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FEBRILE CONVULSIONS: REVIEW OF 284 PATIENTS AND THE EVALUATION OF INTERMITTANT PROPHYLAXIS

Gülhis Deda* • Uğur Karagöl** • Serap Uysal*** • Alev Güven***

SUMMARY

Two-hundred eighty four children with febrile seizures (FS) admitted to our hospital were evaluated between 1992 and 1996. The onset of febrile seizures in 268 children were between 1 and 72 months (mean: 21,2 months). Two-hundred fifty three children (89%) had simple and 31 children(11%) had complex febrile seizures. The duration of seizures could be detected in 236 children and in 22 children seizures lasted for 15 minutes or longer. Eighty-five children (30%) had positive family history for FS. Electroencephalography (EEG) was performed in 196 children (69%) after the first febrile seizure. Pathologic findings on EEG in 59 children (30,1%) were detected. Intermittent rectal diazepam prophylaxis was administered to 178 children, when the child's fever was 38,5 C and above. Sixty children (33,7%) came to their follow-ups. Follow-up period was 3-48 months (mean: 14,75 months). In 47 children seizures did not recur. Recurrence of seizures were noted in 13 children, because rectal diazepam could not be applied at the time of high fever. Phenobarbital was given to 28 children as initial prophylactic therapy and 27 children came to their follow-ups. The follow up period was 12-48 months. In one patient seizure recurred during therapy. Eleven children were treated with Na valproate. In 6 children seizures did not recur within 2 years. Follow up was lost in 5 children. Five children developed afebrile seizures. Afebrile seizures occurred in 2 cases after the termination of phenobarbital therapy and they were put on valproate therapy. Long term prophylaxis with phenobarbital because of its side effects is not preferred. Rectal diazepam administration at the onset of fever decreased the recurrence rate of FS and was devoid of major side-effects. Therefore rectal diazepam is preferred for prophylactic treatment of FS.

Key words: *Febrile seizure, rectal diazepam*

Febrile seizures (FS), usually occur between 3 months and 5 years of age associated with fever but without evidence of intracranial infection. FS occur in 2-5% of the childhood population (1,2).

The cause of FS is still unknown. The predisposing factors are biological, enviromental and genetical features. Certainly genetic factors play an important role. Many hypothesis, including autosomal dominant, autosomal recessive and multifactorial inheritence are suggested (3).

FS usually have a favorable outcome without any treatment. Long-term prophylaxis with antiepileptic drugs are not preferred, because of their side effects. Oral or rectal diazepam administration at the onset of fever decrease the recurrence rate of FS and is devoid of major side effects (1,2,4).

MATERIALS AND METHODS

In this study, 284 children with FS admitted to our hospital were evaluated between 1992 and 1996.

All children under the age of 6 years who developed their first seizure, focal or generalized, during a febrile illness, were considered to have FS. Children with previous afebrile or unprovoked seizures were excluded, as were children with intracranial infections. Questionarry were given to all families and the patients were examined physically and neurologically.

We classified FS as simple and complex. A complex seizure has one or more of the following features: a)partial onset b)prolonged duration (15 minutes or longer) c)or repeated seizures within 24 hours (5).

* Associate professor of Pediatric Neurology, Ankara University Medical School Department of Pediatric Neurology, Ankara, Turkey
** Professor of Pediatric Neurology, Ankara University Medical School Department of Pediatric Neurology, Ankara, Turkey
*** Fellow of Pediatric Neurology, Ankara University Medical School Department of Pediatric Neurology, Ankara, Turkey

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Table 1. The relation of recurrence to age, fever, duration and family history in FS

	AGE at Onset of Convulsions (years)			FEVER (°C)						DURATION (minutes)				FAMILY HISTORY
	2 ↓	2 & ↑	not known	38	38.5	39	39.5	40	not known	0-5	5-15	15 ↑	not known	
Number of cases	171	109	4	24	12	33	15	26	174	122	92	22	48	85
Recurrence (number)	129 %75.4	64 %58.7	4	15	12	17	13	133	85	7	58	18	36	69 %81.2
Recurrence	P<0.05			p > 0.05						p < 0.001				P<0.05

The EEG findings and the long-term treatment offered to children with FS versus intermittant treatment was reviewed.

Student's t test and Chi square tests were used for statistical analysis.

