THE TURKISH JOURNAL OF PEDIATRICS

A joint publication of the
Turkish National Pediatric Society
and the Hacettepe University
Institute of Child Health

ADDRESS FOR SUBSCRIPTIONS AND CORRESPONDENCE
The Turkish Journal of Pediatrics
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This Journal is listed in Current Contents, Index Medicus, Abstracts on Hygiene and Communicable Diseases, Tropical Diseases Bulletin, the CAB Abstracts database and the Excerpta Medica database EMBASE.

VOLUME: 37 NUMBER: 1 JANUARY - MARCH 1995

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Owner: The Turkish and International Children's Center and the
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The Turkish Journal of Pediatrics 1995; 37: 1-5

LEFT VENTRICULAR SIZE FOLLOWING SHUNT OPERATION IN TETRALOGY OF FALLOT*

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SUMMARY: Özkutlu S, Saraçlar M, Öztunç F, Bozer AY, Özme Ş. (Cardiology Unit, Department of Pediatrics and the Department of Cardiovascular and Thoracic Surgery, Hacettepe University Faculty of Medicine, Ankara, Turkey). Left ventricular size following shunt operation in tetralogy of Fallot. Turk J Pediatr 1995; 37: 1-5.

This study was performed in 24 patients with tetralogy of Fallot in whom shunt operation was performed instead of total correction because of small left ventricular end-diastolic dimension. Left ventricular end-diastolic dimension was measured using M-mode and two-dimensional echocardiography pre-and at least one year postoperatively.

There was no change in the postoperative left ventricular size in two patients. However, in the other 22 patients, the left ventricular dimension was increased to 70 to 103 percent of normal left ventricular size.

According to the findings of this study, we can conclude that the patients in whom shunt operation was performed would most likely have an increased left ventricular size over time. *Key words: echocardiography, left ventricular size, tetralogy of Fallot, shunt procedure.*

In tetralogy of Fallot (TOF) it has been demonstrated that the left ventricle is smaller in size than normal, and it is believed that a small left ventricle indicates a somewhat greater risk for complete repair[1-8]. Some centers consider this to be an indicator for a shunt operation rather than open-heart repair, with the expectation being that the resulting increase in pulmonary venous return will improve the capacity of the left heart over time[1-13].

Studies have been performed to evaluate the left ventricular size that might affect the operative mortality in TOF[6-8,12,14,15]. There are, however, only a few reports of increase in left ventricular size after shunt operation[10,15].

In order to evaluate the effect of shunt operation on the left ventricular size preoperatively and at least one year postoperatively, echo-cardiographic measurements were obtained.

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Material and Methods

This study was performed on 24 patients with TOF in whom shunt operation was applied because their left ventricular end-diastolic dimension was small (less than 66 percent of normal). Eleven of the patients were female and 13 were male. Their ages ranged from six months to seven years (mean three years eight months).

Echocardiography was performed in all of the cases. A Toshiba Sonolayer-S SSH 60 echocardiograph with 3.75 and 5 mHz transducers was used. Additionally, cardiac catheterization was performed in 16 patients.

The left ventricular end-diastolic dimensions were measured on M-mode echocardiographic recordings obtained in the standard two-dimensional cursor position.

Evaluation was made from the septal surface to the posterior wall endocardium of the left ventricle at the time of ventricular depolarization as indicated by the Q or R wave of the simultaneous electrocardiogram. Measurements were obtained in at least three cardiac cycles, and their mean values were compared with the normal values of left ventricular end diastolic dimensions determined by Gutgesell and Paguet[16].

Results

Pre-and postoperative left ventricular end-diastolic dimension, the percentage comparison with the normal, and the time interval between the date of the operation and the postoperative echocardiographic evaluation are shown in Fig. 1.

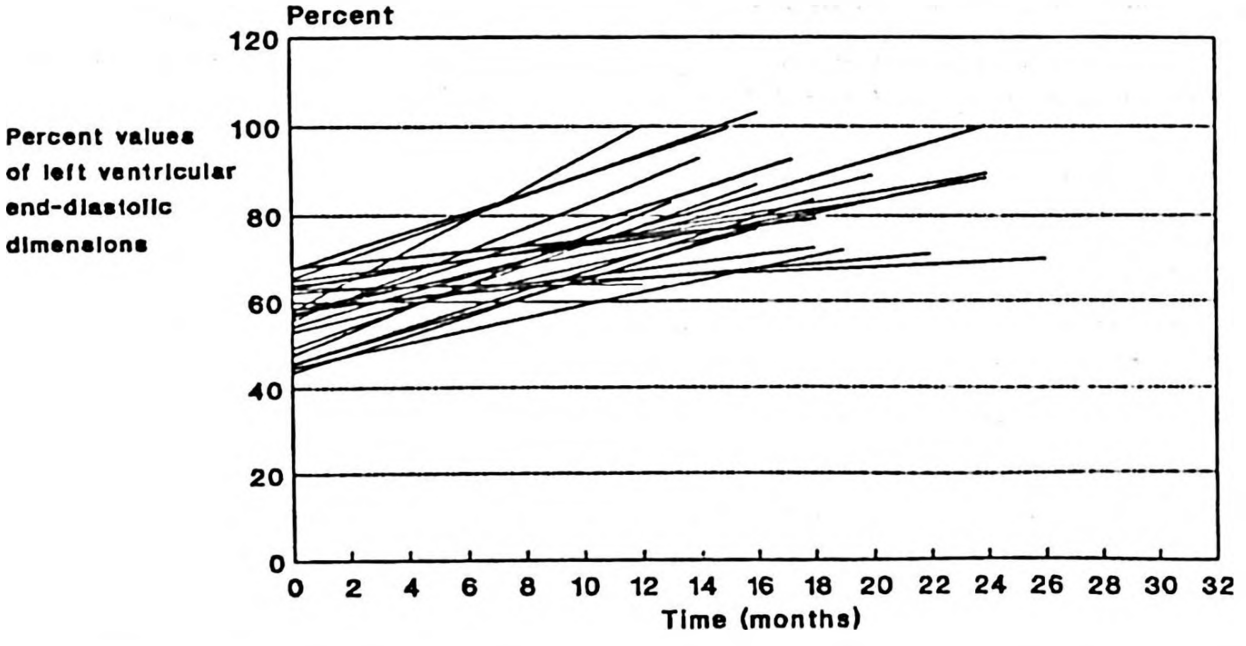

Fig. 1: Percent values of the left ventricular end-diastolic dimensions obtained by the comparison between those of normal and patients; and their changes following shunt operation are shown.

The left ventricular end-diastolic dimension did not change in two patients. However it increased (8%-45%) in 22 patients.

Seventeen of the 24 patients underwent total correction. In no cases were early postoperative death or low cardiac output syndrome observed.

When anlayzed by using paired sample t test, the difference between pairs of observations was found to be statistically significant ($P < 0.05$).

Discussion

The presence of a decreased left ventricular end-diastolic volume has been reported in patients with TOF both in cineangiographic and echocardiographic studies and anatomical specimens[1-6]. Although some authors[17,18] have reported that a small-sized left ventricle is not associated with surgical mortality, this theory has not been accepted by most others[1-14].

Graham et al. proposed that the shunt operation be carried out on cases whose angiographic left ventricular volume was less than 55 percent of the normal[7,8].

Oberhansli and Friedli[15] recorded that young children with severe left ventricular hypoplasia have a higher corrective surgery mortality. They proposed that a left ventricular size of at least 65 percent of normal measured by M-mode technique would be a criterion for successful total correction[15]. Miller et al.[4] found that left ventricular size was about 70 percent of normal in most of their cases. However, they noticed that if the size is less than 60 percent of normal, the case would be severe.

Naito et al.[11] recommended that in cases with an end-diastolic volume index of less than 30 ml/m^2, palliation by the systemic to pulmonary arterial shunt procedure is indicated. Setsuie et al.[14] suggested an initial shunt procedure in patients with an end-diastolic volume index of less than 40 ml/m^2. Nomoto et al.[12] reported that a left ventricular end-diastolic volume of 60 percent of the normal values is a safety limit for total correction in patients under two years of age.

According to our previous study in which left ventricular size was measured by M-mode echocardiography, 70 percent of the cases whose dimensions were less than 66 percent of normal died following total correction due to left heart failure[6]. Given these results, we suggested that the limit line for the left ventricular dimension be 66 percent of the normal values for the decision of corrective surgery, or shunt operation[6]. After this criterion was incorporated in our institution, 24 patients whose left ventricular end-diastolic dimension was below 66 percent of normal underwent shunt operation, and their left ventricular end-diastolic dimensions were measured one to two years (mean 18.4 months) after surgery.

Among the echocardiographic methods, M-mode measurement of left ventricular end-diastolic dimension on two-dimensional image of parasternal long-axis view was arbitrarily preferred in our study since it has been accepted to be simple and reproduceable[15,19].

All patients, excluding two whose left ventricular end-diastolic dimension did not increase displayed significant development in left ventricular size following shunt operation. This enabled the patients to have total correction more safely.

Oberhansli and Friedli[15] showed in five patients who had undergone a previous palliative procedure before total correction, that left ventricular dimensions approached or exceeded normal values (range 81 to 105 percent). Jarmakani et al[10], reported that preoperative left ventricular end-diastolic volume was less than normal in cyanotic children more than two years of age. This variable increased significantly after either a functioning shunt procedure or complete correction. In eight patients who had undergone a shunt procedure, while the preoperative left ventricular end-diastolic dimension was 95 ± 13 percent of normal, postoperatively these values reached 144 ± 12%[10]. In our study, although left ventricular end- diastolic dimensions were between 70 and 103 percent of normal (mean 28.7%) in 22 patients, in the remaining two cases the values did not change one year after surgery.

Kirklin et al.[18] and Malm et al.[17] concluded that the left ventricle would not be small if the patients were over four or five years of age. Contrary to these reports, in our previous study, 13 patients who died after total correction operation and whose ventricular end-diastolic dimensions were below the 66 percent limit line, ranged in age from three to 16 years. In addition, in the present study the age of seven patients was above four years. Those findings do not support Kirklin[18] and Malm[17]'s report. Furthermore, data obtained from our three and seven-year-old patients whose left ventricular end-diastolic dimension did not show any increase following shunt operation over time is against their belief.

In conclusion, we can suggest shunt operation in patients with a small left ventricle. Thus, left ventricular size is expected to be enlarged over time to enable an increased chance for total correction.

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The Turkish Journal of Pediatrics 1995; 37: 7-13

RENAL REPLACEMENT THERAPIES FOR CRITICALLY ILL PEDIATRIC PATIENTS*

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SUMMARY: Sakarcan A, Karaböcüoğlu M. (Department of Pediatrics, University of Texas Southwestern Medical Center, Dallas, Texas). Renal replacement therapies for critically ill pediatric patients. Turk J Pediatr 1995; 37: 7-13.

It could be a a great challenge for a nephrologist to prescribe a renal replacement therapy for a critically ill, hemodynamically unstable pediatric patient. Intermittent hemodialysis and peritoneal dialysis frequently fall short of being an optimal renal replacement therapy for such a patient. Continuous hemofiltration is offering new alternatives that can deliver sufficient clearance to meet the needs of a critically ill child. High fluid intake required for total parenteral nutrition and medications can easily be fulfilled by these modalities without compromising the cardivascular system. Of these techniques, continuous veno-venous hemofiltration is superior to continuous arterio-venous hemofiltration because it delivers a consistent ultrafiltration rate dependent on pump-driven blood flow and does not require the insertion of a large-bore catheter into an artery. Thus, various modalities of hemofiltration can offer an alternative to the critically ill child with acute renal failure. *Key words: critically ill pediatric patient, hemofiltration, end-stage renal disease, renal replacement therapies.*

The mortality rate associated with acute renal failure (ARF) complicating catastrophic medical illness in pediatric patients is reported to be between 83 and 100 percent[1-3]. Surgical acute tubular necrosis treated with hemodialysis also has a mortality rate as high as 70 percent[4]. On the other hand, ARF requiring hemodialysis for a primary nephrologic disorder results in a 90 percent survival rate[1]. The aggressive application of peritoneal dialysis (PD) or hemodialysis (HD) has had little impact on these mortality figures, perhaps because of the severity of the underlying medical or surgical condition. PD and intermittent HD are technically feasible procedures for infants and children, but with some major problems. Since acute intermittent HD tends to cause rapid osmolar shifts and hemodynamic instability, it is not well tolerated, particularly by children[5,6]. PD is contraindicated in patients with abdominal trauma or surgery and may also worsen respiratory function in a critically ill patient[5,7]. It may be complicated by access difficulties, peritonitis and metabolic derangements[8,9]. Newer techniques that combine dialysis and filtration on a continuous basis now offer excellent control of azotemia, solute and water removal, and hemodynamic instability[10-15].

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The purpose of this article is to discuss these new modalities in renal replacement therapy (RRT) for critically ill pediatric patients with brief case presentations.

Case 1

The patient was an eight-year-old white male admitted to the pediatric intensive care unit with high fever and seizure activity. Intravenous antibiotic and antiepileptic therapy was initiated. On the second day of hospitalization, the patient developed anuria. The laboratory results showed an increase in BUN from nine to 30 mg/dl, and in creatinine from 0.8 to 2.5 mg/dl. The patient suffered cardiorespiratory arrest due to hyperkalemia (K: 9.0 mEq/L), which necessitated HD. Meanwhile, his muscle enzyme level was found to be very high, leading to the diagnosis of rhabdomyolysis (creatine phosphokinase 6450 IU/L). On the third day of hospitalization, the patient's weight increased from 30 kg to 33 kg. He frequently developed hypotension during HD sessions due to aggressive fluid removal. Due to the limitations of his fluid intake, his calorie intake was only 11 kcal/kg/day, with a protein intake of 0.3 g/kg/day. He was placed on continuous arterio-venous hemofiltration (CAVH) using diafilter 20 cartridge (Amicon, Danvers, MA) with a blood flow of 150 ml/min at an ultrafiltration of 1000 ml/hr. He was treated with this modality for six days. Because of the unlimited allowance of fluid intake, his calorie and protein intake increased to 43 kcal/kg/day and 1.4 g/kg/day, respectively. He was transferred from the intensive care unit to the ward with normal kidney function.

Case 2

A four-month-old male, a neonatal intensive care unit graduate, was admitted to the pediatric intensive care unit with candida meningitis. He was placed on Amphotericin B. On the third day of hospitalization, he developed hemodynamic instability and acute respiratory distress syndrome that required mechanical ventilation. On the fourth day of hospitalization, his blood culture grew Pseudomonas auregenosa, and the patient was placed on gram negative antibiotic coverage. Subsequently, he developed anuria that did not respond to aggressive diuretic therapy. Laboratory results yielded an increase in BUN from 22 to 40 mg/dl and creatinine from 1.3 to 2.5 mg/dl. His weight increased from 4 kg to 5.5 kg with a concomitant increase in ventilatory support. Inotropic support was also initiated due to persistent hypotension. The patient was placed on continuous veno-venous hemofiltration (CVVH) with bm 11 Blood Monitor Pump (Baxter, Illinois) using a diafilter 20 cartridge (Amicon, Danvers, MA) with a blood flow of 140 ml/min and an ultrafiltration rate of 800 ml/hr. Five filters were changed due to clotting. On CVVH his calorie intake increased from 60 kcal/kg/day to 100 kcal/kg/day, and the protein intake was up to 2.9 g/kg/day

from 2.2 g/kg/day. The patient developed hypothermia, which was ameliorated by mounting a blood warmer to the circuit. After seven days of CVVH, the patient no longer required any RRT. On the 20th day of hospitalization, he was discharged with normal kidney function.

Discussion

There are at least five basic configurations to the clinical application of continuous hemofiltration: continuous arterio-venous hemofiltration (CAVH), slow continuous ultrafiltration (SCUF), continuous arterio-venous hemodiafiltration (CAVHD), continuous veno-venous hemofiltration (CVVH) and continuous veno-venous hemodiafiltration (CVVHD) (Table I).

Table I: Renal Replacement Therapies For Critically Ill Patients

Modality	Goals	Solute Transport	Uremia Control	Tolerance by Unstable Patient
HD	Complete RRT	Diffusion and convection	Excellent	Poor
PD	Complete RRT and convection	Diffusion	Good	Fair to good
SCUF	Continuous removal of plasma water and solutes without replacement	Convection	Poor	Excellent
CAVH	Continuous removal of uremic plasma water replaced with balanced electrolyte solution	Convection	Good only when large volumes replaced	Excellent
CAVHD	Combines CAVH and HD without blood pumps	Convection and diffusion	Good to excellent	Excellent
CVVH	Continuous removal of uremic plasma water replaced with balanced electrolyte solution	Convection	Good	Excellent
CVVHD	Combines CAVH and HD with blood pumps	Convection and diffusion	Excellent	Excellent

HD : hemodialysis.
PD : peritoneal dialysis.
SCUF : slow continuous ultrafiltration.
CAVH : continuous arteriovenous hemofiltration.
CAVHD : continuous arteriovenous hemodiafiltration.
CVVH : continuous venovenous hemofiltration.
CVVHD : continuous venovenous hemodiafiltration.
RRT : renal replacement therapy.

Continuous RRT was first described as CAVH in 1977[15]. The simplicity of the CAVH system is striking; a small filter, which is highly permeable to water and small solutes (500 to 30.000 daltons) but impermeable to plasma proteins and the formed elements of the blood, is placed in a low-resistance extracorporeal circuit connecting a large artery and vein. The patient's arterial-to-venous pressure gradient provides sufficient perfusion pressure to drive the system. The ultrafiltrate is concurrently replaced using a fluid with an electrolyte composition that is, either similar to that of normal plasma or specifically designed to correct abnormalities present in the individual patient[7].

SCUF is a variation of CAVH, where fluid is removed from the patient without specific replacement on an ongoing basis[7]. In CAVH, which is driven by the patient's blood pressure gradient, fluid removal with ultrafiltration could be efficient, but urea clearance is low because it depends only on convection. The convection occurs when a solute molecule is swept through the membrane by a moving stream of solvent (solvent drag). In order to increase the solute removal, the process that allows dialysate to flow through the ultrafiltrate compartment of the filter, so creating diffusive transport which depends upon the solute concentration gradients that exist between blood and the dialysate, can be added to create CAVHD[7]. Since hemofiltration besides SCUF can give an ultrafiltration of 1 L/hr with simultaneous administration of replacement fluid, it is possible to achieve normovolemia and metabolic homeostasis without exposing the patient to sudden fluid and metabolic shifts. Case 1 above is a good example of how CAVH can effectively provide RRT when the patient suffers from complications of HD. Since HD is not well tolerated by young infants[5], this RRT modality has already found an application int his patient population[5].

Despite all these advantages, CAVH or CAVHD has some self-limiting features. When the mean arterial blood pressure falls, the driving force for ultrafiltration diminishes and slow blood flow results in filter clotting. These two factors can lead to inefficient ultrafiltration and frequently to its complete cessation. Systemic heparinization is generally required to prevent clot formation in the filter and is utilized as the anticoagulation modality in the two index cases.

