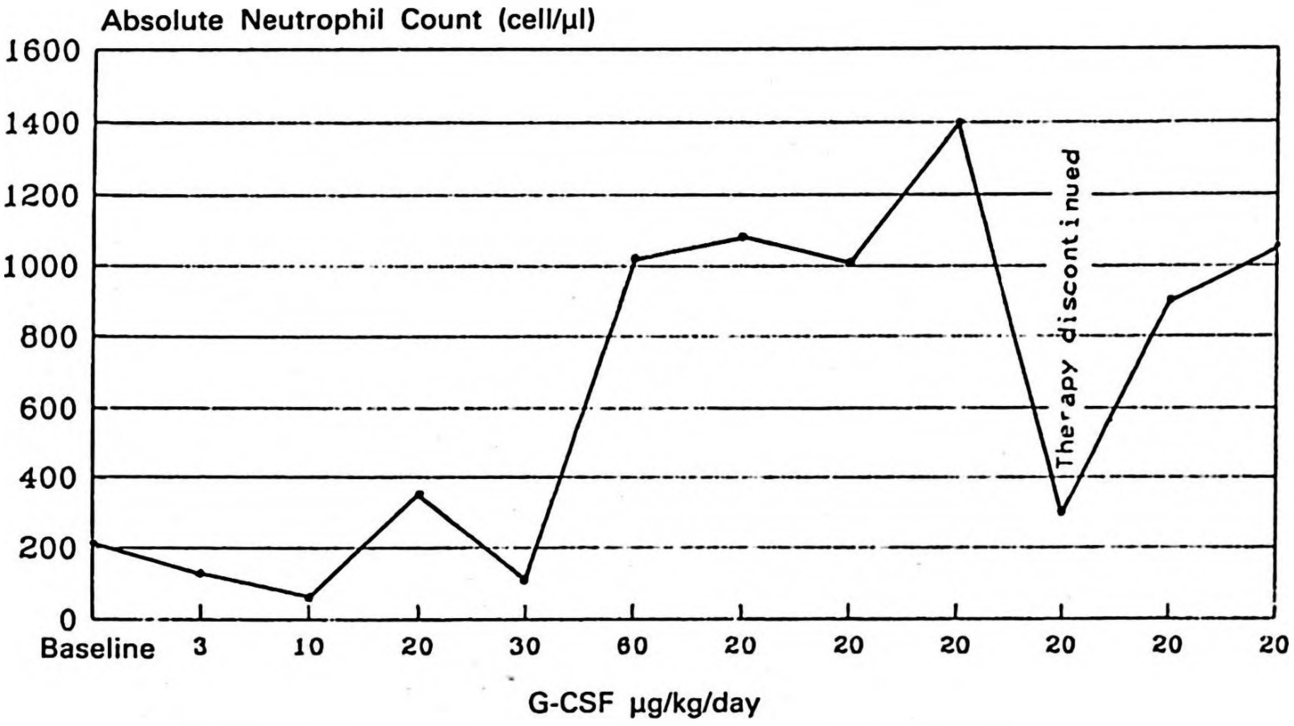

Fig. 1: The changes in the absolute neutrophil count releated to G-CSF dose

Discussion

The patient was diagnosed with Kostmann's syndrome because of progressive pulmonary infections resistant to antibiotics, recurrent skin infections, peripheral neutropenia, eosinophilia, and monocytosis with maturational arrest at the myeloid stage in the bone marrow. Allergic factors for eosinophilia were excluded in the etiology before the diagnosis of Kostmann's syndrome was made. The unremitting decreases in the level of absolute neutrophil count with recurrent infections in the follow-up period confirmed the diagnosis.

Table I: Hematological Findings Before and After G-CSF Treatment

	Hb (g/dl)	Ret (%)	WBC (10^9/L)	Neutrop (%)	Lymph (%)	Eosinop (%)	Basop (%)	Monoc (%)	Thromboc (10^9/L)
Baseline	5.8	3	8.2	64	16	17			433
G-CSF 20 µg/kg/day (Maintenance)	11.5		7.1	14	66	16	2	2	250

Hb : Hemoglobin.
Ret : Reticulocyte.
WBC : White blood cell.
Neutrop : Neutrophil.
Lymph : Lymphocyte.
Eosinop : Eosinophil.
Basop : Basophils.
Monoc : Monocyte.
Thromboc : Thrombocyte.

Although Kostmann's syndrome is a rare disease, it is a model for the design of therapy in different neutropenic states. G-CSF, which is a one of the recently purified, molecularly cloned hematopoietic growth factors, promotes the proliferation and differentiation of granulocytes, both in-vivo and in-vitro.

Our patient responded to G-CSF therapy, achieving a neutrophil count greater than 1000 cells per microliter in peripheral blood and the maturation neutrophil stage at a dose of 60 µg / kg / day. These results remained at the same level for six months while the patient was receiving subcutaneous therapy decreased to one third of the maximum intravenous dose. These findings are similar to those documented in the literature[8,9]. No clinical or laboratory side effects of G-CSF have been detected in our patient so far. Preexisting chronic infections have resolved clinically, and the number of infectious episodes have decreased. Our patient's favorable progress reflects the effect of G-CSF on the number and function of neutrophils in congenital severe neutropenia. We thus conclude that this therapy could be useful for patients with other types of neutropenia.

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