RESULTS

One hundred fifty five patients were male (54,6%) and 129 were female (45,4%).The male/female ratio was 1,2. The age of the patients were between 1,5-6 years (mean 3,1 years).

In 268 children first febrile seizure occurred between 1-72 months of age (mean: 21,2 months). In 171 children, first seizure was before 2 years of age and was found to be associated with an increased risk of recurrence (Table 1).

Two hundred fifty three (89%) had simple and 31 children (11%) had complex FS.

Body temperature could be taken from 110 children during the seizure (Table I).

The duration of seizures were detected in 236 children and in 22 children seizures lasted for longer than 15 minutes. Duration of seizures were not known in 48 children (17%).

The long duration of seizure was found to be associated with an increased risk of recurrence (p<0,001) (Table 1).

There was no correlation between the degree of fever and recurrence of febrile seizure (p>0,05) (Table 1).

The type of seizures in 284 children were as follows: Generalized tonic-clonic seizures in 253 children (89%), generalized tonic seizures in 19 children (6,7%), generalized clonic seizures in 1 children (0,4%), atonic seizures in 9 children (3,2%), focal seizures in 2 children (0,7%)

Family history of febrile seizure was found in 85 children (30%). History of FS was detected in 22 children's father (25 %), in 7 children's mother (8,2%), in 11 children's siblings (13%) and in 30 children's first degree relatives (35,2%). Among these 85 children 69 (81,2%) had seizure recurrence. Family history of febrile seizure was found to be associated with an increased risk of recurrence (Table 1).

Family history of epilepsy was found in 11 children (3,5%).

In 196 children (69%), EEG was performed after the first febrile seizure. EEG findings were classified as follows; normal, epileptic, and slow-wave paroxysm. Pathologic findings were detected in 59 children (30,1%) (Table 2).

Intermittent rectal diazepam was recommended to 178 children when the child's fever was 38,5 C and above. Sixty children were followed up (33,7%). The follow-up period was 3-48 months (mean: 14,75 months). In 47 children, seizures did not recur. In 13 children seizures recurred because rectal diazepam could not be applied at the time of high fever.

Phenobarbital was given to 28 children as initial prophylactic therapy (5 mg/kg/day).

Twenty seven children came to their follow-ups regularly . Follow-up period was 12-48 months. In one patient seizure recurred during therapy.

Table 2. The EEG findings of patients with FS

EEG	CASES NO	%
Epileptic	18	9,2
Slow wave paroxysm	41	21
Normal	137	69,8
Total	196	100

Eleven children were treated with Na valproate (20 mg/kg/day). In 6 children, seizures did not recur within 2 years. Follow- up was lost in five children.

Five children developed afebrile seizures. Afebrile seizures were detected in 2 children during the phenobarbital therapy, and they were put on valproate therapy. Afebrile seizures occured in 2 cases after the termination of phenobarbital therapy.

DISCUSSION

FS are common in early childhood and now recognized as a benign syndrome. Approximately one third of children who have a febrile seizure have recurrences (6,7). The risk factors of recurrences are; history of a first degree relative for febrile seizure, young age of onset, multiple initial seizures and low temperature at the initial seizure (7).

In our study, there were positive correlations between the recurrence of febrile seizure and long duration of seizure and the young age of onset and positive family history. In several studies, positive family history for FS has been shown to be a major risk factor for the recurrence of FS (8,9). In contrast to other studies the degree of fever during the first febrile seizure was not found to be associated with increased risk of recurrence in our study.

The risk of epilepsy in children who have had FS is 1,1%. The incidence in the general population is 0,5% (3). Risk factors predispose the child with FS to subsequent epilepsy are: complex FS, antecedent developmental and neurologic abnormality, onset of FS prior to 1 year of age, multiple recurrences of FS and a positive family history of epilepsy (1,3).

In our study, afebrile seizures developed in 5 children,2 of whom had complex FS.

The EEG is of little value in FS (3). EEG can be normal or paroxysmal abnormalities can be found in approximately 20% of patients (10). Stores, (11) found a far lower incidence of paroxysmal discharges (1,4-3%). In our study, paroxysmal abnormality in EEG was found in 41 children (20,9%), EEG was normal in 137 children (69,1%).

Previously, daily phenobarbital administration has been the drug of choice for the prevention of FS and in most studies it had been effective (12).

More recently, long term prophylaxis with antiepileptic drugs are not preferred because of their side effects. There is no evidence that long term prophylaxis of FS prevents subsequent afebrile seizures (1). We detected afebrile seizures in 5 children, 4 of whom were treated with phenobarbital.