Anticoagulation either with heparin or prostacyclin and even as regional heparinization may lead to external bleeding or internal hemorrhage[5,16-18]. Clotting requires changing the hemofilter, which could be associated with air bubbles, heparinization, rupture of capillaries and infection.

One of the most important disadvantages of CAVH or CAVHD is the requirement for arterial cannulation, which can expose the patient to complications such as hematoma, fistula formation and significant bleeding on catheter dislodgement[17,19]. This type of procedure is much more difficult in a neonate

and can also compromise the blood flow to a limb[6] or lead to a theoretical risk of limb shortening.

CVVH technique is similar to CAVH, However, instead of depending on the patient's mean arterial blood pressure as the driving force, a blood pump is used to ensure adequate blood flow through the hemofilter to maintain the required ultrafiltration rate. The blood pump rate is set between 80 and 200 ml/min to achieve an ultrafiltration rate between 500 and 1000 ml/min. Case 1, whose body weight was 30 kg, had a blood flow of 150 ml/min and an ultrafiltration rate of 1000 ml/hr on CAVH, whereas Case 2, despite being a 4 kg patient, had a comparable blood flow of 140 ml/min and ultrafiltration rate of 800 ml/min on CVVH. In our institution, ultrafiltration of 1 L/hr can be achieved with diafilter 20 cartridge (Amicon, Danvers, MA) regardless of the patient's weight (4 kg to 50 kg) without causing any hemodynamic instability (unpublished data). CVVH requires only a single double-lumen venous access[5]. Using a double-lumen catheter could be technically difficult in small infants. This problem can be overcome by using two single-lumen catheters and placing the suction catheter into the upper part of the right atrium[5]. In comparison to CAVH, blood flow rates and urea clearance were significantly higher during CVVH, probably due to its dependence on the pump[5].

CVVH has also found an application in the treatment of intractable hyperphosphatemia due to tumor lysis syndrome in a six-year-old patient with ALL[20]. In our institution, CVVHD has been found to be very effective in delivering the required higher calorie and protein to critically ill patients with hypercatabolism (unpublished data). CVVH could also remove both TNF-α (tumor necrosis factor) and Interleukin-1β from the circulation of septic, critically ill patient[21]. This cytokine extraction may prove to be of benefit in attenuating the progression of multiple organ dysfunction in patients with sepsis-associated renal failure who are receiving CVVH with dialysis.

As seen in the above-cited cases, continuous hemofiltration, especially CVVH, can ensure optimum nutrition. In a series of 11 patients treated in our institution, CVVH increased calories from 33.3 ± 8.9 calories/kg/day to 54.6 ± 9.2 calories/kg/day and protein intake from 0.73 ± 0.2 g/kg/day to 1.45 ± 0.23 g/kg/day ($p < 0.05$) (unpublished data). The enhanced recovery from ARF associated with total parenteral nutrition has been previously emphasized in the literature[22,23]. Although CAVHD has been complicated by hyperglycemia[18], metabolic alkalosis[24] and metabolic acidosis[25,26], CVVH has not been reported in association with these complications in our experience.

One theoretical risk associated with all hemofiltration modalities is infection. Although in our institution this complication is carefully monitored with daily blood

cultures, we did not notice an increased risk, as was also not reported in the literature.

Cost is an important factor to be considered when comparing RRT's for a critically ill child with ARF. According to the only adult study reported in the literature[27], seven-day CAVHD costs 809 dollars, whereas the expense for five treatments of four-hour HD done in one week is only 251 dollars, excluding nursing expenses. The actual difference in cost is reduced somewhat by factoring in the amortized costs of a water purity system and dialysis machine.

The pediatric literature reports a mortality rate of up to 83 percent in patients with ARF complicating medical or surgical illness, whereas ARF due to primary renal disease had only a 10 percent mortality rate[2]. The positive impact of continuous hemofiltration on mortality in critically ill children with ARF has been addressed by Zobel et al[5]. The survival rates in CAVH and CVVH patients were 60 percent and 35 percent, respectively. In our institution, six of 11 CVVH patients survived (unpublished data).

In conclusion, CAVH and CVVH are effective methods of renal support in critically ill pediatric patients. CVVH may have advantages that make it the preferred continuous RRT. Although it is unlikely that hemofiltration will replace acute PD and HD in pediatrics, it should be the RRT for hypotensive, critically ill, highly catabolic, volume-overloaded pediatric patients. As our experience with hemofiltration grows, the applications for these modalities will surely expand.

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The Turkish Journal of Pediatrics 1995; 37: 15-17

APPLICATION OF ICE WATER TO THE FACE IN INITIAL TREATMENT OF SUPRAVENTRICULAR TACHYCARDIA*

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SUMMARY: Aydın M, Baysal K, Küçüködük Ş, Çetinkaya F, Yaman Ş. (Department of Pediatrics, Ondokuz Mayıs University Faculty of Medicine, Samsun, Turkey). Application of ice water to the face in initial treatment of supraventricular tachycardia. Turk J Pediatr 1995; 37: 15-17.

Supraventricular tachycardia (SVT) is a life-threatening dysrhythmia in childhood. Initial treatment includes classic vagal maneuvers, some pharmacological agents, cardioversion and application of ice water to the face. In this paper we report our results of ice water application to the face in SVT. The study included ten patients between the ages of seven days and 15 years who were admitted to our hospital with supraventricular tachycardia in the previous year. Ice water was applied to their faces for five seconds immediately and all of them were digitalized. This procedure was utilized in 28 out of 36 SVT attacks, and was found to be effective in restoring sinus rhythm on 27 of 28 occasions (96%). Tachycardia recurred a total of 18 times in three of the ten patients. There was no recurrence in six patients. No response was noted in only one patient. Application of ice water to the face is an easy, safe, effective and repeatable procedure in the initial treatment of supraventricular tachycardia. *Key words: supraventricular tachycardia, treatment, diving reflex.*

Supraventricular tachycardia (SVT) is dangerous and potentially fatal. Rapid conversion to sinus rhythm is imperative. Many methods of treatment have been recommended, such as classic vagal maneuvers, some pharmacological agents and cardioversion[1]. However, these methods are usually insufficient in terminating tachycardia and may have fatal risks.

Application of ice water to the face (AIWF) stimulates "the diving reflex", and may stop tachycardia. We used this procedure in the treatment of SVT in ten patients.

Material and Methods

The patient group consisted of six males and four females between the ages of seven days and 15 years. The ventricular rate during SVT varied from 200 to 290 beats/min. One patient had been diagnosed with cardiomyopathy two years earlier.

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Procedure: The diving reflex was stimulated through immersion of the patients' faces in a basin of ice water (3-5 °C) for five seconds, and all patients were digitalized[2].

Results

AIWF was used in 28 of 36 SVT attacks and was found effective in restoring sinus rhythm on 27 of 28 occasions (96%). Tachycardia recurred a total of 18 times in three of the ten patients. No recurrence occurred in six patients, and only one patient did not respond to the procedure (Table I).

Table I: Results of AIWF in Initial Treatment of SVT

Patient No.	Age	Sex	SVT Attacks	AIWF	Conversion to Sinus Rhythm	Recurrences
1[a]	8 yr	m	12	6	6	5
2[b]	6 yr	f	2	1	1	–
3	4 mo	m	1	1	1	–
4[c]	2 mo	m	1	1	–	–
5	16 d	m	1	1	1	–
6	7 d	f	6	6	6	5
7[b]	11 yr	f	2	1	1	–
8[d]	8 yr	m	9	9	9	8
9	15 yr	m	1	1	1	–
10	2 mo	f	1	1	1	–
			36	28	27	18

[a] The procedure was not applied in the first six attacks.
[b] The procedure was not applied in the first attack.
[c] Patient had meningitis.
[d] Patient had cardiomyopathy.

m : male
f : female
mo : month
d : day

Spontaneous remission was seen in the first attack of Case 7.

Discussion

The diving reflex is an oxygen-conserving reflex consisting of striking bradycardia and peripheral vasoconstriction for increasing blood flow of the brain and heart. It is initiated partly through the stimulation of the afferent nerve ending in the area of the mouth and nose with cold water. The afferent limb of the reflex is mediated by increased sympathetic stimulation to peripheral vessels and, simultaneously, by intense vagal stimulation to the heart[3-5].

Application of ice water to the face is rapidly effective in more than 90% of cases. It is an easy, safe, noninvasive and painless procedure with no side

effects. Recurrence of tachycardia is fairly common, but the treatment is easy to repeat. This maneuver is also useful in patients who are receiving digitalis[6].

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The Turkish Journal of Pediatrics 1995; 37: 19-23

THE EFFECTS OF NALTREXONE IN AUSTISTIC CHILDREN: REPORT OF TWO CASES*

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SUMMARY: Akkök F. (Department of Educational Sciences, Middle East Technical University, Ankara, Turkey). The effects of naltrexone in autistic children: report of two cases. Turk J Pediatr 1995; 37: 19-23.

This paper reports the observations associated with a brief course of administration of naltrexone (NTX) to two autistic children. One male and one female child, aged 5.3 and 4.4, respectively, completed the trial. The children were placed on NTX for two weeks for six administrations. The dose was 0.5 mg/kg. The Behavior Summarized Evaluation and Childhood Autism Scale were completed by the teacher and the social worker for baseline and post-experimentation observations. The patients' parents were asked to fill out the Parental Satisfaction Survey. Although the literature indicates that NTX is effective in some children, our observations confirm that NTX is effective in the two cases with different degrees of severity of disease. *Key words: Naltrexone, autism treatment.*

Autism is a disorder of childhood and of development. It affects all of mental development and is characterized by powerful cognitive and affective dysfunctions[1]. Repetitive stereotyped behavior patterns and a deviant development of cognitive, language, and communicative functions are observed in autistic children[2]. Deficiencies in information processing have been established in austim by means of psychophysiological studies[3,4]. Behavioral, emotional and cognitive symptoms of autism suggest that the central nervous system functioning is altered in this pervasive developmental disorder[5], and neurotransmitters appear to be involved in behavior disturbances. Recently, it has been suggested that autism is a disorder of primary socialization, Findings indicate that endogenous opioid systems of the brain are a critical part of the processes of primary socialization[6]. The idea that Naltrexone (NTX) is a medicine suitable for the treatment of autism follows from the realization that salient features of autism resemble dosing with opioid agonists, such as morphine, and observations leading to the suggestion that endogenous opioidergic systems were associated with primary socialization.

NTX as a medicine for autism has found support in the data from a number of trials, including double-blind, placebo-controlled trials. Several researchers[6-10] have found that NTX decreased motor stereotypes and increased productive

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This study was conducted at the Wildwood School, Albany, United States of America.

attention, social interactions and communicative intent. NTX, a drug that blocks the cells' uptake of natural opium-like substances, is a promising treatment for autistic withdrawal, self-injury and other symptoms. Several studies indicate that the dose of naltrexone needed for maximum control of self-injurious behavior tends to be high (about 1.5 mg/kg), while lower doses (about 0.5 mg/kg) appear to have a greater effect on social behaviors. Their speculation is that the different receptors of brain cells may be affected by the differing dosages[10]. However, these studies have also indicated that only some children benefitted from the treatment.

Despite the growing data base supporting the idea that NTX is a medicine for the treatment of autism, a number of critical issues need attention. In order to gain some first-hand information to address these issues, the effects of NTX when given to two children were observed as preliminary data for further comprehensive studies. The purpose of this paper was to report the observations associated with a brief course of administration of NTX to two autistic children.

Material and Methods

Subjects

Two children with autism, one male and one female, aged 5.3 and 4.4 years, attending Wildwood School completed the trial. The children had previously taken no medication. Their parents volunteered for the study.

A, a 4.4-year-old girl who lived with her parents and one sibling, had autistic symptoms. She had been attending the Wildwood School for a year at the time of the study.

B, a 5.3-year-old boy, lived with his parents and two older siblings. He had been attending this school for two years.

Design and Medication

Following the baseline observations by the researchers, the teacher and the social worker filled out the Behavior Summarized Evaluation (BSE) and the Chlidhood Autism Rating Scale (CARS). The children were placed on NTX for two weeks for six administrations. The dose was 0.5 mg/kg. Medication was given by the school nurse in a single morning dose at 9 A.M. The parents, teacher, social worker and researchers were blind. The parents were asked to make detailed observations, keep a diary and record their interactions with their child during the study. Parents have the most intense and close interactions with their children, and the home environment is the child's most natural environment. Therefore, observations by the parents are an important aspect of evaluating the effects of NTX. Both children were observed at school and at home by parents at two different time. One was two hours after the administration of medication and the other was 24 hours later. At the end of

the two week period, the teacher and the social worker completed the BSE and CARS. Both mothers and fathers field out a Parental Satisfaction Survey (PASS). Also, the researchers had a meeting with the parents, teacher and social worker to discuss their observations and evaluations in detail. No biochemical examinations were carried out during or after the experiment. Parents chose to use NTX therapy voluntarily through their personal physicians.

Results

The effects of NTX therapy on two cases are discussed below.

Case 1

A grew in the areas of language development and social interaction. She was previously ritualistic and hyperactive. With the NTX treatment, a showed improvement in her behaviors. According to the teacher's and social worker's observations, A started to have more appropriate play, become more aware of peers, and seek out people more frequently. Her verbalization increased. However, she continued to have temper tantrums, but they were shorter in duration.

According to her parents' observations and daily records, she began appropriate and imaginative play, specifically with her dollhouse, and was attending more to the stimuli around herself (i.e., looking outside, looking at hands a lot, looking at herself in the mirror, responding to the doorbell much more). Her curiosity increased. She became more cooperative and responsive to her parents' instructions. Her bed-time behavior improved significantly. Her mother observed that she was behaving and playing more happily. She had subtle improvements in her behavior. Her verbalization and vocalization increased, she started to use a different tone of voice when playing with dolls and repeated many words. Her imitation increased. The mother was delighted at A's spontaneous kisses. A tolerated a haircut, and was quiet and cooperative. She continued to have temper tantrums, but they were shorter in duration. There was no change in her appetite, thirst, anger or toilet training.

Case 2

With NTX treatment, B manifested self-stimulative behavior, hyperactivity and unrealistic fears. According to the educators' observations, his clinging increased dramatically. It became very hard to pull him off. His appetite decreased. He developed an overall general anxiety. His hyperactivity decreased and he had short periods of attending a toy.

His parents' observations were controversial. According to his mother's observations and PASS, he showed substantial improvement in smiling and eye contact. He also showed clear impovement in his activity level (a decrease in hyperactivity), curiosity, interest and attempts to communicate a number of word

sounds. He was rebelling more and showing more emotion. There was marginal change in his stereotyped behavior (teeth grinding), number of "good days" and his play and imitative behavior. However, there was no change in his play behavior and life habits, and he was irritable. His appetite decreased and he started to ask for sweet things. His father observed marginal improvement in his stereotyped behavior and activity level. However, he observed no change in expressions of motivation, social responsiveness, communicative and cognitive abilities and life habits.

The average CARS and BSE scores of the educators indicated no improvement in either child's behavior. PASS data are summarized in Fig. 1.

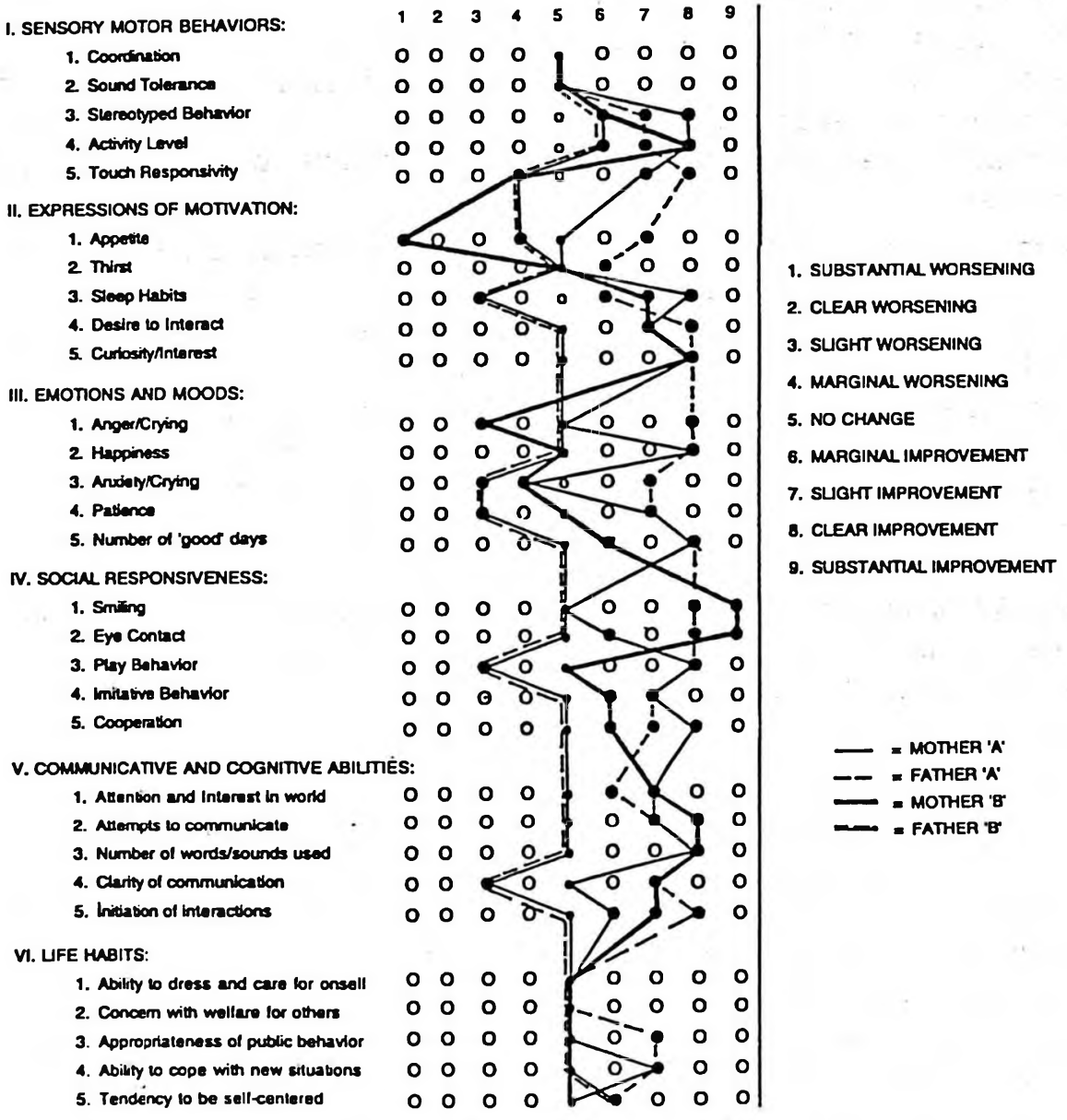

Fig. 1: Parental satisfaction survey (PASS) data.

Discussion

Our observations confirm some of the conclusions emerging from the limited available literature. The two children responded well to NTX, a potent, opiate antagonist, which has appeared to be a promising agent in several studies. Under NTX, autistic children appear less socially distant and more amenable to social interaction. They tend to engage in more creative object play, parallel play and social interactive play. However, NTX is effective among some children. Biochemical and neurometric predictors seem to differ in responders and nonresponders. In one study[10] it was detected that physiological changes accompany the behavioral changes in NTX-treated subjects. Levels of peptides that were abnormally elevated before treatment began are normalized by NTX administration. Further research should address these parameters to identify who will respond and who will not. Furthermore, the scales designed to diagnose autism, in contrast to other developmental disorders, do not appear to be sensitive to shifts in severity of the characteristic symptoms. To more fully assess NTX's effects, it seems necessary to devise new procedures that objectify professionals' and parents' judgments.

Further studies should address the effects of different dosages and the biochemical examinations to screen the responders and nonresponders to contribute to the effective use of NTX.

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The Turkish Journal of Pediatrics 1995; 37: 25-29

SERUM CARNITINE, β-HYDROXYBUTYRATE AND AMMONIA LEVELS DURING VALPROIC ACID THERAPY*

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SUMMARY: Toksoy HB, Tanzer FN, Atalay A. (Departments of Pediatrics and Biochemistry, Cumhuriyet University Faculty of Medicine, Sivas, Turkey). Serum carnitine, β-hydroxybutyrate and ammonia levels during valproic acid therapy. Turk J Pediatr 1995; 37: 25-29.

This study was performed in order to determine the effects of valproic acid on serum free carnitine, β-hydroxybutyrate and blood amamonia. Serum free carnitine, β-hydroxybutyrate and blood ammonia levels were measured in 24 epileptic children and in 24 age and sex-matched controls. The mean serum free carnitine level was significantly lower in patients taking valproic acid (33.5 ± 13.1 nmol/ml) than in control subjects (50.8 ± 14.6 nmol/ml) ($p < 0.001$). The mean blood ammonia level was significantly higher in patients receiving valproic acid (93.9 ± 20.5 μg/dl) than in controls (79.6 ± 21.4 μg/dl) ($p < 0.002$). The mean serum β-hydroxybutyrate level was significantly lower in patients taking valproic acid (2.26 ± 2.24 mg/dl) than in controls (4.38 ± 2.43 mg/dl) ($p < 0.001$).

Our results support the decision that valproic acid induces hypo-carnitinemia, hypoketonemia and an increased blood ammonia level. *Key words: blood ammonia, carnitine, valproic acid.*

Valproic acid (VPA) is used for the treatment of many seizure types, including generalized tonic-clonic, absence, myoclonic seizures and recurrent febrile convulsions[1,2]. VPA therapy is known to be associated with mild abdominal disturbances, alopecia, edema, apnea, pancreatitis, thrombocytopenia, leukopenia and reversible hyperammonemia[1,3-5]. It has rare but serious side effects such as Reye-like syndrome and toxic hepatitis[5-8].

Carnitine, a naturally occurring trimethylamine, plays an essential role in mitochondrial β-oxidation of long-chain fatty acids by facilitating their transfer across the mitochondrial membrane[9]. Serum levels of carnitine have been found to be lower in patients treated with VPA than those of controls[10-16]. Thus, some investigators have suggested that carnitine deficiency has a possible role in VPA- induced hepatopathy[5,10,11]. This study was carried out in order to determine whether VPA actually induces hyperammonemia, hypocarnitinemia and hypoketonemia.

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Material and Methods

Serum free carnitine, blood ammonia and β-hydroxybutyrate levels were measured in 24 children suffering from epilepsy and 24 children who were apparently healthy. The group of patients treated with VPA monotherapy included five female and 19 male patients. The mean age of patients receiving VPA was 7.6 years (range one to 15 years). The dose of VPA in the treatment group was 20 mg/kg/day. The duration of antiepileptic treatment was between six months and seven years (mean duration 17.5 months). In all patients and controls, blood ammonia and β-hydroxybutyrate levels were determined in the same sample, and blood for serum free carnitine was taken simultaneously.

Blood ammonia was immediately analyzed by the chromatographic-spectro photometric, phenol-hypochlorite method (Bio Systems, COD 11013). Serum β-hydroxybutyrate concentrations were measured by kit (Sigma diagnostics, 310 UV). Serum free carnitine levels were determined by the enzymatic method. Free carnitine concentrations were assayed spectrophotometrically as reported by Marquis and Fritz[17].

Differences between the means were employed using at the two-tailed t test and the Mann-Whitney U test.

Results

Serum free carnitine, blood ammonia and β-hydroxybutyrate values for VPA treatment and controls are shown in Table I.

Table I: Mean Serum Free Carnitine, Blood Ammonia and Serum β-hydroxybutyrate Concentrations in Patients Treated with Valproic Acid and in Normal Subjects. (All Values Expressed as Mean ± SD)

Variable	Valproic Acid Monotherapy (n = 24)	Controls (n = 24)	p
Free carnitine (nmol/ml)	33.5 ± 13.1	50.8 ± 14.6	$p < 0.001$*
Ammonia (μg/dl)	93.9 ± 20.5	79.6 ± 21.4	$p < 0.002$*
β-hydroxybutyrate (mg/dl)	2.26 ± 2.24	4.38 ± 2.43	$p = 0.0001$**

* t test
** Mann Whitney U test.

The mean serum free carnitine concentration in the VPA monotherapy group was 33.5 ± 13.1 nmol/ml (range 16.0-54.2 nmol/ml). It was 50.8 ± 14.6 nmol/ml in the age- and sex-matched control group (range 19.5-70.5 nmol/ml) (Fig. 1). The difference was statistically significant ($p < 0.001$).

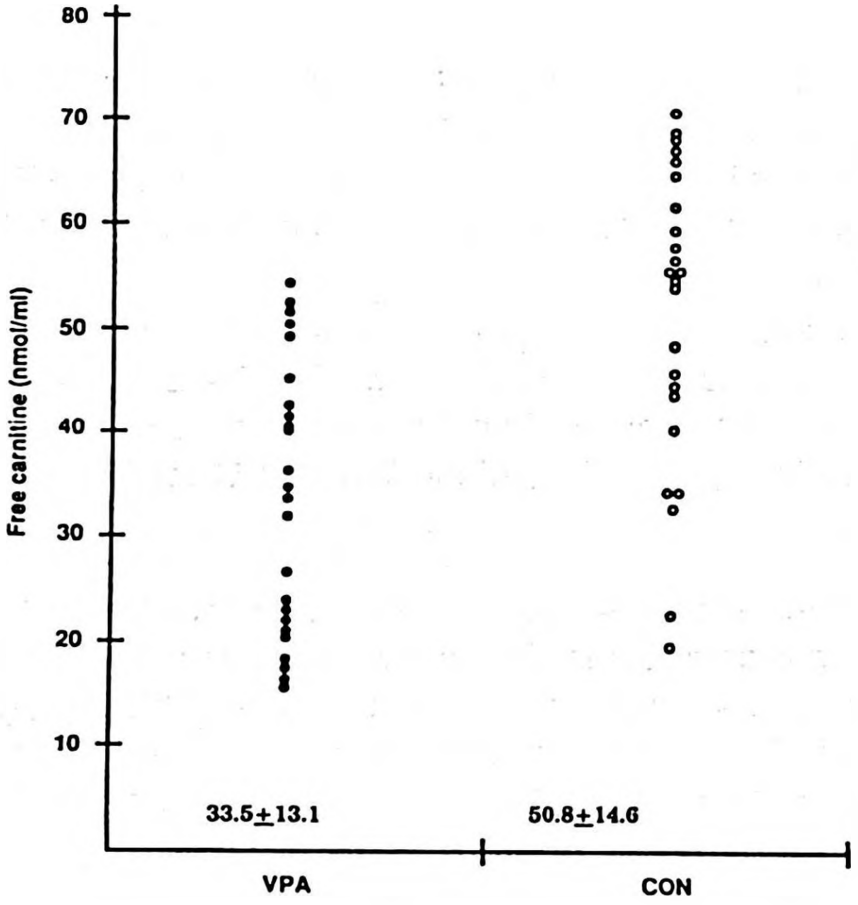

Fig. 1: Serum free carnitine in two study groups (VPA: valproic acid; CON: control).

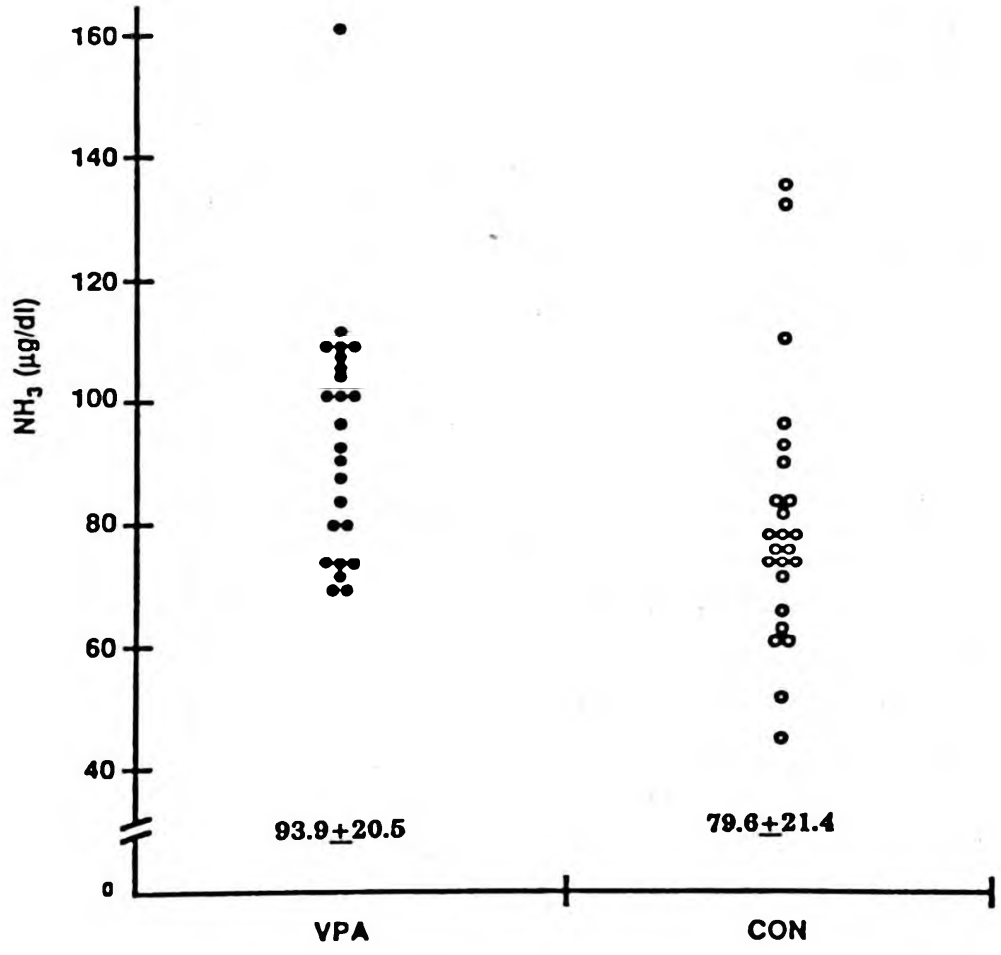

Fig. 2: Blood ammonia values in two study groups (VPA: valproic acid; CON: control).

The mean blood ammonia level in the VPA monotherapy group (93.9 ± 20.5 µg/dl) was significantly higher than that in the control group (79.6 ± 21.4 µg/dl) ($p < 0.02$) (Fig. 2). The levels of blood ammonia ranged from 68.7 µg/dl to 161.4 µg/dl in the VPA monotherapy groups and from 44.9 µg/dl to 136.2 µg/dl in the control group.

The mean β-hydroxybutyrate level of patients receiving VPA monotherapy was 2.26 ± 2.24 mg/dl (range 0-9.26 mg/dl); it was 4.38 ± 2.43 mg/dl (range 0.74-10.50 mg/dl) in the control group. The difference between the two groups was statistically significant ($p = 0.0001$, Mann Whitney U test).

Discussion

It has been reported that VPA treatment causes hypocarnitinemia in epileptic patients[5,10-16]. In our data, serum free carnitine levels in the VPA monotherapy group were significantly lower than those in controls. This finding is consistent with the findings of Opala et al.[15] and Hug et al.[16] Our report supports previous findings that administration of VPA results in a lowering of carnitine levels[10-16].

The mechanisms by which VPA administration produces hypocarnitinemia remain obscure. Several investigators have reported that the lowest serum free carnitine levels were found in the group treated with VPA polytherapy[11,13,15]. They suggested that drug interactions can lead to enhanced VPA metabolism and further impairment of carnitine values[11,13,15]. Laub et al.[11] found that patients taking VPA had significantly higher serum acylcarnitine levels and a significantly higher acylcarnitine/free carnitine ratio than patients taking other antiepileptic drugs without VPA. They suggested that there was a loss of carnitine via carnitine esters through a renal leak. In addition to this, Laub et al.[11] suggested that the impairment of β-oxidation might therefore be another factor leading to low cranitine values during VPA treatment. However, some authors suggested that carnitine deficiency could distrub β-oxidation[5,14].

In our study, serum levels of β-hydroxybutyrate in VPA-treated children were significantly lower than those of controls. This finding was in contrast to Beghi et al.[13], but was in accord with the findings of Melegh et al.[14] These findings show that hypoketonemia may be due to impairment of β-oxidation of fatty acids.

Hyperammonemia-associated VPA has also been reported in the literature[10,18-21]. We found significantly higher blood ammonia levels in VPA-treated patients than in controls. The mechanisms of VPA-induced hyperammonemia are not fully understood. Suggestions from investigators include a reduction of N-acetylglutamate in the liver, a carbamylphosphate synthetase deficiency, and inhibition of mitochondrial ammonia metabolism[10,19,20]. An increase in blood ammonia concentration observed in this study might well be a reflection of mitochondrial dysfunction induced by VPA.

In conclusion, we suggest that further controlled trials are required in order to clarify the benefits of carnitine supplementation in chronic VPA patients, on hypoketonemia, hypocarnitinemia and hyperammonemia induced by VPA.

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The Turkish Journal of Pediatrics 1995; 37: 31-43

TRANSPLANTATION OF HEMATOPOIETIC PROGENITOR CELLS WITH EMPHASIS ON THE RESULTS IN CHILDREN*

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SUMMARY: Thomas ED. (Fred Hutchinson Cancer Research Center, Seattle, Washington, USA). Transplantation of hematopoietic progenitor cells with emphasis on the results in children. Turk J Pediatr 1995; 37: 31-43.

Attempted human allogeneic marrow transplants in the 1950's and 60's were largely unsuccessful. In the past two decades the probability of success has improved steadily depending on the type and stage of disease. All marrow transplant teams have observed that the results for children are better than for adults. Long-term survival and apparent cure rates range from about 90 percent for non-malignant diseases transplanted early to 15 percent for patients with advanced leukemia. Most marrow transplants have involved an HL-A matched sibling donor but, more recently, through the worldwide marrow donor registries a matched unrelated volunteer marrow donor can be found for many patients without a family donor. Current research involves new preparative regimens for elimination of malignant cells, better prevention of graft-versus-host disease (GVHD), and the use of hematopoietic growth factors and cytokines. Autologous transplants, which use the patient's own marrow, are increasing. The hematopoietic stem cell, which is responsible for marrow regeneration after a transplant, has been isolated and characterized. Stem cells for transplantation can now be obtained from the peripheral blood after mobilization of these cells by chemotherapy or hematopoietic growth factors. *Key words: bone marrow transplantation, hematopoietic progenitor cells, children.*

In 1949, Leon Jacobson and his colleagues, while studying the mechanism of death from total body irradiation (TBI), showed that shielding the spleen allowed mice to recover from otherwise lethal irradiation[1]. Lorenz et al.[2] then showed that infusion of syngeneic marrow also provided an irradiation protection effect. In 1955, Main and Prehn showed that mice protected with an allogeneic marrow infusion would accept permanently a skin graft from the marrow donor[3]. Ford, et al. showed by cytogenetic techniques that the irradiation protection effect was due to the transfer and survival of hematopoietic cells from the donor[4]. In 1956, Barnes and Loutit treated leukemic mice by irradiation and marrow transplantation[5]. These studies formed the cornerstones of the field of marrow transplantation.

The potential therapeutic application of supralethal chemo-irradiation and marrow grafting to leukemia and other diseases of the marrow was soon investigated by several groups. Dr. Joseph Ferrebee and I and our colleagues in

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Cooperstown, N. Y., began a human marrow grafting program in 1955. Our first publication in 1957 discussed our reasons for concluding that allogeneic marrow grafting in our species would be very difficult[6]. We were able to show that large quantities of marrow could be infused intravenously with safety, but only one patient showed transient engraftment. Subsequently, two children with refractory acute lymphoid leukemia who had an identical twin were given supralethal irradiation and a syngeneic marrow infusion[7]. Their prompt hematologic recovery and well-being provided proof that an intravenous infusion of marrow could protect against otherwise lethal irradiation although their leukemia recurred in a few months.

We began in 1955 to study the dog as a readily available outbred animal commonly used for transplantation research and amenable to clinical procedures comparable to those used for human patients[8]. We found that dogs given 1000 R (9.2 Gy) and an infusion of their own stored marrow routinely survived and lived a normal life span[9], while only about 10 percent of dogs given an allogeneic marrow infusion survived[10]. It was clear from studies in both rodent models and dog models that a successful allogeneic marrow graft depended upon close histocompatibility matching between donor and recipient[11]. Under the impetus of kidney grafting, human tissue typing based on human leukocyte antigens (HL-A) proceeded rapidly in several laboratories. We developed dog antisera for detection of DL-A antigens which enabled us to show that marrow grafts between littermates matched with these sera were almost always successful if followed by a few weeks of immunosuppression with methotrexate to suppress the graft-versus-host reaction[12].

My colleagues and I began in 1967 to assemble and train the Seattle team of doctors and nurses for critical care of patients with leukemia undergoing allogeneic marrow grafts who would be without marrow function and subject to opportunistic infections. In November of 1968 Dr. Robert Good and his colleagues at the University of Minnesota carried out the first marrow transplant from a matched sibling for an infant with an immunological deficiency disease[13]. In March of 1969, we carried out our first transplant for a man in the blastic phase of chronic myeloid leukemia who had a matched sister to serve as donor. The experimental background and the early clinical successes and problems were reviewed in the New England Journal of Medicine in 1975[14]. Thus, the "modern" era of human marrow transplantation began.