Alternative therapy is the treatment of febrile episodes with administration of rectal diazepam. Studies with rectal diazepam reveal decreased recurrence of FS. Side effects of diazepam were infrequent (13,14).

We applied rectal diazepam to 178 children with FS. Number of regularly controlled children were 60. We did not encounter side effects of rectal diazepam. Recurrence of seizures were noted in 13 children, because rectal diazepam could not be applied at the time of high fever.

We conclude that rectal diazepam can be a drug of choice for prophylaxis of FS.

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BULGING OF THE FONTANEL DURING MALNUTRITION TREATMENT*

Sevgi Başkan Gülnar** • Betül Ulukol*** • Gönül Öcal**** • Eyüp Ekici*****

SUMMARY

Malnutrition in early childhood often results in diminished intellectual functions. Cerebral atrophy can be considered a major pathological finding in malnourished children. As cerebral atrophy reverses, intellectual functions improve rapidly with nutritional rehabilitation. The aim of this study was to find the relationship between weight gain, bulging of the fontanel, improving of the intellectual functions and thyroid functions. Our sample included 18 children aged 1.5 to 16 months who were admitted to hospital for treatment of malnutrition. Eight of these children were marasmic, ten were marasmic-kwashiorkor. All the children were evaluated clinically, biochemically, and with anthropometric measurements. Lumber punctures were performed to measure cerebrospinal fluid pressures upon admission to hospital and again at the time of bulging. Thyroid functions were also evaluated at these stage. Significant correlations between an increase in body weight and increased intracranial pressure was found during the early phase of treatment. During this period, improvement in intellectual performances was also noted. No differences in thyroid functions were detected during treatment. The findings of this study suggest that bulging of the fontanel is an indicator of the effectiveness of treatment and accelerated growth of the brain.

Key words: *Childhood, Bulging of the fontanel, Malnutrition*

Malnutrition is a problem that is frequently encountered in developing countries and the proper treatment of these cases has a significant role in public health. Protein energy malnutrition is known to be associated with cerebral atrophy, which may be detrimental to intellectual development (1-3) . During effective treatment, a rapid phase of growth is seen in these children in overcoming deficiencies in weight and height. During the early phase of therapy the malnourished child begins to smile and becomes more interested in and responsive to others. There is also accelerated growth in head size, which suggests accelerated brain growth. Diastasis of the sutures and bulging of the fontanel are reported clinical findings (4-7). These findings are also suggestive of increased intracranial pressures due to other causes such as infections, intracranial masses or hydrocephalus. Although most of these children are fortunately asymptomatic and eventually recover spontaneously, bulging fontanel can be a perplexing problem and, unless recognised, can lead to unnecessary diagnostic procedures.

Therefore, the purpose of this study was to examine the relationships between weight gain, bulging of the fontanel and pressure of cerebrospinal fluid (CSF) during the early nutritional treatment phase of malnourished infants. Studies have not yet clarified the reasons behind the symptoms of increased intracranial pressure during the treatment of malnutrition. It is known that, during thyroid hormone replacement, for various reasons signs of increased intracranial pressure may be seen. During the course of nutritional treatment of malnutrition there is an increase in metabolism. We postulated that this increase in metabolism results in an increase in circulating thyroid hormone levels and that this may be a causal factor in signs of increased intracranial pressure. Therefore, the second

* This study was presented as a poster in the 22. International Congress of Pediatrics in the Netherlands, 9-14 August 1998

** Doç. Dr., University of Ankara, School of Medicine, Department of Social Pediatrics
*** Dr., University of Ankara, School of Medicine, Department of Social Pediatrics
**** Prof. Dr., University of Ankara, School of Medicine, Department of Endocrinology
***** Dr., Zekai Tahir Burak Maternity Hospital

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purpose of this study was to determine whether there is a relationship between thyroid hormone levels and signs of increased intracranial pressure during the treatment of malnourished children. This particular study was carried out to put forward reasons for this and also to determine the relationship between the thyroid functions and the acceleration of the metabolism in the recovery period.

MATERIAL AND METHOD

Eighteen infants were admitted to the pediatric word for treatment of protein-energy malnutrition. There were eight girls and ten boys with a mean age of 7.8 months (range: 1.5-16 months). The Wellcome classification criteria were used for the classification of malnutrition (8). Children with a history of previous disease involving the central nervous system were excluded. On admission to hospital, a blood sample was taken for estimation of serum protein levels, electrolyte values and any other investigations necessary for the clinical care of the child.

The patients were evaluated from anthropometric measurements such as weight, height, head circumference (HC), and mid-arm circumference (MAC) at the beginning of treatment and at the time of appearance of the bulging fontanel. Symptoms of an increased metabolic rate such as sweating, symptoms of psychosocial development such as smiling and fontanel bulging were monitored, and head circumference was measured daily. In order to explain the bulging of the fontanel, CSF pressure was measured using the lumbar puncture technique at the beginning of treatment and at the time of bulging. The brain and the position of the sutures were assessed by cranial X-ray and ultrasonography (US). All subjects were well hydrated and clinically stable at the time of the lumbar puncture and the cranial US.

In order to show the correlation between the metabolic acceleration in the period of rapid weight gain and thyroid hormone levels, the total T3 (tT3), total T4 (tT4) and Thyroid Stimulating Hormone (TSH) levels of fifteen patients were measured using radioimmuno-assay techniques. The infants were fed with a variety of energy-protein enriched diet regimens including: lactose-free formula, human-milk and infants' formula. Additional folate, multivitamins, trace elements, and iron (2 mg per kg) were also given. Five infants, who were diagnosed as having infections, two cases with pneumonia and three with acute otitis media, were treated with appropriate antibiotics.

The data were evaluated and compared statistically using the Paired-samples t test and Pearson correlation test.

RESULTS

Of the eighteen patients studied, eight were marasmic and ten were marasmic-kwashiorkor. The bulging of the fontanel was observed between the 7^{th} and 40^{th} days (average 25 days) of therapy. Smiling and sweating were observed between the 7^{th} and 35^{th} days (average 18 days). Symptoms of increased intracranial pressure such as nausea and vomiting were not observed in our cases.

Table 1 shows the mean weight, height, head circumference, and mid-arm circumference of the cases

Table 1. Mean of anthropometric measurements before treatment and at the time fontanel bulging appears.

	Weight X±SE (gr)	Height X±SE (cm)	Head Circumference X±SE (cm)	Mid-arm Circumference X±SE (cm)
Pre-treatment Period	4137.5±357.9	58.7±1.9	38.5±0.9	8.7±0.4
Fontanel bulging period	4809.4±389.9	60.8±1.9	40.2±0.8	10.5±0.4
P *	< 0.0001	< 0.0001	<0.0001	<0.0001

* P value for Paired-samples t test

Table 2. Differences in CSF pressure and weekly weight gain at the time of bulging of the fontanel

Cases (no)	Weekly Weight Gain (gr)	Difference in CSF Pressure (cm/H_2O)
1	160	10.0
3	190	28.5
4	100	3.5
5	140	7.0
6	115	12.5
7	290	16.5
8	150	11.5
9	150	2.0
10	247	24.0
11	133	20.0
11	220	10.0
12	166	24.0
13	162	0.0
14	125	3.0
15	170	7.0
16	285	19.0
17	185	10.0
18	450	25.0
Mean ± SE	191±19.8	12.9±2.1

before treatment and at the time of the bulging of the fontanel. The difference between these values was found to be statistically significant (Paired-samples t test). The cranial circumference values of the patients remained in the normal range according to their age groups.

The CSF pressures were measured via lumbar puncture before the treatment and at the time of bulging. The increase in CSF pressures and weekly weight gain (WWG) at the time of the bulging of the fontanel are shown in Table 2. Changes in the CSF pressure and WWG were found to be statistically significant (Pearson correlation test P: r = 0.019). When cranial x-rays were taken to evaluate cranial sutures and determine the reason for fontanel bulging in the recovery period, the sutures of only one patient were found to be minimally departed. Cranial US was done during this period, revealing no significant pathology.

The thyroid functions (tT3, tT4, TSH) of the 15 patients were examined before treatment and at the time of the bulging of the fontanel.

When the results were compared, there was no statistical significant difference (Table 3) to be found.