At the present time marrow grafting is being applied to a variety of malignant, non-malignant, and genetically determined diseases. The tremendous increase in application of allogeneic marrow grafting around the world, numbering more than 10.000 per year, has been documented by the International Bone Marrow Transplant Registry[15].

Types of Marrow Transplants

A marrow transplant is really a transplantation of primitive hematopoietic progenitor cells (PHPCs) that have the capacity to proliferate and repopulate the marrow spaces. These PHPCs can be obtained from marrow, peripheral blood or cord blood. The type of the transplant is determined by the relationship between the donor and the recipient.

Syngeneic Transplant: A transplant between identical twins.

Autologous Transplant: A transplant using the patient's own PHPCs that have been collected before intensive therapy and returned after the therapy.

Allogeneic Transplant: A transplant between donor and recipient of different genetic origin.

Matched Sibling Transplant: A transplant between donor and recipient siblings who have inherited the same two human leukocyte antigen (HL-A) regions on chromosome 6, one from each parent (a genotypic match).

Matched Unrelated Donor Transplant: A transplant using a donor who is unrelated to the patient but phenotypically matched for the HL-A antigens.

During the 1970's and most of the 1980's the majority of marrow transplants utilized matched sibling donors. Therefore, the longest and most extensive data involve transplants of this type which will be described below. Only about one-fourth of patients will have an HL-A identical sibling. Examination of the extended family may identify members who share one HL-A haplotype, with the other haplotype being phenotypically matched or partially mismatched[16]. These donors can be used with success comparable to that of matched siblings. The U.S. National Marrow Donor Program now has registered more than one million volunteer donors and similar panels are being enlarged in several cooperating countries. Transplants using unrelated donors who are phenotypically matched or differing by only one HL-A antigen are showing promising results[17].

If a suitable allogeneic marrow donor cannot be found, the patient's own marrow my be removed, stored and given back after the preparative regimen. The pirinciples of long-term cryopreservation of marrow and autologous marrow transplantation are well established[18]. Autologous marrow transplant regimens and procedures for removing malignant cells that might be contaminating the marrow are being studied by many marrow transplant teams[19,20]. Long term survivals are being reported. Autologous transplants avoid the problems associated with GVHD but lose the advantage associated with the graft-versus-leukemia effect[21]. The reported results show a higher incidence of recurrent malignancy after autologous grafts compared to allogeneic grafts but, in many instances, almost equivalent long-term survival due to the absence of problems associated with GVHD.

It has long been known that hematopoietic progenitor cells are present in the circulating blood and that these cells can repopulate the marrow after lethal irradiation[22]. It has now been shown that the number of these stem cells in the blood is greatly increased after sublethal chemotherapy or after the administration of hematopoietic growth factors such as granulocyte colony stimulating factor (G-CSF). With continuous-flow centrifuges, quantities of stem cells suitable for transplantation can be collected from the blood, thus avoiding the need of the operating room and a general anesthesia for marrow procurement[23]. The major use of peripheral blood stem cells has been for autologous grafting, either alone or combined with marrow. Allogeneic grafts can now be achieved with peripheral blood stem cells, and this technology may well replace marrow as the source of stem cells.

Problems with Marrow Grafting

Graft-Versus-Host Disease: GVHD is a major problem even when donor and recipient are HL-A identical siblings. Several immunosuppressive drugs have been evaluated to suppress the graft-versus-host reaction. The best regimen yet reported is the combination of a short course of methotrexate combined with six months of cyclosporine[24]. Although removal of T-cells from the donor marrow in vitro is effective in preventing GVHD, it is associated with an increased risk of graft failure and/or recurrence of malignancy[25]. Chronic GVHD occurs in approximately one-third of recipients. Treatment with alternate day glucocorticoids over several months will control most, but not all, cases[26].

Relapse: Recurrence of disease following the marrow graft is the major cause of failure of transplants for malignancy. The initial regimen in Seattle consisted of high dose cyclophosphamide (CY) and 10 to 12 Gy total body irradiation (TBI). Since then, many marrow transplant teams, in an effort to achieve a greater kill of malignant cells, have employed a variety of high dose chemotherapy regimens with or without TBI. Santos and Tutschka developed a regimen of cyclophosphamide combined with busulfan without irradiation. The regimen is equivalent to the cyclophosphamide-total body irradiation regimen but avoids the exposure to irradiation and is easier to use[27].

Efforts to increase the intensity of the transplant preparative regimen are limited by life-threatening damage to organs other than the marrow, especially the lung, liver and heart. This problem is illustrated by a Seattle study of leukemic patients prepared with two doses of CY and randomized to receive either 12 GY or 15.75 Gy of TBI[28]. Although the higher dose of irradiation resulted in fewer leukemic relapses, there were more deaths from organ toxicity, so that disease-free survival was not improved.

As conventional chemotherapy of malignant disease before transplantation and the marrow transplant regimens have become more intensive, veno-occlusive disease (VOD) of the liver is a more frequently recognized problem and an increasing cause of death[29]. Treatment is largely palliative. Although the kidney does not seem to be a primary target of the marrow grafting regimens, renal failure is not uncommon because of nephrotoxic drugs, associated liver failure, and fluid and electrolyte problems.

Following an allogeneic marrow graft and especially with immunosuppressive treatment of GVHD, patients are profoundly immunoincompetent and at great risk for opportunistic infections[30]. Bacterial disease, P.carinii and some fungal diseases can be controlled with appropriate antibiotics, at times supplemented with granulocyte transfusions. Herpes simplex and Varicella zoster can now be prevented with acyclovir. A leading cause of death was cytomegalovirus (CMV) pneumonia. The use of CMV negative blood products (if donor and recipient are sero-negative) and the treatment or prevention of CMV infection with ganciclovir have resulted in a reduction in CMV-related problems[31,32].

Results of Marrow Grafting in Children

Marrow transplant teams have uniformly reported that children show better long-term disease-free survival than adults, perhaps due to a lower incidence and severity of GVHD. In the 1970's most transplants were carried out in patients with far advanced disease. In the past decade, transplants have been carried out much earlier in the course of the disease. However, even now many children are referred because the referring physician believes that they have one or more poor prognostic factors, which makes comparison to conventional therapy difficult. Based on expected outcome as well as a few randomized prospective trials, it is clear that marrow grafting is a preferred therapy for many diseases and stages of disease, and, in many instances, the only curative approach.

Allogeneic Marrow Grafts

Acute Lymphoblastic Leukemia (ALL): Fig. 1 shows a Kaplan-Meier plot of the disease-free survival and Fig. 2 the probability of relapse for children transplanted from a matched sibling in Seattle from 1972 to 1992, analyzed in August, 1994. It should be kept in mind that the earlier patients did not have the benefit of recent improvements in technology and that most patients transplanted in first remission were chosen on the basis of poor prognostic factors.
The International Bone Marrow Transplant Registry (IBMTR) reported the experience with children transplanted from matched siblings in 1984-1990, showing a disease-free survival probability of 0.62 for those in first remission, 0.42 for second remission and 0.18 for relapse[33].

Acute Myeloid Leukemia (AML): In 1979 the Seattle team reported a series of patients with AML transplanted in first remission from a matched sibling donor after preparation with CY and TBI[34]. Of the six children in that report, four are living in remission 15 to 17 years later. Fig. 3 shows the survival of all children with AML transplanted in Seattle from 1972 to 1992 and analyzed in July, 1994.

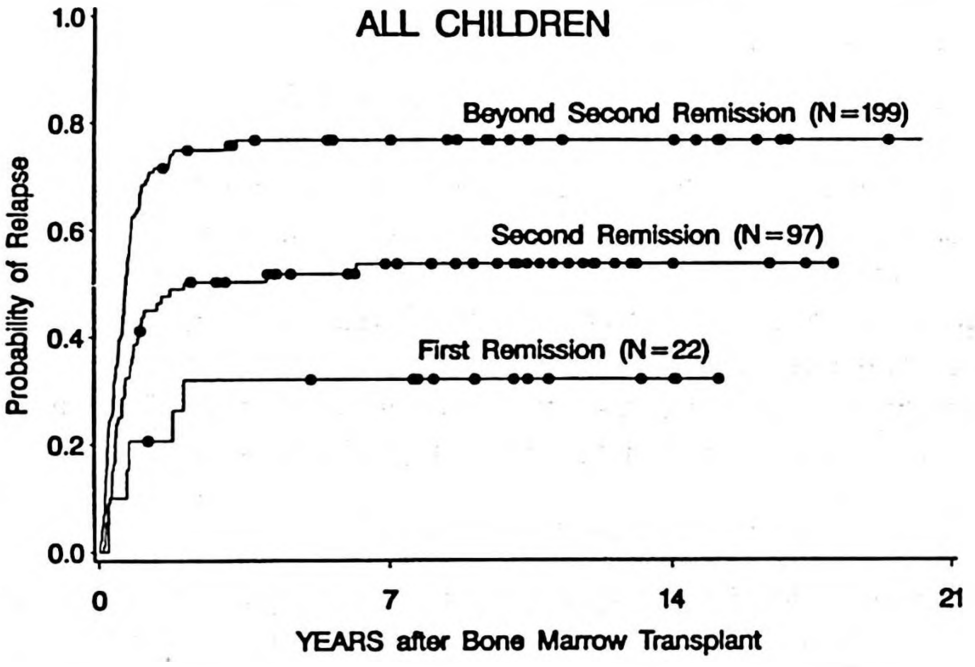

Fig. 1: Kaplan-Meier product limit estimates for the probability of disease-free survival for all patients with ALL under the age of 18 years transplanted in Seattle from a matched sibling donor between 1972 and 1992 and analyzed in August, 1994.

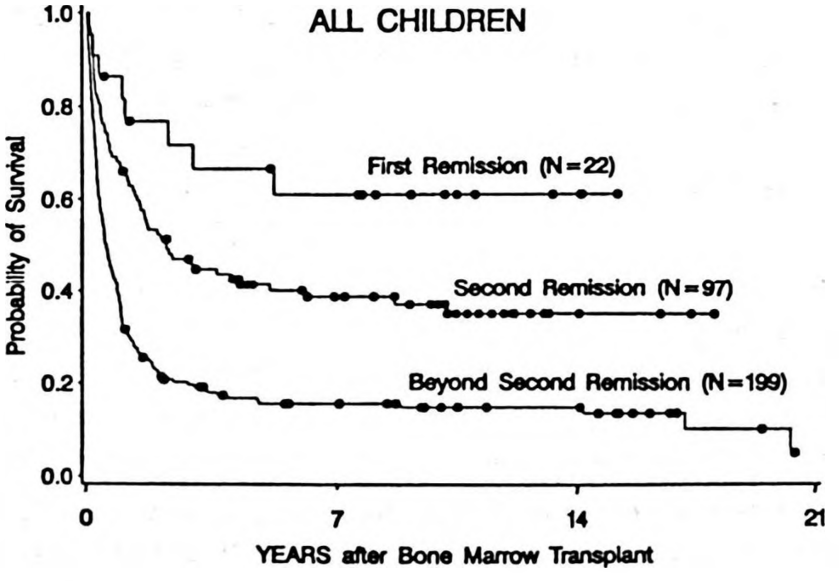

Fig. 2: Kaplan-Meier product limit estimates for the probability of relapse for all patients with ALL under the age of 18 years.

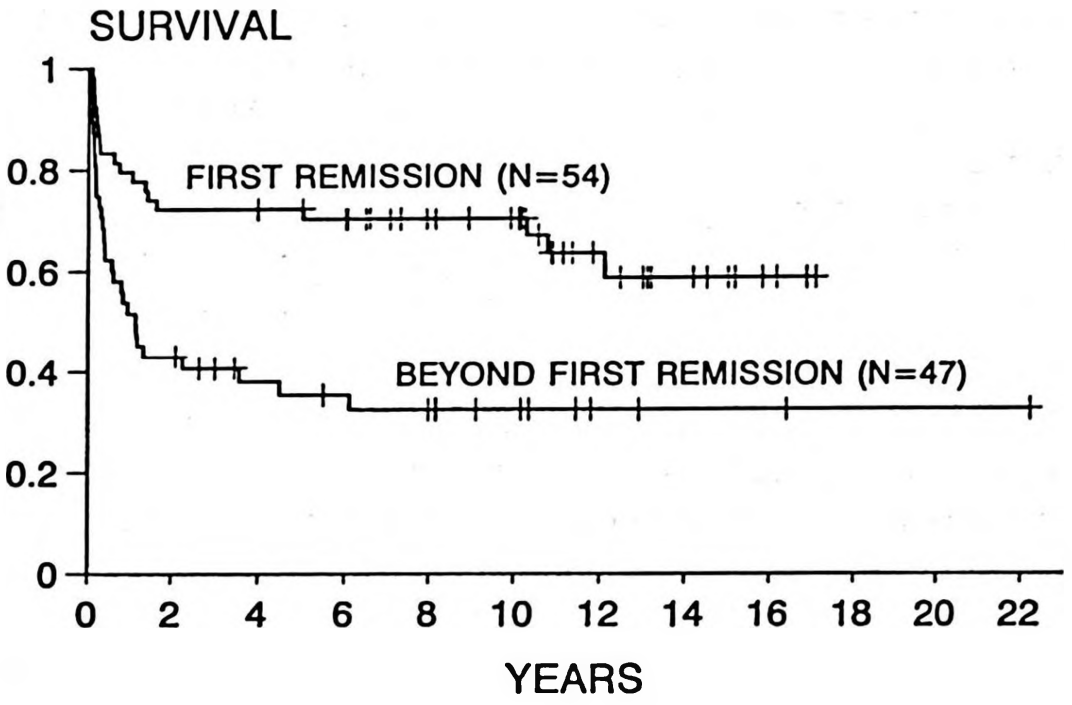

Fig. 3: Kaplan-Meier product limit estimates for the probability of disease-free survival for all patients with AML under the age of 18 years transplanted in Seattle from a matched sibling donor between 1972 and 1992 and analyzed in July, 1994.

The Children's Cancer Group reported a study of 508 patients with AML. Those achieving a remission with a matched sibling were allocated to marrow transplantation after preparation with CY-TBI, while those without a donor received additional combination chemotherapy. With all patients followed for at least eight years, the survival was 47 percent for those treated with marrow transplantation compared to 41 percent for those treated with combination chemotherapy[35].

In a subsequent study, the Children's Cancer Group described a 55 percent three-year survival in a series of 16 such children transplanted after preparation with BU-CY[36]. In Seattle 18 children who achieved a first remission have been prepared with BU-CY and given a matched sibling marrow graft (Sanders et al., unpublished observations). One died early. Two relapsed and are again in remission after a second transplant. With follow-up to six years, the survival probability is 0.94, and the disease-free survival probability is 0.83.

The IBMTR reported a large series of children transplanted with a variety of regimens. They found a seven-year disease-free survival probability of 0.62 for children transplanted in first remission, 0.38 for those transplanted in second remission and 0.21 for those transplanted in relapse[33].

Chronic Myeloid Leukemia (CML): Philadelphia chromosome positive CML is an uncommon disease in children. The Seattle team has recently published a prospective study in 142 patients with CML ages 7-60 randomized to receive either CY-TBI or BU-CY[27].

Only seven of those patients were under the age of 20. Two have relapsed, both had received BU-CY and are clinically well on interferon, a survival probability of 1.0 and disease-free survival of 0.71. The IBMTR reported a probability of 0.60 at seven years for these children transplanted from a matched sibling donor while in chronic phase[33]. All reports show a poor long-term survival for transplantation in accelerated or blastic phase. Since this disease is not cured by chemotherapy, marrow transplantation should be considered early after diagnosis if a matched donor can be found.

Juvenile Chronic Myelogenous Leukemia: Few reports of marrow transplantation for this very rare but aggressive disease are available. The Seattle team reported 14 such patients given matched or partially matched marrow after preparation with CY-TBI[37]. Six patients became long-term survivors, showing that this disease can be cured with a marrow grafting regimen.

Hodgkin's Disease and Non-Hodgkin's Lymphomas: The variety of these diseases and their rarity has made it difficult to acquire definitive data on the results of marrow grafting as compared to conventional therapy. In general the results parallel the leukemias with good survival if the transplant is carried out early in the course of the disease and very poor results for those transplanted in the end stages.

Aplastic Anemia: The Seattle team has employed CY (50 mg/kg on each of four days) as the preparative regimen for patients with severe aplastic anemia given a marrow graft from a matched sibling donor. With methotrexate (MTX) given post-grafting to prevent GVHD, the long-term survival was about 60%. With the combination of MTX with cyclosporine (CSP) to prevent GVHD survival was improved. Most recently, the addition of antithymocyte globulin (ATG) to the regimen has produced long-term survival of better than 90% for both children and adults[38]. Sanders et al. have provided details of the Seattle experience with children transplanted for severe aplastic anemia prior to the regimen with ATG[39].

Thalassemia Major: The first patient to be cured of Thalassemia major was prepared with dimethyl busulfan and CY and transplanted from a matched sibling in Seattle 13 years ago[40]. The patient is well and growth and development have been normal. The largest series and the best results of transplantation for Thalassemia major have been reported by Laucarelli et al. using a preparative regimen of BU-CY[41]. They described an approximate 90 percent long-term disease-free survival for patients who are transplanted before complications arise, and approximately 65 percent for patients with iron overload or hepatitis. This disease is but one of some 40 genetically determined diseases of the marrow that have been treated with marrow transplantation.

Autologous Marrow Transplantation

In the past five to seven years, the number of autologous marrow transplants being performed for a variety of diseases has been increasing rapidly. Because of the relatively shot follow-up time, few definitive reports of disease-free survival in children are available.

Billett et al. reported 51 children with ALL in relapse after a long first remission who were prepared with combination chemotherapy and TBI and given an autologous marrow graft purged with monoclonal antibodies. The event-free survival at three years was 0.53[42]. Schmid et al. described 22 children with advanced ALL after treatment with the German BFM regimens who were prepared with VP-16 and TBI and given an autologous marrow graft. The probability of event-free survival at three years was 0.18[43]. Lonnerholm et al. reported 25 children, two in first remission with poor prognostic indicators and 23 in second or third remission, given an autologous graft of purged marrow. After a median follow-up of 50 months, the probability of disease-free survival was 0.65[44]. Colleselli et al. reported 56 children with ALL in second or subsequent remission given an autologous marrow graft with a four-year event-free survival of 0.21[45]. The Children's Cancer Group described 58 children with AML in first remission given an autologous marrow graft after preparation with BU-CY[36]. The actuarial disease-free survival at three years was 0.51.

A few reports describe studies of high-dose therapy and autologous marrow transplantation in children with lymphoma[46-49]. These reports show that long-term disease free survival in some children can be achieved, but controlled trials have not been done.

From these reports it is evident that autologous marrow grafting after intensive preparative regimens is effective in achieving disease-free survival in patients with acute leukemia. Much longer follow-up time is needed for full evaluation.

Syngeneic Marrow Transplantation

A special form of "autologous" stem cells for transplantation is a syngeneic marrow transplant. The normal twin donor cells are not contaminated with malignant cells, a major source of concern with the usual autologous transplant. Syngeneic marrow transplants can lead to long-term survival in patients with acute leukemia transplanted in first remission[50] or in relapse[51] and with CML[52]. Survival after a syngeneic transplant is comparable to that of a matched sibling transplant because the higher relapse rate associated with a syngeneic transplant is offset by the absence of complications due to GVHD.

Growth and Development

Growth and development are of major importance and concern for children who have had a major illness and who undergo intensive therapy and a marrow

graft. Chronic GVHD and its treatment are further threats to normal growth and development. Long-term studies of these problems are ongoing in many marrow transplant centers. In brief, growth and development appear near normal in those patients treated for non-malignant disease who are prepared for grafting with CY and/or other immunosuppressive regimens. Those children who receive intensive cytotoxic therapy and/or irradiation show a spectrum of long-term effects ranging from normal to severe impairment. Details of these studies have been provided by Sanders[53].

Recent Developments

The use of growth factors anad cytokines produced by recombinant molecular biological techniques is among the most exciting recent developments in marrow transplantation. In clinical trials it has been shown that G-CSF and granulocyte-macrophage colony stimulating factor (GM-CSF) can accelerate recovery of granulocytes after both allogeneic and autologous marrow grafts with consequent significant shortening of the time in the hospital[54]. Several other growth factors and combinations of growth factors are in clinical trial. The recent cloning of thrombopoietin offers hope for facilitating recovery of platelets after marrow grafting[55-57]. Biological response modifiers including IL-2[58], cloned T-cells[59] and interferon[60] are being explored for a possible increased effect against malignant cells. Of great interest is the fact that infusions of donor T-cells that have not been exposed to IL-2 can bring about remission of relapsed chronic myeloid leukemia after marrow grafting[61].

Identification of the "stem cell" responsible for repopulation of marrow has long been a goal of experimental hematologists. Progress has been made in its isolation[62]. Monoclonal antibodies that recognize stem cells now may be used in conjunction with cell separation technology for separation and concentration of stem cells or for selective removal of malignant cells for autologous marrow transplantation[63]. Perhaps it will soon be possible with the "right" combination of growth factors to culture and expand purified stem cells in vitro.

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The Turkish Journal of Pediatrics 1995; 37: 45-50

EOSINOPHILIC GASTROENTERITIS PRESENTING AS PROTEIN – LOSING ENTEROPATHY*
(Case Report)

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SUMMARY: Karademir S, Akçayöz A, Bek K, Tanyel FC, Sungur M, Çelik İ, Ural C, (Dr. Sami Ulus Children's Hospital, Ankara, Turkey). Eosinophilic gastroenteritis presenting as protein-losing enteropathy. Case report. Turk J Pediatr 1995; 37: 45-50.

Eosinophilic gastroenteropathy is an uncommon, idiopathic disease in children that is characterized by eosinophilic inflammation of the intestine. Predominant involvement of the mucosa is associated with diarrhea and less commonly gastrointestinal protein and fat malabsorption. A seven-year-old female was diagnosed with eosinophilic gastroenteritis. This condition was proven by biopsies attained through an endoscope. The most common symptoms were abdominal pain, diarrhea and edema. The patient had no eosinophilia. Her serum immunoglobulin E level was increased (1590 mg/dl). Barium studies revealed mucosal thickening of the antrum, distal jejunum and proximal ileum and prominent mucosal folds of the colon. Ultrasound examination revealed thickening of the colonic wall. The patient was treated with prednisolone (2 mg/kg/day). The symptoms subsided and serum immunoglobulin E decreased to 500 mg/dl 45 days later. The patient is being followed with a small maintenance dose of prednisolone with no relapse. *Key words: eosinophilic gastroenteritis, protein-losing enteropathy.*

Eosinophilic gastroenteropathy (EG) is an uncommon, chronic, relapsing disorder in which eosinophils constitute the predominant cell type in the inflammatory infiltrate of the gastrointestinal (GI) tract[1-3]. Its etiology remains unknown, and whether eosinophils have a role in tissue damage is uncertain[4].

The clinical manifestations, usually recurrent and protean, relate to the site and depth of GI tract involvement[5,6]. Recurrent abdominal pain and diarrhea are the most common presenting symptoms. usually in association with anorexia, nausea or vomiting[3,7]. Protein loss, gastrointestinal bleeding and malabsorption may lead to significant growth delay in the pediatric age-group.

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In this case report we describe a seven-year-old girl who presented with protein-losing enteropathy and was diagnosed with eosinophilic gastroenteropathy.

Case Report

A seven-year-old-girl was admitted to the hospital in April 1993 with a one-year history of upper quadrant abdominal pain and distention accompanied by diarrhea and edema. She had no history of food intolerance, asthma, allergic rhinitis or atopy.

On physical examination, her weight was 15 kg (below the 3rd percentile) and her height was 103 cm (below the 3rd percentile). The blood pressure was 110/60 mm Hg, pulse rate was 100 beats/min, and body temperature was 37 °C. The head and abdominal circumferences were 50 cm and 65 cm, respectively. She had periorbital and lower extremity edema. Her abdomen was distended without ascites (Fig. 1). The liver was palpable 2 cm below the right costal margin, while the spleen was not palpable. Rectal examination was unremarkable, except for a watery brown stool.

On admission, laboratory studies revealed a hemoglobin level of 7.8 g/dl and white blood cell count of 10,000/mm^3 (58% neutrophils, 36% lymphocytes, 4%

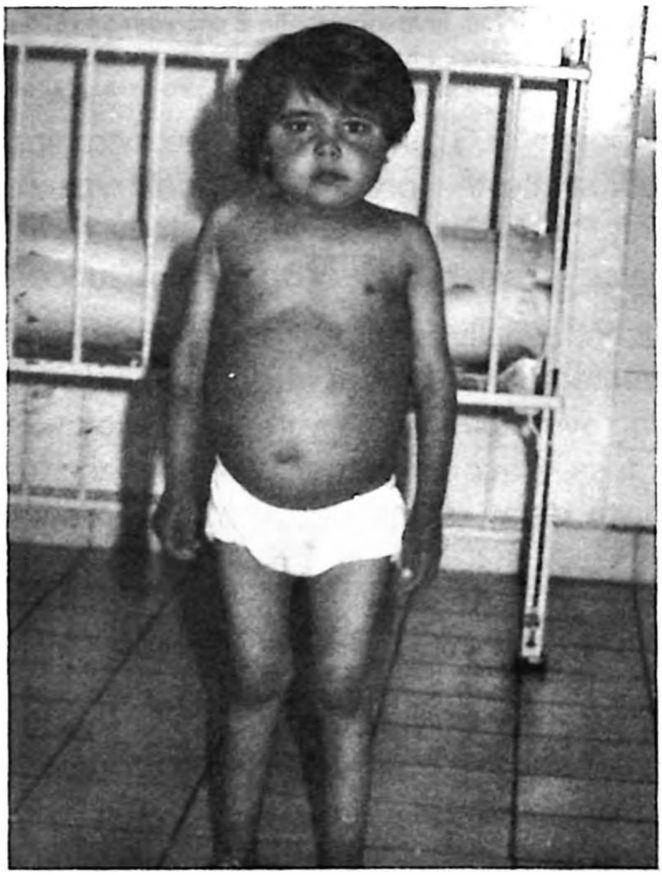

Fig. 1: The photograph taken on admission shows periorbital edema and grossly distended obdomen.

monocytes, 2% eosinophils). Urinalysis was normal. Blood electrolytes, liver and renal function tests, and coagulation studies were within normal limits. Total serum protein and albumin levels were 3.1 g/dl and 1.8 g/dl, respectively. The erythrocyte sedimentation rate was 10 mm/h. Pharynx, urine, stool and blood cultures were all negative. The stool examination was negative for blood, ova and parasites. Stool pH was in the normal range and no sugar was detected in stool samples. Serum iron and iron-binding capacity, vitamin B_{12} and folic acid levels were within normal limits. In immunoelectrophoresis of the serum, the immunoglobulin levels were as follows: IgG 109 mg/dl (normal range: 638 to 1783 mg/dl), IgM 31 mg/dl (normal range: 24 to 98 mg/dl), IgA 24.2 mg/dl (normal range: 89 to 559 mg/dl), and IgE 1590 mg/dl (normal range: 0 to 15 mg/dl). Blood D-xylose concentration was 8.4 mg/dl (normally above 20 mg/dl) after an oral load. The test for HB_sAg was negative. A tuberculin skin test done with 5 TU was negative. The total eosinophil count was 120/mm^3 (normal range: 40 to 400/mm^3).

Ultrasound examination revealed thickening of the colonic wall (8-9 mm), mainly in the rectosigmoid and left flexural regions, and luminal fluid. An upper gastrointestinal x-ray series showed mucosal thickening of the antrum, distal jejunum and proximal ileum. Prominent mucosal folds were noted in the colon on barium enema. A panendoscopy demonstrated erythematous mucosa 7 to 8 cm distal to the splenic flexura.

Histological examination of the specimen from the stomach, duodenum, jejunum and colon showed eosinophilic enteritis predominantly in the mucosa and lamina propria (Fig. 2).

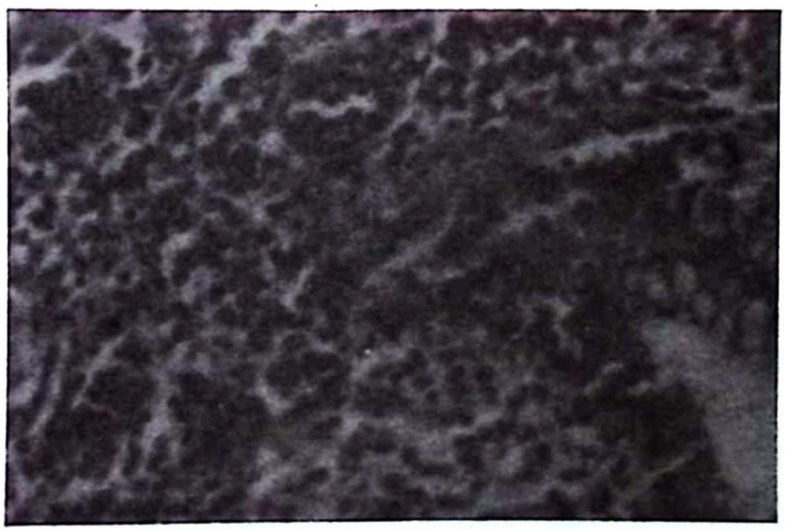

Fig. 2: Colon: lamina propria showing eosinophilic infiltration between the mucosal glands. (H + E, x 400).

During the first two months of hospitalization, the patient was given human albumin 18 times because of severe hypoalbuminemia and edema. She had

findings of intestinal obstruction (vomiting and abdominal distention) five times during this period. After the establishment of the definitive diagnosis of eosinophilic gastroenteritis with typical biopsy findings, the patient was treated with oral prednisolone (2 mg/kg/day). She responded promptly to the therpy. On the tenth day, serum total protein and albumin levels rose to 6.1 g/dl and 3.2 g/dl, respectively. Peripheral edema disappeared. The level of IgE decreased to 500 mg/dl on the 45th day. On the sixth day of the prednisolone therapy, the dose was decreased to 1 mg/kg/day and the patient was discharged. On the follow-up examination performed two months later, her clinical status was good. The abdominal circumference was found to be decreased to 57 cm, with normal levels of serum protein and albumin. The dose of prednisolone was decreased to 5 mg every other day.

Discussion

Eosinophilic gastroenteritis was first described by Kaijser'in 1937[8]. Subsequently, patterns of clinical presentation were correlated with the extent of the eosinophilic infiltration by Ureles et al.[9] and the depth of the eosinophilic reaction by Klein et al.[6] Over 250 cases have been reported in the literature[6-8]. Approximately 15 to 20 percent of the reported cases are in children, and several cases have been documented in early infancy[1,3].

Klein et al.[6] have classified EG according to the layer of gastrointestinal tract involved. Three groups have been described: one with mucosal involvement leading to malabsorption and gastrointestinal protein loss; a second characterized by muscle layer involvement, often leading to pyloric obstruction; and a third with serosal surface infiltration with eosinophils, frequently presenting with ascites. These forms may coexist[5].

In several studies, the most common symptoms were abdominal pain (77-100%), nausea vomiting (48-62.5%), diarrhea (42-62.5%), weight loss (17%), abdominal distention (42%), bloody stool (18%), constipation (5%), ascites (5%) and protein malabsorption (1%). Rarely, fat malabsorption, dysphagia, jaundice, peripheral edema, perianal disease and intestinal perforation could be seen[5-7,10]. In our patient, abdominal pain, vomiting and protein-losing enteropathy dominated the clinical picture. These findings suggested mucosal involvement. Although the biopsy specimen did not include the muscular layer, the findings of intermittent intestinal obstruction suggested involvement of the muscular layer.

Eosinophilic infiltration can be seen over the whole gastrointestinal tract, the most common site being the stomach[7]. With the exception of the esophagus, the frequency of involvement decreases distally through the gastrointestinal tract. Naylor[7] defined it as follows: stomach 43%, ileum 33%, jejunum 31%, duodenum

19%, colon and rectum 11%. The involvement of gallbladder, liver, esophagus, spleen, pancreas or appendix was seen rarely. In our patient, we demonstrated eosinophilic infiltration in the stomach, duodenum, jejunum and predominantly in the colon.

The etiology of EG still remains unknown. The association of systemic allergic symptoms, elevated serum IgE values, and symptomatic response to corticosteroid therapy in some patients suggest that immediate hypersensitivity may be implicated in the pathogenesis of the disease[2].

Hypereosinophilia in peripheral blood is not always present in patients with EG (20-90%) as in our patient[5]. Food sensitivity, especially to milk, appears to play a role in half of these patients[6,7]. Torpier et al.[4] demonstrated that selective release of eosinophil major basic protein from the granule core of eosinophils damaged intestinal tissue. Keshavarzion et al.[11] observed that activated eosinophils were present in tissue biopsies using a monoclonal antibody to eosinophil cationic protein. The cause and meaning of elevated serum IgE in patients with EG are not clear[12,13]. Also, in our patient the level of IgE was elevated although she had no peripheral eosinophilia or allergic symptoms.

Steroids remain the mainstay of therapy for eosinophilic gastroenteritis, with good symptomatic responses being reported[6,7,14]. Similar results were attained in our patient. The value of oral sodium cromoglycate is controversial[13,15] and was not used in our patient.

In conclusion, EG is a rare disease and can be difficult to diagnose. Panendoscopic study may be needed in some patients with unexplained gastrointestinal symptoms.

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The Turkish Journal of Pediatrics 1995; 37: 51-56

TAY – SACHS DISEASE: A CASE REPORT*

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SUMMARY: Arısoy AE, Özden S, Ciliv G, Özalp İ (Department of Pediatrics, İnönü University Faculty of Medicine, Malatya; Department of Ophthalmology, Fırat University Faculty of Medicine, Elazığ; Departments of Biochemistry and Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Tay-Sachs disease: a case report. Turk J Pediatr 1995; 37: 51-56.

Tay-Sachs disease (G_{M2} gangliosidosis I) is an autosomal recessive lysosomal-storage disorder confined to the central nervous system, resulting from deficiency of hexosaminidase A.

The case presented is of a twelve-month-old girl brought to the hospital because of mental-motor deterioration and convulsions. She was the child of first cousins and had a history of the deaths of two siblings with the same manifestations. Generalized hypotonia, macrocephaly, hyperacusis and a retinal cherry red spot appearance were present. There was no organomegaly. The diagnosis of Tay-Sachs disease was made by means of absence of serum hexosaminidase A activity. *Key words: Tay-Sachs disease, hexosaminidase A.*

Tay-Sachs disease (G_{M2} gangliosidosis I) is an autosomal recessive lysosomal-storage disorder that results from a deficiency or defect of the α subunit of hexosaminidase A, which blocks the formation of intact hexosaminidase A[1]. In the absence of enzyme activity, G_{M2} gangliosides cannot be hydrolyzed and therefore accumulate primarily in neuronal tissues. This results in progressive neurologic degeneration. The severity of the disease appears to correlate with the degree of enzyme deficiency[2]. The disease is largely confined to children of Jewish ancestry with Eastern European origin (Ashkenazi) and only rarely has appeared in other Caucasians[3]. At four to six months of age, loss of interest in his or her surroundings, exaggerated startle response to noise (hyperacusis), and progressive psychomotor deterioration are the characteristic clinical findings in a previously well infant[1,3]. With time, hypotonia, loss of previously acquired developmental skills, and then macrocephaly, seizures, hyperreflexia and

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spasticity develop. Nearly all cases have a macular cherry-red spot appearance[1,3,4]. Patients with Tay-Sachs disease usually die before the age of four[1].

The present patient exhibited the classic findings and course of the disease, and is the first in our region in whom the diagnosis has been confirmed by an enzyme-based test.

Case Report

A twelve-month-old female infant was admitted to Fırat University Hospital with symptoms of generalized and myoclonic convulsions that first presented one month prior to admission. She was the fourth child of healthy parents who were first cousins. The gestation, labor and delivery history was unremarkable. She had been irritable since birth. She had showed head control at two months and sat with support at five months of age. However, the parents reported that she had been unduly sensitive to sounds and startled by unexpected noises since four months of age. After five months of age, developmental regression and motor weakness had become evident. At the age of eight months she had become unable to hold her head and sit. She had convulsions for the last month. There was a family history of two siblings dying at the age of two and three years; they had apparently showed similar symptomatology and course, but no diagnosis had been established.

Physical examination revealed a head circumference of 47.5 cm (over 97th percentile), a height of 76 cm (between 75th-90th percentiles) and a weight of 11,500 g (between 90th-97th percentiles). The patient had no interest in her surroundings (Figs. 1, 2). She had a doll-like facial appearance and hyperacusis.

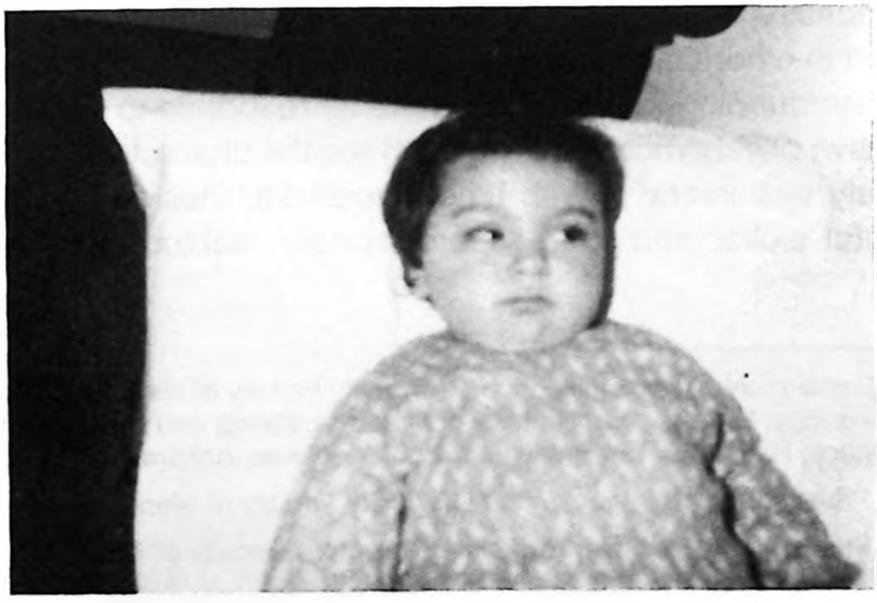

Fig. 1: The doll-like facial appearance in a twelve-month-old patient with Tay-Sachs disease.