DISCUSSION

There have been reports of a loss of brain volume associated with severe protein-energy malnutrition in young children (1-3). The affective changes are accompanied by structural changes in the brain or a temporary reduction in brain interstitial fluid volume. It is accepted that cerebral atrophy can result from metabolic, hemodynamic or infective causes in these ill children. Gunston et al. reported that brain shrinkage - cerebral atrophy associated with malnutrition - reverses rapidly with nutritional rehabilitation (1). Gunston studied cerebral shrinkage, demonstrated by Magnetic Resonance Imaging, in 12 children with kwashiorkor, and found that improvement in brain size was apparent on day 30 of nutritional rehabilitation in the majority of patients. This rapid improvement suggests that the changes in size may relate predominantly to fluid shifts between various compartments, and, to a lesser degree, to fat or protein abnormalities in the brain. Fluid moves out of intravascular spaces as a result of decreased colloid osmotic pressure and floods the subarachnoid spaces, dilates the ventricles, and widens the cisternal spaces and sulci. When nutrition is improved the plasma proteins increase, and the extra cellular fluid moves back into the intravascular space (1). There is a linear relationship between brain weight and protein content and intracranial volume. The symptoms of the pseudotumor cerebri such as bulging and pulsatile fontanel, growth in head circumference, and departing of the sutures are observed during the treatment of malnutrition. It has been suggested that re-feeding causes raised intracranial pressure by stimulating brain growth at a rate faster than that of the cranium (4,6,7,9,10).

In our series, a manifest and statistically significant increase in intracranial pressure was found by CSF pressure measurements at the time of the fontanel bul-

Table 3. Statistical evaluation of thyroid functions in pre-treatment period and fontanel bulging period in 15 patients

Thyroid Functions	Pre-treatment Period	Fontanel Bulging Period	P*
Total T3 (ng/ml)~	1.41±0.12	2.14±0.38	0.082
Total T4 (mcg/dl)~	9.62±0.91	10.19±0.63	0.584
TSH (mcIU/ml)~	2.78±0.60	2.25±0.31	0.454

* P value for Paired-samples t test

~ mean ± SE

ge during treatment. There was found to be a significant correlation between increase in body weight and increased intracranial pressure in the earlier period of treatment. These findings could be used as positive criteria during the treatment of malnutrition.

It is known that severe protein energy malnutrition in early childhood is a factor likely to result in reduced intellectual potential(3). However, intellectual performances of children with malnutrition improve when the cerebral changes are resolved (1) and are taken as criteria of response to therapy. In this study, during this period improvement was seen in intellectual performance, smiling and interest in the environment shown by the patients, and an increase in intracranial pressure was also indicated by the CSF pressure evaluation.

In the catch-up growth period, the metabolism is accelerated, and sweating and an increase in appetite are seen during the treatment of malnourished children. Bulging of the fontanel, one of the symptoms of pseudotumor cerebri, develops at the same time. Pseudotumor cerebri has also been reported in children after the initiation of thyroid replacement therapy (10). We investigated the relation between bulging of the fontanel and thyroid functions at the time of metabolic acceleration. There was no difference in the thyroid functions in the pre-treatment period and during the catch-up growth period. There was also no correlation found between thyroid functions and symptoms such as increase in appetite and sweating at the time of accelerated weight gain, and brain growth and improvement in the intellectual functions.

In conclusion, an increase in CSF, which was exhibited with bulging fontanel, was seen at the time of treatment in malnourished children. This finding is an indicator of the effectiveness of the treatment and accelerated growth of the brain. Although most of these children are asymptomatic and eventually recover spontaneously, bulging fontanel can be a perplexing problem and, unless recognised, can lead to unnecessary diagnostic procedures.

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DIFFERENTIATION OF FOLLICULAR ADENOMAS AND CARCINOMAS BY EVALUATING EPITHELIAL MEMBRANE ANTIGEN, LEU-7 ANTIGEN AND VIMENTIN

Nuri Kamel* • Sevim Güllü* • Serpil Dizbay Sak** • Nilgün Başkal*
A. Rıza Uysal* • Vedia Tonyukuk* • Demet Çorapçıoğlu*