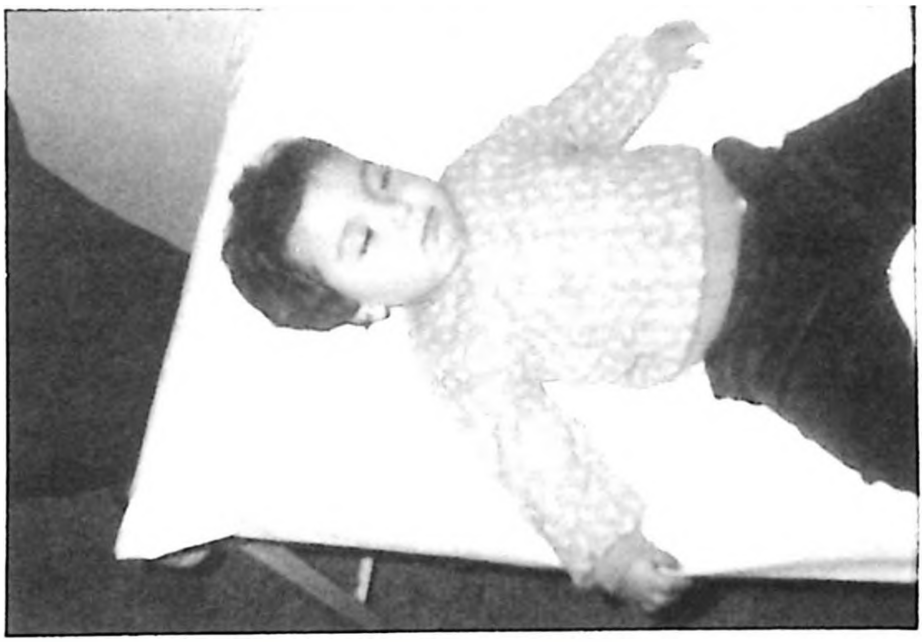

Fig. 2: A twelve-month-old girl with Tay-Sachs disease exhibiting loss of interest in her surroundings.

There was no hepatosplenomegaly. Generalized motor weakness and hypotonia, hyperreflexia and bilateral clonus were present. Fundoscopic examination revealed the cherry-red spot appearance in both macular regions (Fig. 3). The other physical findings were normal.

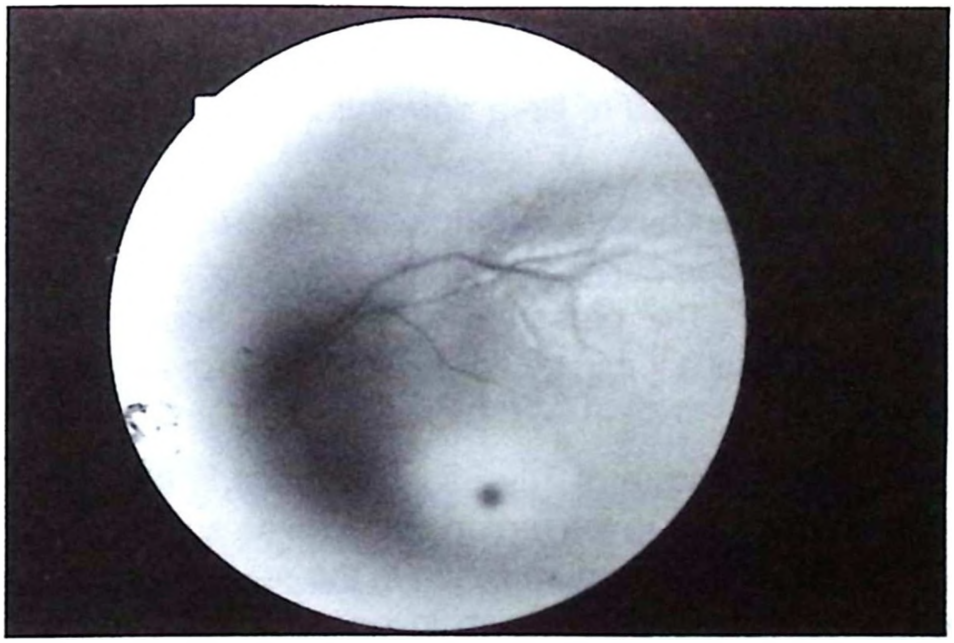

Fig. 3: The characteristic cherry-red spot appearance in a twelve-month-old patient with Tay-Sachs disease.

Laboratory studies revealed normal hematologic and biochemical findings. Urinalysis and roentgenograms of the skull, chest and spine were normal. The bone marrow examination showed no abnormality. Hexosaminidase A enzyme activity in serum was totally absent.

Discussion

Neuronal storage diseases are characterized by accumulation of lipid substances in cerebral neurons. The stored material in Tay-Sachs disease is G_{M2} ganglioside, a sphingolipid which is a main product of the degradative pathway of several gangliosides. The deficiency of hexosaminidase A results in abnormal accumulation of G_{M2} ganglioside within neuronal cytoplasm, causing cell dysfunction and eventually death[1]. Its accumulation starts at an early embryonic age and has been observed in the brain of 18- to 20-week-old Tay-Sachs fetuses[5].

The cherry-red spots of Tay-Sachs disease were first described in 1881 by Tay in a one-year-old child with mental and physical retardation[1]. In 1896, Sachs determined the relationship between the cherry-red spot and progressive involvement of the nervous system, characterized by loss of vision, impairment of hearing, convulsions, psychomotor deterioration and early death, and termed this disorder by the name of "familial amaurotic idiocy"[1].

In the present case, hyperacusis first noted at four months of age, neuromotor deterioration and hypotonia first noted at five months of age, and seizures represented the classical findings and course of the disease. In Tay-Sachs disease, progressive macrocephaly usually develops after the age of 16 months and is due to cerebral gliosis[1,3]. For our patient, the presence of macrocephaly at 12 months of age and the early deaths of two siblings with similar symptoms and course can be considered to be a correlation with the absence of enzyme activity[2].

In classic cases, mental and motor deterioration progress rapidly after one year of age, and progressive deafness, blindness, convulsions and spasticity appear after 18 months of age[1]. The presence of seizures, hyperreflexia and clonus in our twelve-month-old patient can be considered the representations of a severe metabolic defect.

The most characteristic feature of Tay-Sachs disease is the cherry-red spot of the macula, a bright red area in the region of the fovea surrounded by a grayish-white rim which is due to lipid accumulation in the retinal ganglion cells[1,4]. Later the spot becomes darker and brownish in color as the macula degenerates, and opaque whitish streaks, probably lipid deposits, along vessels may be observed[1,4]. The cherry-red spot is not pathognomonic for Tay-Sachs disease. It can be seen in retinal ischemia and contusion of the globe, generalized gangliosidosis, Sandhoff disease, metachromatic leukodystrophy, Niemann-Pick disease, Farber disease and sialidosis (types 1 and 2)[4]. However, the typical course and the absence of organomegaly were strongly suggestive clinical clues of Tay-Sachs disease in our patient.

The diagnostic test for Tay-Sachs disease is the measurement of hexosaminidase A in serum plasma, leukocytes and cultured fibroblasts in affected infants[6-8]. A carrier state affects approximately one in 31 individuals of Ashkenazi Jewish ancestry, but only one in 167 individuals in the non-Jewish population[1].

Heterozygous carriers can be identified by measurement of the enzyme[7]. A newer DNA-based test has proven useful when used as an adjunct to screen carriers for this disorder[2]. Prenatal diagnosis can be accomplished by enzyme assay in amniotic fluid, amniocytes, or chorionic villus samples[9,10]. If one of the siblings had been diagnosed, the parents could have had genetic counseling and a prenatal diagnosis during this pregnancy. No specific therapy for the treatment of Tay-Sachs disease is available. Therapy consists mainly of supportive care for seizures and intercurrent infections.

Hyperacusis since four months of age followed by progressive psychomotor retardation presenting at five months and physical signs consisting of macular cherry-red spot, macrocephaly and absence of organomegaly were the main clinical findings suggesting Tay-Sachs disease in our patient. The definite diagnosis was made by detecting the deficiency of hexosaminidase A in serum.

Anticonvulsive therapy was initiated and genetic counseling offered to the child's parents. We want to emphasize the importance of genetic counseling in such a case in which prenatal diagnosis is currently possible.

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The Turkish Journal of Pediatrics 1995; 37: 57-60

NONKETOTIC HYPERGLYCINEMIA IN A NEWBORN INFANT*

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SUMMARY: Tekinalp G, Coşkun T, Oran O, Özalp İ, Figen G, Ergin H. (Neonatology Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Nonketotic hyperglycinemia in a newborn infant. Turk J Pediatr 1995; 37: 57-60.

A neonate with nonketotic hyperglycinemia who experienced apnea, hiccups and tonic-clonic seizures on the first day of life is reported. The physical findings and laboratory tests including arterial blood gases were normal. However, serial blood and CSF aminoacid analyses demonstrated elevated glycine levels. Serum and CSF glycine levels were 1949 µmol/L and 415.5 µmol/L, respectively. (Normal serum level is 104-254 µmol/L and CSF level is 5 ± 2 µmol/L). The CSF/plasma glycine ratio was 0.11. Oral sodium benzoate and folic acid therapy was initiated. After two weeks of assisted ventilation and clinical improvement, the patient was discharged with a protein-restricted diet. *Key words: nonketotic hyperglycinemia, newborn.*

Nonketotic hyperglycinemia (NKH) is an inherited disorder of glycine metabolism characterized by abnormally high concentrations of glycine in plasma and cerebrospinal fluid (CSF) in the absence of excess organic acids[1,2]. NKH is caused by a defect in the glycine cleavage system (GCS)[2-5]. The clinical picture is variable and seems to relate to the degree of the defect in the GCS. Patients may have neonatal, infantile or late-onset phenotypes. Patients with the neonatal form of the disease either die within months of the initial examination or survive with severe mental retardation. Newborn infants develop rapidly progressing neurological symptoms such as muscular hypotonia, seizures, respiratory distress, persistent hiccups, lethargy or coma[3].

We present the clinical and laboratory findings of a case with neonatal-type NKH. To the best of our knowledge this is the second case report of its type from Turkey[6].

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Case Report

A one-day-old boy was admitted to Hacettepe University Children's Hospital Neonatal Intensive Care Unit because of previous sibling death. This infant was born at full term by cesarean section to a gravida 3, para 2, abortion 1 mother. His Apgar scores were 9 and 10 at one and five minutes, respectively. There was no consanguinity. One female sibling had earlier presented with extreme hypotonia, feeding difficulties and intractable seizures, and had died at the age of seventeen days.

On admission, the physical examination revealed a head circumference of 36.5 cm (90^{th} percentile), weight of 3600 g (90^{th} – 95^{th} percentile) and length of 52 cm (75^{th} – 90^{th} percentile). The neurological examination was normal. Laboratory investigations revealed the following: hemoglobin 21 g/dl and white blood cell count 10.000/mm^3. The blood concentrations of sugar, electrolytes, calcium, phosphorus, creatinine, total protein, albumin, ammonia, pyruvate, lactate, alkaline phosphatase, SGOT and SGPT were all within normal limits. X-rays of the chest and skull were normal as were the findings on cranial ultrasonography.

Arterial blood gases showed no evidence of acidosis or ketosis. At 12 hours of age the infant was markedly hypotonic and lethargic. He began to have apnea, hiccups and tonic-clonic seizures. Serial blood and CSF aminoacid analyses (on a LKB 4151 Alpha Plus Amino Acid Analyzer) demonstrated remarkably elevated glycine levels. The serum glycine concentration was 1949 µmol/L (normal: 104-254 µmol/L) and CSF glycine concentration was 415.5 µmol/L (normal: 5 ± 2 µmol/L). The CSF/plasma glycine ratio was 0.11 (normal: 0.02-0.03).

On the seventh day of life, a decrease in the patient's respiratory rate and apnea were noted. Assisted ventilation was initiated. Oral sodium benzoate therapy was administered along with a protein-restricted diet (1 g/kg/day). Folic acid at a dose of 2-5 mg/day was added to his therapeutic regimen. His general condition partially improved on the 25^{th} day. When spontaneous respiration began, assisted ventilation was discontinued.

Discussion

NKH is an autosomal recessive disorder of glycine metabolism which is characterized by elevation of glycine in plasma, urine and particularly in CSF[1]. Glycine levels in CSF are distinctly higher in NKH as compared with those in ketotic hyperglycinemia, and the ratios of CSF to plasma are clearly different. The high ratio in NKH does not change even when the plasma glycine level falls due to administration of sodium benzoate or to other therapeutic approaches[1,7,8].

In NKH there is a defect in the major pathway of glycine catabolism in the formation of serin from glycine. The glycine cleavage system (GCS), which converts glycine to CO_2, NH_3 and a single carbon tetrahydrofolate derivative, is composed of four protein components: P protein (a pyridoxal phosphate-dependent glycine decarboxylase), H protein (a lipoic acid containing protein), T protein (a tetrahydrofolate-requiring enzyme) and L protein (Lipoamide dehydrogenase). It has been proposed that a defect in any of these four components may lead to the development of NKH[1,3,9].

The GCS is specifically expressed in the liver, kidney and brain. Liver biopsy is, therefore, currently necessary for enzymatic diagnosis of NKH. Transformed lymphoblasts are also used for the diagnosis of NKH[10]. A large body of recent evidence suggests that enhanced activation of the N-methyl D aspartate (NMDA) type of excitatory aminoacid receptors may contribute to the pathophysiology of NKH and is important in the regulation of developmental synaptic plasticity. Evidence indicates that a high CSF concentration of glycine in NKH may contribute to the pathogenesis of this disease by overactivating NMDA receptors via an action at the associated glycine modulatory site[11,12].

The neonatal type is the most common type of NKH. Patients develop rapidly progressing neurological symptoms in the neonatal period such as muscular hypotonia, depressed Moro response, seizures (often myoclonic), apneic attacks and lethargy or coma. Most patients die within a few weeks of life, whereas the survivors show severe psychomotor retardation[4]. Our patient showed the clinical picture of the neonatal onset form of the disorder. The high CSF glycine/plasma ratio gave further evidence to the diagnosis of NKH. Luder et al.[13] described transient nonketotic hyperglycinemia in two neonates. Unlike these cases, in our case hyperglycinemia was established on the third day of life.

Various forms of treatment have been tested in NKH. Exchange transfusion or peritoneal dialysis may be life-saving in the neonatal period, but its effect is only temporary[9]. The plasma glycine concentration may be lowered by the restriction of protein intake and by the administration of sodium benzoate. We gave a protein-restricted diet with sodium benzoate to our patient, which was partially effective in the control of symptoms. Recently, the NMDA receptor antagonist, ketamin, was administered to a patient with hNKH, and improvement in hyperirritability, voluntary movement and electroencephalographic findings was noted[11]. These therapeutic approaches are merely supportive and may lower the blood glycine level but not that of CSF. It can be said that they have no effect on the outcome of this metabolic disorder.

Prenatal diagnosis of NKH has become possible in recent years. Thus the diagnosis of NKH should be considered in markedly hypotonic newborns in

order to give genetic counselling to the parents and offer them a prenatal diagnosis in subsequent pregnancies[14].

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The Turkish Journal of Pediatrics 1995; 37: 61-65

HYPOPHOSPHATASIA IN A NEWBORN INFANT*

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SUMMARY: Tekinalp G, Yükselen A, Balkancı F, Coşkun T, Yurdakök M. (Neonatology Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Hypophosphatasia in a newborn infant. Turk J Pediatr 1995: 37: 61-65.

Infantile type hypophosphatasia, an autosomal recessive disease with severe clinical manifestations, is characterized biochemically by subnormal activities of circulating alkaline phosphatase. In this report, we presented a five-day-old male with this rare disorder. His parents were first cousins, and he was first seen for jaundice. He had soft calvaria, large fontanel, extremely wide cranial sutures, low-set ears, a depressed nasal bridge, funnel chest, and short and bowed distal limbs. Roentgenographic studies showed widened sutures and poor ossification of the skull, bowing of the femora and slight modeling defects in the long bones. A low serum alkaline phosphatase activity led us to measure excretion of phosphoethanolamine and found it to be increased.

To our knowledge this is the first case of this rare disease reported in the neonatal period from our country. *Key words: hypophosphatasia, newborn.*

Hypophosphatasia is a heritable form of rickets-osteomalasia that is characterized by decreased activity of the tissue-nonspecific (liver, bone, kidney) isoenzyme of alkaline phosphatase (TNS-ALP), and endogenous accumulation of pyridoxal 5-phosphate, phosphoethanolamine (PEA) and inorganic phosphate[1]. Based on the age of clinical presentation, hypophosphatasia can be classified into four forms: perinatal, infantile, childhood and adult. Most of the patients with perinatal or infantile-type hypophosphatasia die shortly after birth or within the next few months due to severe bony deformities[1,2].

This paper presents an infant with the infantile form of hypophosphatasia. To our knowledge, this is the first case of this rare disease reported in the neonatal period from our country.

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Case Report

A five-day-old male infant was first seen at the emergency department for jaundice. He was born at 39 weeks gestation to a 23-year-old, primigravid woman after an uncomplicated pregnancy and delivery. The mother had not been exposed to any drug during her pregnancy. The parents were first cousins. The patient's birth weight was 2700 g, length 46 cm, head circumference 32.5 cm, body temperature 36.5 °C (axillary), pulse rate 136/min (rhythmic) and respiration rate 48/min. The patient was active and in good general condition. On physical examination he had soft calvaria, large fontanel (metopic fontanel), extremely wide cranial sutures, low-set ears, a depressed nasal bridge, funnel chest, and short and bowed distal limbs.

Laboratory studies including a complete blood count, blood sugar, serum electrolytes, blood and urine aminoacids were all within normal limits. Serum total and direct billirubin were 17.5 and 0.5 mg/dl, respectively. Direct Coombs was negative. Glucose-6-phosphate dehydrogenase and thyroid stimulating hormone levels were within normal limits. One remarkable laboratory finding was a low (41 U/L) alkaline phosphatase activity (normal range is 62-348 U/L in term neonates). Serum calcium and phosphorus levels were normal.