SUMMARY

Histopathological differentiation of follicular adenoma and carcinoma is difficult. Identification of malignancy depends on the presentation of evidence of capsular or vascular invasion, so many patient undergo to surgical intervention when cytological diagnosis of follicular lesion was made by thyroid fine needle aspiration biopsy (FNAB). In order to avoid unnecessary operations for benign lesions identifying a marker or markers which can also be applicable to FNAB specimens are needed. The purpose of this study was to find a marker to be used as an adjunct to the histopathological criteria to differentiate between follicular adenoma and carcinoma. Epithelial membrane antigen (EMA), Leu-7 antigen and vimentin was investigated in 17 normal thyroid tissue, 17 follicular adenoma and 10 follicular carcinoma specimens. Immunohistochemical staining of these antigens were evaluated in formalin fixed and paraffin embedded specimens of patients who experienced thyroid surgery between 1994 and 1997. Atypical follicular adenomas were not included to the study. EMA was found to be expressed in 16 of 17 normal thyroid tissue, 15 of 17 follicular adenomas and nine of 10 follicular carcinomas. No difference could be detected in staining pattern and intensity between adenomas, carcinomas and normal tissue. Only colloidal staining with Leu-7 antigen was observed in sixteen normal tissue, in contrast to strong tissue staining in adenomas (thirteen of 17), carcinomas (five of 10) and in one normal thyroid tissue. Vimentin staining also failed to differentiate benign lesions from malignant lesions, three normal thyroid tissue, six follicular adenoma and five follicular carcinoma demonstrated staining with vimentin. In conclusion, the presence of reactivity in both follicular adenomas and follicular carcinomas, with similar intensity and pattern, suggests that EMA, Leu-7 and vimentin are not useful markers to differentiate these lesions.

Key Words: *EMA, Follicular Adenoma, Follicular Carcinoma, Leu-7, Thyroid Neoplasms, Vimentin*

The differentiation of follicular adenoma from follicular carcinoma may be difficult on the microscopic cytologic morphology and even on the routine pathologic examinations since the diagnosis of follicular carcinoma depends on the existence of capsular and/or vascular invasion (1). In a patient in whom a diagnosis of follicular adenoma was made cytologically, a thyroid scan is mandatory. If a cold nodule is detected in scan, surgery is suggested for treatment since cytology alone can not differentiate malignant lesions of follicular origin from benign lesions. But, most of these operations are unnecessary since most of the lesions are benign. Therefore, in order to avoid unnecessary operations, a search for new markers, which can be used on cytological specimens for differentiation, and can make the diagnosis possible before operation, is essential.

Leu-7 is an antigen and was first described as a marker of normal lymphocytes and Natural killer cells (2). Leu-7 antigen expression was also found in neuroendocrine tumors, hyperplastic and carcinomatous prostatic tissue, sweat gland tumors of the skin and in some ovarian, endometrial, renal, pulmonary and breast carcinomas (3). It was also investigated in thyroidal lesions and significant expression of Leu-7 antigen were reported in both papillary and follicular thyroid carcinomas(3-5). Although Leu-7 reported to be useful in differentiating benign and follicular lesions of thyroid gland (3), some other studies failed to show different staining patterns (4,5).

Epithelial membrane antigen (EMA) is a glycoprotein expressed by several epithelial and mesothelial neoplasms (5). Its appearance in thyroidal neoplasms

* Ankara University Medical School, Department of Endocrinology and Metabolic Diseases Ankara, Turkey
** Ankara University Medical School, Department of Pathology Ankara, Turkey

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has also been reported and has been proposed as a prognostic factor in papillary carcinomas and in neoplasms of follicular origin (5-9). In one study (5) its expression was found to be different in adenomas and carcinomas and proposed as an useful marker in differentiating benign and malign follicular neoplasms.

Vimentin is part of the intermediate filament proteins and as such is part of the cytoskeleton. Although the presence of vimentin in epithelial cells is considered to be rare, it has been reported in cultured carcinoma cells, mesotheliomas, renal cell carcinomas and thyroid carcinomas (10-16).

Previous studies done by above-mentioned markers in differentiating follicular adenomas from follicular carcinomas are conflicting. So we planned to study the expression of these antigens in normal thyroid tissue and follicular thyroid neoplasms and to evaluate their roles in differentiating follicular adenomas from follicular carcinomas.

MATERIALS AND METHODS

Formalin-fixed, paraffin-embedded blocks of thyroid lesions obtained from the patients who underwent surgical intervention after 1994 were evaluated. Hematoxylin-eosin-stained slides of these cases were reviewed and the specimens with clear morphological structure and definite pathological diagnosis were included to the study. Atypical follicular adenomas were excluded because of their uncertain nature and behavior. Seventeen normal thyroid tissues, 17 follicular adenomas and 10 follicular carcinomas were used for immunohistochemical study.