Radiological findings revealed widening of sutures and poor ossification of the calvarium, marked in the frontal and parietal bones. Both femurs were bowed in their middle thirds, and there were some slight modeling defects in the humerus, radius and thin ribs (Figs. 1-2). The metaphyses were normally

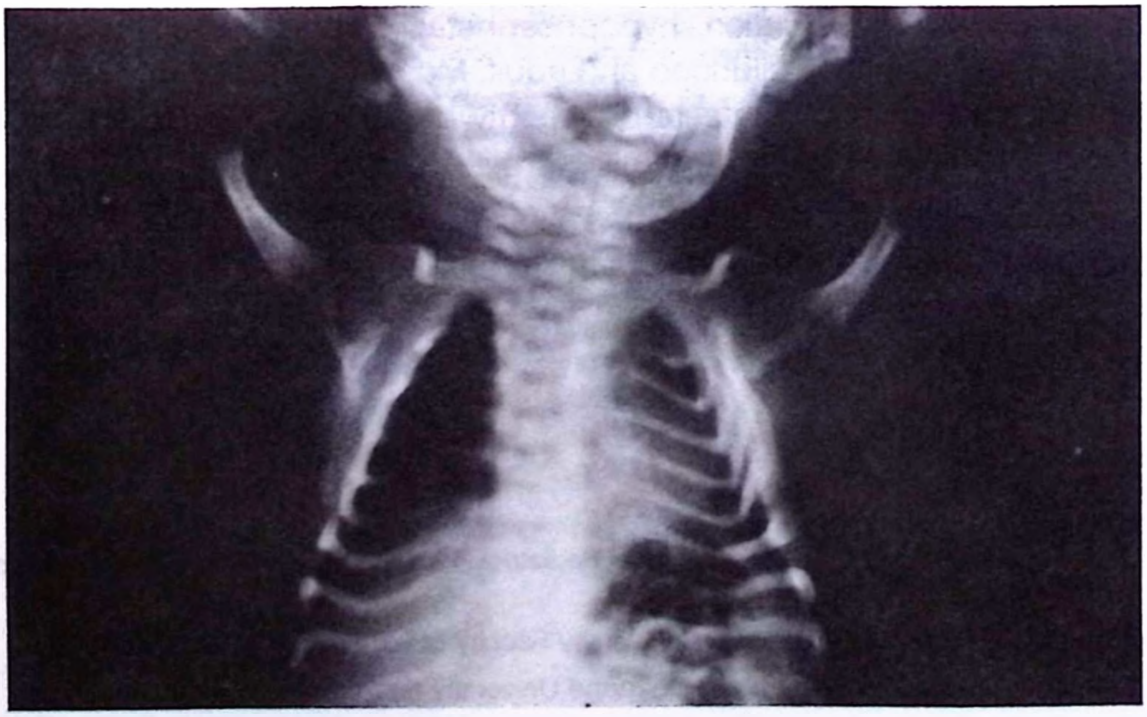

Fig. 1: Posterior-anterior chest x-ray showing generalized osteopenia, slight modeling defects in humerus and radius with deformed, thin ribs.

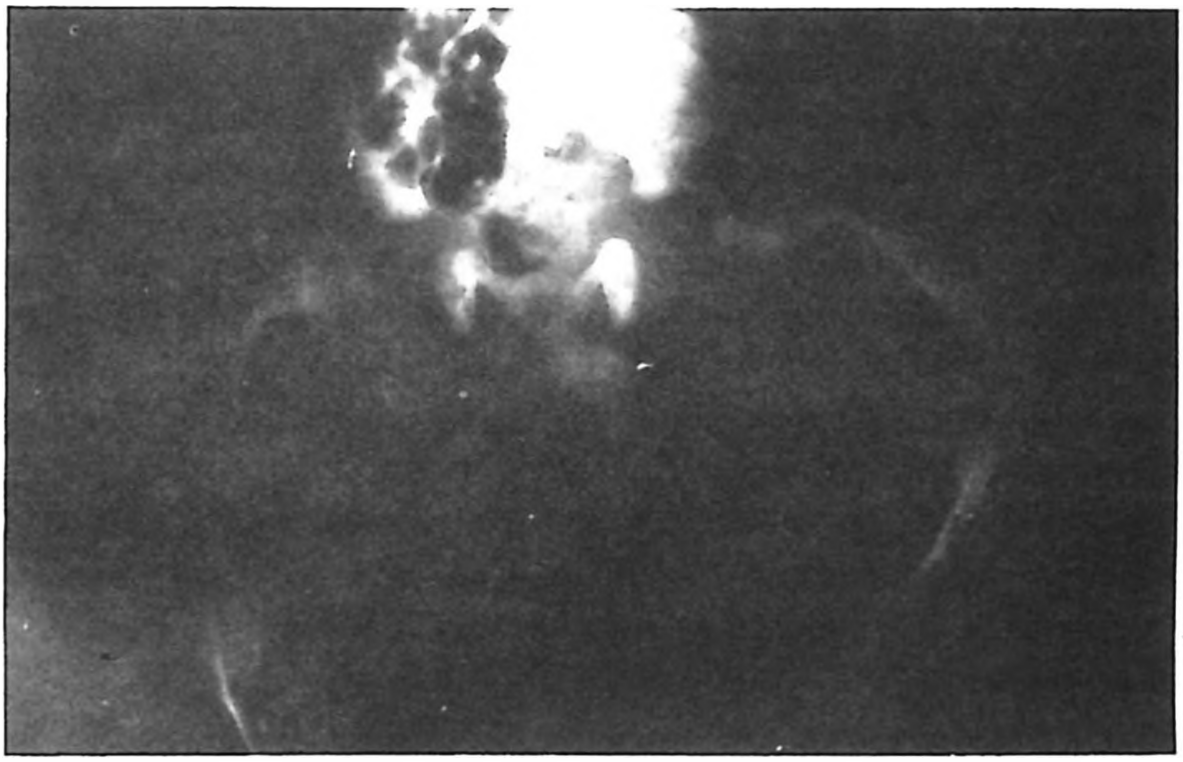

Fig. 2: Defective ossification of the long bones, and bowing of the femora.

mineralized. Because of the low alkaline phosphatase activity as well as phenotypic and radiologic findings resembling hypophosphatasia, we measured the urinary phosphoethanolamine level and found it to be increased (1.4 mmol/g creatinine; normal < 0.3 mmol/g creatinine). The patient was managed for indirect hyperbilirubinemia with phototherapy and exchange transfusion. On the seventh day he was discharged with no clinical problem. Genetic counseling was given to the parents.

Discussion

Hypophosphatasia, which is characterized by a reduced or abesnt alkaline phosphatase activity in the liver, kidney and bone, is transmitted by different modes of inheritance. Perinatal (lethal) and infantile types of hypophosphatasia are autosomal recessive diseases, whereas childhood and adult types have been described as autosomal dominant forms[1,2]. The severity of hypophosphatasia correlates directly with the degree of deficiency of TNS-ALP activity in serum and tissues[3]. Perinatal hypophosphatasia, which manifests at birth, is lethal. Infantile hypophosphatasia presents during the first six months of life, and the disease is also lethal in over half of affected subjects[1,4].

Our patient might be classified as having infantile hypophosphatasia. Moor et al.[2] also described a case of infantile-type hypophosphatasia who was diagnosed on the first day of life and whose brother died of the same disorder. On follow-up, most cases with infantile hypophosphatasia have failure-to-thrive and rachitic like skeletal deformities that result in recurrent respiratory difficulties and hypercalcemia[1,2].

The characteristic radiographic findings are irregularity of the metaphyses of various bones, generalized osteopenia, delayed ossification of the cranial vault, defective ossification of the ribs and long tubular bones, and bowed or deformed long bones. In childhood, metaphyseal lesions may simulate rickets. Bowing deformities and increased bone fragility are characteristically present in both the most severe form (seen in infants) and the mildest form (seen in adults) of hypophosphatasia. Thanatophoric dwarfism has also been taken into consideration in the differential diagnosis[5,6].

In our case, bowing of the femora and the appearance of the metaphyses were different from that seen in rickets. Thanatophoric dwarfism is differentiated by well-ossified calvaria, flat vertebral bodies and short-bowed long bones.

The laboratory findings of pseudohypophosphatasia are quite different from hypophosphatasia, with elevated urinary phosphoethanolamine but normal serum alkaline phosphatase[7].

The methods employed so far in the prenatal diagnosis of infantile hypophosphatasia include ultrasonographic examination of the fetus, measurement of alkaline phosphatase activities in amniotic fluid, and cultured cells from amniotic fluid or chorionic villi[4,8]. Recently, prenatal diagnosis of the disease was successfully carried out using the cDNA for the human-liver-type alkaline phosphatase as a probe with chorionic villi samples[9]. As in our case, the diagnosis of the index case is important, because genetic counseling can be given to the parents.

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The Turkish Journal of Pediatrics 1995; 37: 67-71

GANGRENE AFTER PENICILLIN INJECTION*
(A Case Report)

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SUMMARY: Özel A, Yavuz H, Erkul İ. (Department of Pediatrics, Selçuk University Faculty of Medicine, Konya, Turkey). Gangrene after penicillin injection: a case report. Turk J Pediatr 1995: 37: 67-71.

A patient with right lower limb gangrene that developed after penicillin injection is presented. Accidental intraarterial administration of penicillin may cause gangrene necessitating amputation. To avoid this severe complication, every intramuscular injection should be given with meticulous attention to proper technique, with adequate restraint of the patient, and with full knowledge of local anatomy and potential complications. *Key words: intramuscular injection, gangrene, penicillin procaine.*

Intramuscular (IM) injection is a common practice in medicine. The inadequacy of the gluteal muscle mass and the high risk of sciatic nerve injury make thigh muscles more appropriate for IM injection in infants. However, this approach is not entirely safe either. The injury of a. femoralis or its branches due to IM injection may cause tissue damage in areas of the body that are supplied by these vessels.

In this report an infant who developed limb necrosis after IM injection of penicillin into the thigh is described in order to call attention to a preventable complication.

Case Report

A seven-month-old male infant was diagnosed with acute tonsillitis in a rural health center, and therapy with IM procaine penicillin was administered. On the fifth day of therapy, immediately after the injection diffuse purple discoloration appeared around the injection site in the right thigh, extending to the abdomen and left lower limb. As the color changes became deeper and a marked feeling of coldness was noticed in the right leg, the patient was brought to our hospital.

Physical examination revealed a child with an axillary temperature of 37.2 °C, weight 6700 g and height 69 cm. The systolic blood pressure was 100 mmHg, pulse rate 116/min, and both a. femoralis pulses were present. The right thigh was six cm wider than the left side. There were purpuric lesions over the periumbilical, inguinal and right hemiscrotal areas.

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Ecchymotic and gangrenous changes were present in a spotty fashion over the entire right lower extremity and the toes (Figs. 1 and 2).

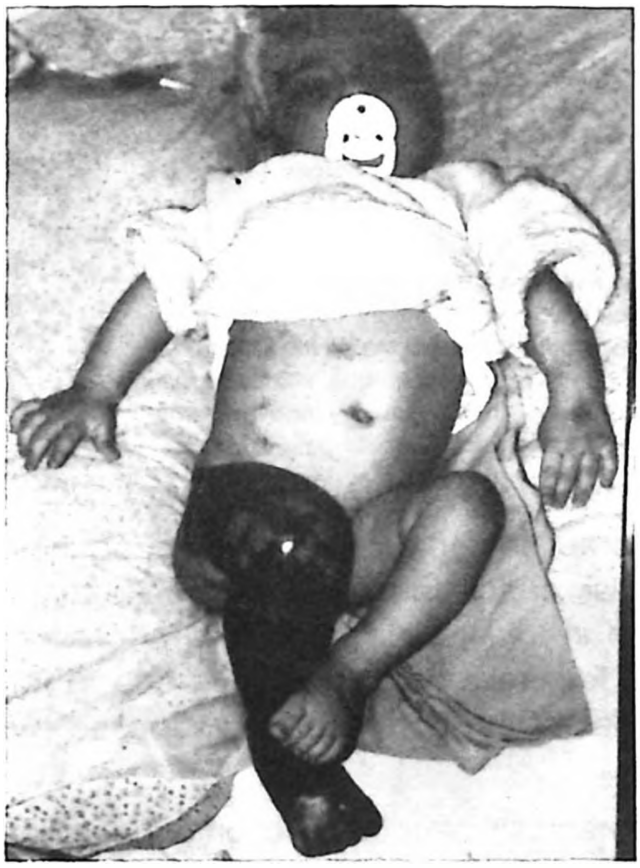

Fig. 1: Discoloration, edema and bullae in the right lower extremity.

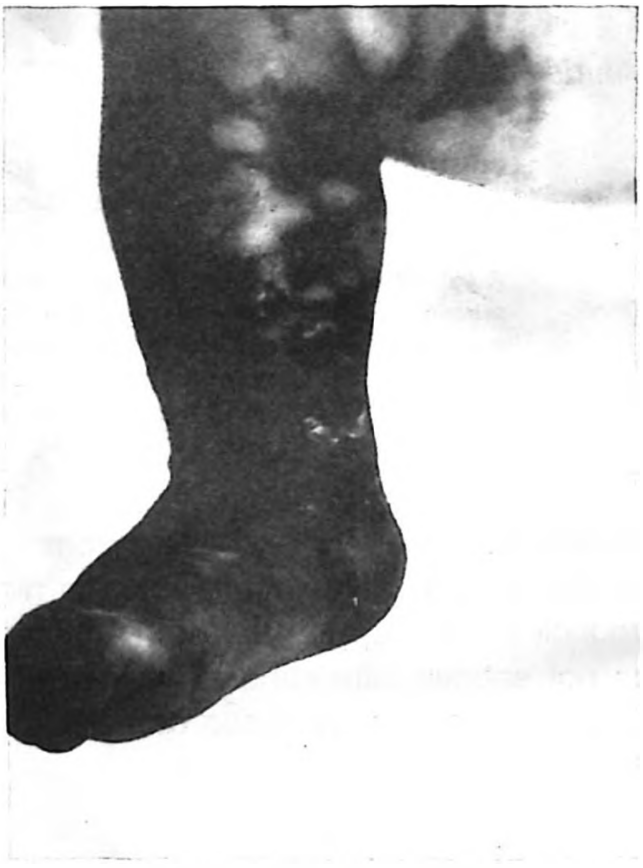

Fig. 2: Necrotic areas especially prominent at tiptoes.

Laboratory investigations yielded a normal urinalysis, hematocrit 38 percent, white cell count 3000/mm^3, and platelet count 568,000/mm^3. A peripheral blood smear was normal. The direct Coomb's test was negative. Both the prothrombin and the partial thromboplastin times were normal, and the level of fibrin degradation products was 10 mg/dl.

Therapy with heparin 50 U/kg and prednisolone 0.5 mg/kg, q 6 h, intravenously was started with the suggestion of vascular injury due to IM injection. Ceftriaxone was added to the therapy upon development of bullae over the ecchymotic lesions. The edema in the lower extremity disappeared gradually and the general status of the patient improved. Although distal pulses became palpable, gangrenous changes necessitating amputation developed in the toes and the sole, and the patient was referred to the Department of Plastic and Reconstructive Surgery.

Discussion

The most serious complications of intramuscular (IM) injections are muscle contracture and nerve injury. Abscess, intramuscular hemorrhage, tissue necrosis

and gangrene may also occur. The muscles of the gluteal area and the rectus muscles of the thigh are the most frequently locations for IM injections. Rectus muscles that have relatively larger mass are preferred in young infants whose gluteal muscles are not sufficiently developed. When injected in this area, vessel and nerve injury are not likely to occur because of the absence of important vessels and nerves in the anterior lateral aspect of the thigh. However it has been reported that 78 percent of quadriceps muscle contractures in children occurred postinjection[1].

Allergic reactions being the most important, penicillins have hematologic, pulmonary, cardiac, neurologic, psychiatric, and vascular side effects[2-4]. Vascular complications can be seen in two patterns. One is Hoigne's syndrome, which occurs as a result of the accidental intravenous injection of a drug. This syndrome expresses itself as brief transient central nervous system changes and coma developing soon after injection. Sometimes death may ensue[5]. Ischemic or gangrenous changes complicating penicillin injection are due to the intraarterial injection of the drug[5,7]. Although no tissue reaction is seen after periarterial injection of penicillin in animal studies, ischemic changes follow the intraarterial injection[6]. In addition, failure of therapy to reverse vasospasm supports that the main mechanism responsible for tissue injury is vascular occlusion.

The signs that occur following intraarterial injection need not occur only distal to the injection site, but they may be seen in the proximal areas too. Since the distal part of the vessel is narrower, the drug may be forced retrograde[5]. The relatively lower blood pressure of children eases the retrograde filling. The drug may easily reach the aorta, as the distance is shorter in children[8]. Tissue injury follows the distribution of the lower aorta. Vascular occlusion up to the level of the aortic bifurcation leads to ipsilateral damage, whereas further retrograde filling may cause ischemic or necrotic changes on both sides. Obstruction of the upper parts of the aorta may result in transverse myelitis by interfering with the arterial supply to the spinal cord[8,9]. If the needle is inserted horizontally to the thigh, it may reach the femoral artery. The occlusion of the femoral artery or its branches causes ischemic changes in the foot or the leg[10,11]. The arterial injuries that may occur in the forms of transverse myelitis, sciatic neuropathy. drop foot, local necrosis, local or distant gangrenes are mostly seen in children under three years of age[5]. Amputation of the leg due to necrosis after intrarterial injection of benzathine penicillin has also been reported[12].

It is suggested that some properties of the drug could have been effective in the occurrence of the ischemic or gangrenous changes. The crystals of benzathine penicillin or procaine penicillin that are bigger than the erythrocytes may occlude the small arterioles. The embolisation of other substances in the preparations or allergic or idiosyncrathic reactions to them could also play a

role in the development of tissue damage[5]. The aggregation of the platelets on the vascular endothelium which is damaged by the caustic effect of the drug will halt the blood flow[6].

When receiving an injection, a baby may struggle and the needle may penetrate the vessel[6]. When choosing the method of therapy, particularly in infants, the indication should be very carefully determined. Before giving the drug, the syringe should be checked for the presence of blood by frist aspirating. The opacity and the high viscosity of the IM penicillin preparations may prevent the recognition of blood within the injector. The blood can only traverse in the center of the injector since the drug is highly viscous and it can only be seen at the near end of the piston, which is an atypical place to look for an aspirate[5,11,13]. It has been reported that the insertion of the needle into a vessel might be unnoticed unless there was as much blood as the drug within the injector[13]; however we could not prove that opinion. We dissolved 800,000 units of procaine penicillin in 2 ml of distilled water and observed for color change by aspirating blood with a transparent syringe. When a minimal amount of blood was aspirated, it could be seen at the distal end of the injector, where as blood in the syringe first became visible at the proximal end of the piston with an amount of 0.2 ml.

In thigh injections, the upper lateral quadrant of the thigh should be used. The needle must be inserted at a 45° angle to both the horizontal and long axes of the leg. Meanwhile, by holding the lateral muscles of the thigh with the free hand, both the stabilization of the leg and the injection of the drug can easily be accomplished[1]. The junctional parts of the needle and the injector must be transparent so as to allow for the perception of color changes. Maximum attention must be paid for the appearence of blood both at the distal end of the injector and just below the piston. If blood is seen in the injector or any discoloration occurs, the needle should be withdrawn immediately. Then the drug should be prepared with a new syringe and the injection should be tried in another area[14]. Local bleeding beyond what is usually expected after injection should arouse the suspicion of intraarterial injection, and the patient must be observed closely[12].

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The Turkish Journal of Pediatrics 1995; 37: 73-77

FATAL AGRANULOCYTOSIS DEVELOPED IN THE COURSE OF CARBAMAZEPINE THERAPY*

A Case Report and Review of the Literature

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*Münevver Büyükpamukçu MD****, *Kalbiye Yalaz MD****

SUMMARY: Olcay L, Pekcan S, Yalnızoğlu D, Büyükpamukçu M, Yalaz K. (Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Fatal agranulocytosis developed in the course of carbamazepine therapy: a case report and review of the literature. Turk J Pediatr 1995; 37: 73-77.

A case of fatal agranulocytosis in an adolescent who was on carbamazepine therapy is presented. The clinical and laboratory findings suggest that the primary cause of the disorder was neutropenia rather than infection, and the preceding factor for neutropenia was carbamazepine. The timing of occurrence of the hematologic picture, its dependency on dose increments, and the lack of symptoms until infection supervened are consistent with an idiosyncratic-toxic drug reaction (type 2 drug reaction). This is the first reported agranulocytosis case due to crabamazepine in adolescence.

As carbamazepine is a commonly used, major anticonvulsant, physicians should be aware of its side effects, such as agranulocytosis[1]. We have not encountered any report in the literature of agranulocytosis due to carbamazepine during childhood or adolescence. We present a case of fatal agranulocytosis with skin rash and a former reaction against phenytoin in the adolescent period.

Case Report

S.Z., a 14-year-old boy, underwent surgery with the diagnosis of "triventricular hydrocephaly" due to a right temporal arachnoid cyst in the third ventricle one month earlier. His leukocyte count was 8600/mm^3 at that time. Phenytoin (6 mg/kg) administration was initiated post-operatively for prophylactic purposes and carbamazepine (8 mg/kg) was added the next day, after the patient's first convulsion. He developed a high fever on the tenth day of treatment, which subsided after discontinuation of phenytoin.

The carbamazepine dose was increased to 12 mg/kg on the fifteenth day of admission when the patient's leukocyte count was found to be 4800/mm^3. He was discharged on the twentieth day of therapy in good general health. One

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day later he was admitted to the Pediatrics Service with complaints of fever and skin rash which covered his trunk and extremities. He had not ingested any drug except carbamazepine for fifteen days.

The patient's vital signs included a body temperature of 38.5 °C, pulse 112/min, respiratory rate 32/min, blood pressure 110/80 mmHg. The trunk and limbs were covered with a erythematous maculopapular rash. The neurological examination revealed brisk deep tendon reflexes, bilateral Babinski response, patellar clonus and bilateral optic atrophy as in his previous examination one month before.

Laboratory findings were as follows: hemoglobin 14 g/dl, hematocrit 44%, leukocyte count 2000/mm^3. All of the 23 leukocytes which could be detected on the blood smear were lymphocytes. thrombocytes were abundant, and erythrocytes were normochromic and normocytic. Urine analysis, liver and kidney function tests and chest x-ray were normal. Computerized cranial tomography showed triventricular hydrocephaly. A ventricular tap showed normal cerebrospinal fluid values. The recurrent bacterial cultures of blood, urine, throat, stool and cerebrospinal fluid were negative. Antinuclear antibody, anti-DNA, C3 and C4 were normal. The specimen of bone marrow aspiration was acellular.

Mezlocillin, amikacin and hydroxyzine administration was initated with the diagnosis of neutropenic sepsis and allergic reaction. Carbamazepine was discontinued. The patient had severe gastroenteritis between the third and eighth days of admission. On the fourth day, the leukocyte count fell to 1400/mm^3, and all of the 10 leukocytes which could be detected on the blood smear were lymphocytes. The leukocyte count began to increase and the fever resolved on the fifth day. On the blood smear, relative lymphocytosis and relative monocytosis preceded the development of early granulocyte precursors, band forms and polymorphonuclear leukocytes. On the sixth day, mezlocilline was discontinued and vancomycin, piperacillin, ornidasole and fluconazole were added as the patient's condition deteriorated. On the seventh hospital day, the patient developed adult respiratory distress syndrome (ARDS), symptoms of which supervened to symptoms of severe gastroenteritis and then intrinsic renal failure. Peritoneal dialysis and assisted ventilation were initiated. He died on the twenty-second day, just after developing disseminated intravascular coagulation as a complication of ARDS and pneumothorax. Post-mortem blood culture revealed Klebsiella.

Discussion

The patient displayed an acquired single cytopenia as neutropenia, the other series being unaffected. The etiology of acquired neutropenia is suggested to be drugs and toxins, preleukemia, systemic diseases and infections, and idiopaty[2]. Drugs and/or infection seem to be the most likely causes of our patient's

neutropenia. It cannot be distinguished precisely whether primarily an infection caused the neutropenia or whether infection supervened a primary neutropenia. The most common viral infections associated with leukopenia are infectious hepatitis, infectious mononucleosis, rubella, measles and occasionally influenza[3]. None of these infections seem to be the primary cause of our patient's neutropenia, fever and skin rash, which were noted one day after his discharge and one day before his readmission to the hospital. During his stay in the hospital he had no symptoms attributable to any infection up to the date of discharge. It would seem unlikely that the causative agent of his initial fever associated with skin rash was bacteria as we had failed to grow bacteria in the consecutive blood cultures. We believe that gastroenteritis developed due to mucosal damage caused by serious bacterial invasion of the bowel wall by the microorganisms of the flora because of the limited granulocytic response[4], leading to sepsis which gave rise to ARDS, Thus we searched for other possible causative factors, such as a medication, carbamazepine was the only medication the patient had been ingesting.

The most common hematologic side effect of carbamazepine was reported to be thrombocytopenia followed by aplastic anemia, agranulocytosis, pancytopenia and bone marrow suppression. The incidence of agranulocytosis due to carbamazepine was found to be 0,71/506,000[1]. Although cases of agranulocytosis due to carbamazepine have been reported in adults, we did not encounter any case in the literature regarding children or adolescents.

Leukopenia due to carbamazepine which may be persistent or transient is compatible with a toxic or idiosyncratic drug reaction (type 2 reaction)[5-7] because of its development after dose increments and liability to emerge in patients with low or low-normal leukocyte counts, its initiation during the first and second weeks of treatment and its asymptomatic nature unless an infection supervenes[1,5,6]. As expected in a type 2 reaction, leukopenia due to carbamazepine rarely turns to agranulocytosis or aplastic anemia[1]. However, it has been pointed out that no case of leukopenia due to carbamazepine precede marrow suppression[8]. Essentially, the cases in the literature involve severe leukopenia and agranulocytosis which have arisen abruptly within one month of therapy without following a definite period of leukopenia. Our case is consistent with those in the literature from the viewpoint of the starting time. Besides, the development of agranulocytosis symptoms six days after the dose increment and the association with fever reinforces the resemblance to a type 2 agranulocytosis reaction.

Our knowledge about the bone marrow morphology in cases of carbamazepine-induced agranulocytosis is quite limited[6,9,10]. In our patient we could not obtain material on bone marrow aspiration during the neutropenic period and could

not repeat it because of the patient's deteriorated condition. Nevertheless, the rapid rise in the leukocyte count after the cessation of the drug, the emergence of the early myelocyte precursors which preceded the stab forms and neutrophils, and the transient monocytosis during the first two days indicated that recovery of hypoplastic or aplastic bone marrow which is usually observed in type 2 agranulocytosis cases had begun[5].

Another interesting point in our case was the presence of a reaction against both phenytoin and carbamazepine. There are many reported cases in which at least one or more findings such as skin rash, blood dyscrasias, fever, and deterioration of liver function tests are found during sequential phenytoin and carbamazepine therapies[6,11]. The reactions of our patient against both phenytoin and carbamazepine probably resulted from his increased production and/or decreased detoxification of the common arene oxide metabolites[11]. His ingestion of the two drugs together for ten days is expected to have raised the level of these toxic metabolites and may have deteriorated the reaction. This points out that carmazepine and phenytoin should not be used together or sequentially, if any adverse effect is encountered with one of them.

The third interesting point in the case is the presence of agranulocytosis with skin rash, which may arise in various forms[1,12]. Skin rash has been declared as an indication for the cessation of the drug[6]. A patient who elicited simultaneous skin rash and agranulocytosis on the twenty-first day of carbamazepine therapy, as in our patient, was previously reported[13]. On the other hand, it has been proposed that rash would not be seen in leukopenic patients[14].

Although some authors advise hematologic monitoring[15,16]. It is not generally recommended because it will detect only reversible leukopenia of which the incidence is 10-12%, but not fatal and rapidly developing leukopenia[1,8]. Our patient's leukocyte count on the seventeenth day (4800/mm^3) was found to be normal, but severe leukopenia and agranulocytosis were discovered five days later.

If we could have investigated the effect of carbamazepine on the granuloid precursors (C colony assay) of the patient after his recovery and shown a decrease in CFU-C colony numbers when carbamazepine was added in the culture, we could have proved that the causative agent was carbamazepine; however, the deteoriated condition of the patient made this investigation impossible. On the other hand, absence of any other medicine besides carbamazepine on admission and absence of any report of agranulocytosis after cessation of phenytoin strongly suggests that agranulocytosis was caused by carbamazepine.

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The Turkish Journal of Pediatrics 1995; 37: 79-82

A CASE REPORT OF PENIS RECONSTRUCTION FOR PARTIAL PENIS NECROSIS FOLLOWING CIRCUMCISION*

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SUMMARY: Erk Y, Kocabalkan O. (Department of Plastic and Reconstructive Surgery, Hacettepe University Faculty of Medicine, Ankara, Turkey). A Case report of penis reconstruction for partial penis necrosis following circumcision. Turk J Pediatr 1995; 37: 79-82.

Circumcision is one of the most common operations performed world-wide and is usually done for religious and social reasons. Although it is a simple procedure, serious complications may result. These complications may range from hemorrhage to total amputation. Reconstruction of a partial amputation of phallus due to circumcision by full-thickness skin grafting is presented in this paper. *Key words: circumcision, complication, penis reconstruction.*

Circumcision is one of the most commonly performed operations in the world. It is a routine practice in some ethnic and religious groups. In Islam, circumcision of a male child is a "must" and is usually performed before puberty with a ceremony called a "circumcision wedding", where all relatives and neighbors witness the boy entering manhood. Usually this procedure is performed by a local man with no medical training. It can be done with a mechanical device such as a cutting ring, and is usually performed without anesthesia. Recently more and more boys in Turkey, especially in large cities, are being circumcised under a doctor's supervision. Although it is a simple procedure, in inexperienced hands it may result in devastating complications in the short-and long-term. Possible complications of circumcision include hemorrhage, edema, infection, meatal stenosis, urethral fistula, unsightly scars, penile curvature, shortness of the shaft skin, and, in the extreme, partial or total penile loss. The true incidence of the complications is not known in Turkey, since in the male-dominant Turkish population it is considered a shame to have any deformity concerning one's penis. Frequently these patients seek medical attention for other health problems.

There are few reports about reconstruction of subtotal amputation of the penis due to circumcision. However, several cases and reconstruction methods have been reported for partial and complete penis loss for other reasons[2-5].

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We are presenting a young boy with a partial penis loss following circumcision, which was reconstructed using a full-thickness skin graft in our clinic.

Case Report

A five-year-old boy was taken by his uncle to our clinic with the complaint of having no penis. He was circumcised at age two by a local "circumciser". After the procedure, he experienced edema and vascular compromise and lost most of his penis. On physical examination the child seemed to have no extruding phallus and no palpable corporal tissue within the scarred perineum. During healing, the skin probably pulled the penile shaft and disguised the actual length of remaining penis (Figs. 1a and 1b). A voiding cistography was performed to visualize the length of the urethra distal to the bladder neck. Before the operation

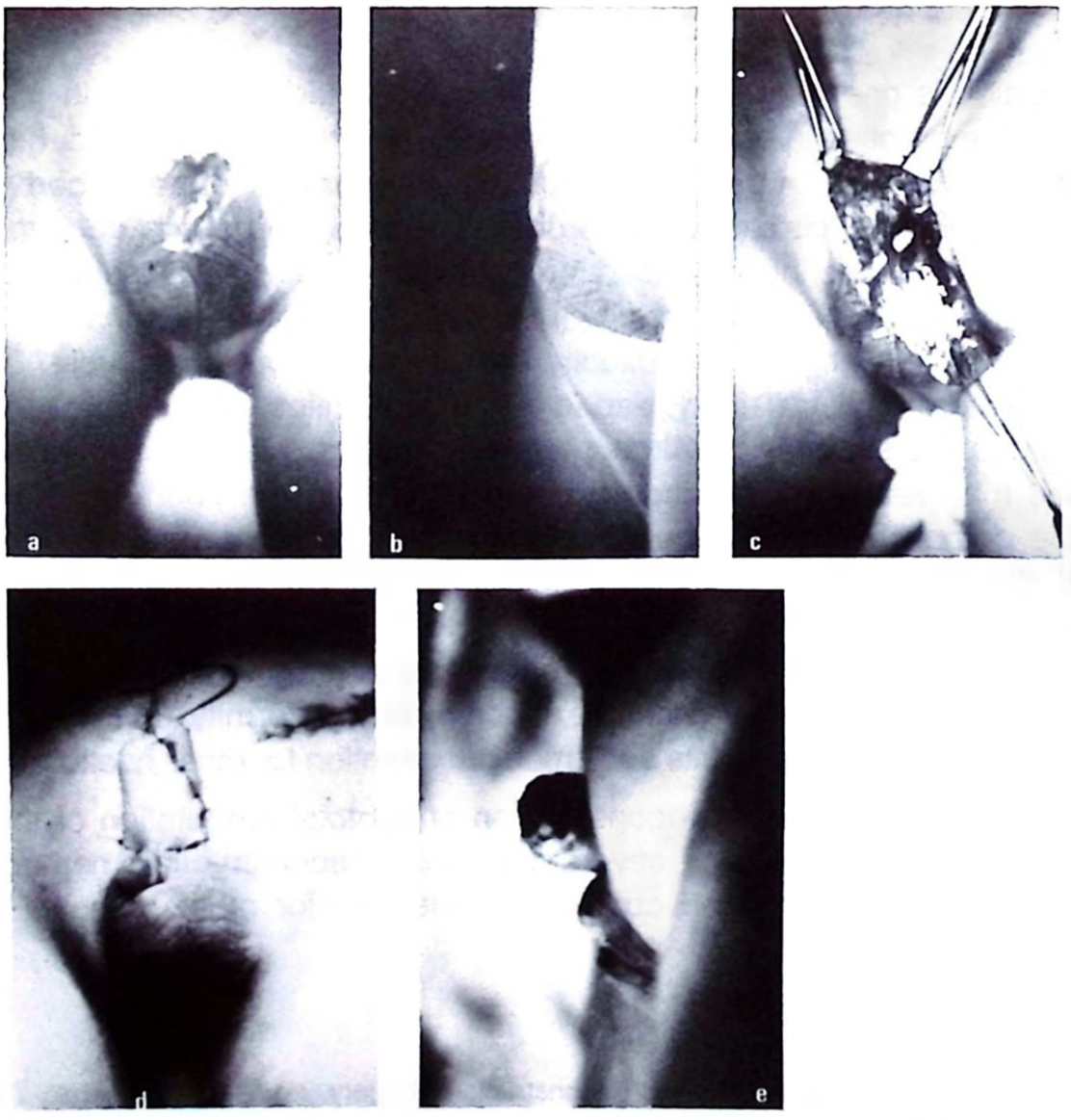

Fig. 1. Child's penis from (a) anterior and (b) lateral view. Corporal bodies dissected down to the pudental neurovascular bundle (c) Full-thickness skin graft harvested from left thigh applied over penis shaft (d) Post-operative week three with uneventful healing (e).

a silicon feeding tube was inserted as a stent into the urthra in order to drain urine so as not to soil the dressing. A circumcision type of incision was employed around the urethral meatus with more than 1 cm of skin left on the urethral side. Surprisingly, after dissecting the scar and the soft tissue, corporal bodies were encountered. An artificial erection was provided by saline injection into the corporal bodies using a No: 23 needle. This was done to allow easy dissection of the corporal bodies (Fig. 1c). The corpora cavernosa and the corpus spongiosum were dissected over the tunica albuginea, and the corporal bodies were stripped down to the pudental neurovascular bundle; thus, relase of the suspensory attachments was accomplished. During the dissection the internal pudental neurovascular bundles which provide dominant blood and nerve supply to the penis and scrotum were located and preserved in order to provide a functional and viable penis. Unnecessary mobilization of the corpora was avoided in order not to displace the penis further below the symphysis. The stretched penile length was considered to be within the normal limits for the patient's age. In order to match the skin color, a 12 x 3 cm full thickness skin graft was harvested from the left inguinal region with a number 10 surgical blade. 6/0 chromic catgut sutures were used to suture the graft around the penis (Fig. 1d). The suture lines were kept to the ventral aspect of the penis in order to improve the aesthetic appearance. The penile shaft skin was sutured down to the base of the penis, and the suprapubic skin was sutured to the rectus fascia with 6/0 prolene sutures. Post-operatively the skin graft healed with no complications (Fig. 1e).

Discussion

Various studies supporting or opposing circumcision have been published[6,7]. Some authors recommend circumcision for its medical advantages, while others consider both the pain and possible psychological effects of circumcision as reasons not to perform routine circumcision. Religious, cultural and traditional factors remain the primary determinants in the parents' decision as to whether the child will be circumcised.

Possible complications of circumcision include hemorrhage, edema, infection, meatal stenosis, urethral fistulas, unsightly scars, penile curvature, shortness of shaft skin, and, in the extreme, partial or total penile loss. If circumcision is done, it must be performed by experienced medical personnel in order to minimize possible complications.

Skin grafts, local flaps or distant flaps can be used for reconstruction of partial penis amputation following circumcision. Because in our case-the shaft length was within normal limits, we preferred skin grafting the remaining corporal bodies instead of recreating a penis with other techniques.

Full-thickness skin grafts give durable and aesthetic results in penis reconstruction, and a skin graft from the inguinal region matches the color of the penile skin. Also, full-thickness skin grafts appear to grow at the same rate as the patient. Baran and Horton[7] have experimentally demonstrated this parallel growth in minipigs. We expect the child's penis will grow in accordance with his total body growth, resulting in a functional penis size.

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