Immunohistochemistry:

For immunohistochemical study, 4-6 μm thick sections were obtained from representative paraffin blocks and placed on poly-L-Lysine coated slides. Immunostaining with Leu-7 (Biogenex, San Ramon, USA), EMA(DAKO-PATTS, Glostrup, Denmark) and vimentin (DAKO-PATTS, Glostrup, Denmark) were performed using the streptavidin-biotin-peroxidase complex technique (17,18). Appropriate sections were used as positive controls and for negative control primary antibody was substituted with buffer.

Staining Intensity:

Staining intensity were subjectively graded as 1+, 2+ or 3+ for weak, moderate and strong staining respectively.

Statistical Analysis:

X^2 test was used for analysis and p value less than 0.05 was accepted as significant.

RESULTS

Results of EMA, Leu-7 antigen and vimentin expressions of the normal thyroid tissue and follicular lesions are given in table 1.

Sixteen of 17 normal thyroid tissues expressed EMA(94%). Fifteen of 17 follicular adenomas (88%) stained with anti-EMA antibody and nine of 10 follicular carcinomas also showed EMA expression (90%). No statistically significant difference could be found between adenomas and carcinomas ($p>0.05$).

Expression of Leu-7 antigen was not found to be different between follicular adenomas and follicular carcinomas($p>0.05$). Thirteen of 17 follicular adenomas (76%) and five of 10 follicular carcinomas (50%) stained with anti-leu-7 antibody. But expression of the antigen was observed only in one of 17 (5%) normal thyroid tissue specimen. On the other hand 16 of 17 normal thyroid tissue (95%) showed only colloidal staining with anti-Leu-7 antibody.

Vimentin staining was observed in six of 17 (35%)

Table 1. Expression of epithelial membrane antigen (EMA), Leu-7 and vimentin in normal thyroid tissue, follicular adenomas and follicular carcinomas.

		EMA	Leu-7	Vimentin
	n	number staining (%)		
Normal Thyroid Tissue	17	16 (94)	1 (5)	3 (17)
Follicular Adenoma	17	15 (88)	13 (76)	6 (35)
Follicular Carcinoma	10	9 (90)	5 (50)	5 (50)

Table 2. Staining patterns of epithelial membrane antigen(EMA), Leu-7 and Vimentin in benign, malign and normal thyroid tissues.

	Number Staining	Staining Pattern	Staining Intensity
EMA			
Normal Thyroid Tissue	8	Focal Luminal	1+/ 3+
	2	Luminal/Cytoplasmic	2+
	6	Diffuse Luminal	2+
Follicular Adenoma	7	Focal Luminal	1+/3+
	6	Diffuse Luminal	1+/3+
	2	Luminal/Cytoplasmic	1+/3+
Follicular Carcinoma	6	Diffuse Luminal	2+/3+
	3	Luminal/Cytoplasmic	2+/3+
Leu-7			
Normal Thyroid Tissue	16	Colloid	
	1	Luminal/Cytoplasmic	2+
Follicular Adenoma	1	Diffuse Luminal	2+/3+
	1	Luminal/membranous	2+/3+
	3	Focal Cytoplasmic	1+/2+
	6	Diffuse Cytoplasmic	2+/3+
	2	Luminal/Cytoplasmic	2+
Follicular Carcinoma	1	Diffuse Luminal	2+
	1	Focal Cytoplasmic	2+
	3	Diffuse Cytoplasmic	1+/2+
VIMENTIN			
Normal Thyroid Tissue	3	Focal Cytoplasmic	2+/3+
Follicular Adenoma	2	Focal Cytoplasmic	2+
	4	Diffuse Cytoplasmic	2+/3+
Follicular Carcinoma	5	Diffuse Cytoplasmic	1+/2+

follicular adenomas and in five of 10 (50%) follicular carcinomas and this was not statistically significant ($p>0.05$).

The pattern and intensity of the stainings are given in Table 2. Neither the staining pattern nor the staining intensities of all three markers were found to be different between follicular adenomas and carcinomas ($p>0.05$ for all).

DISCUSSION

Epithelial membrane antigen expression by thyroidal neoplasms has been well documented and reported by some investigators (5-9). Wilson et al demonstrated its expression in 9 of 10 papillary carcinomas and 7 of 10 follicular carcinomas (9). Pinkus et al reported EMA immunoreactivity in one out of three follicular carcinomas (6). Cheifetz et al (5) showed a significant difference in EMA expression by follicular carcinomas as compared to follicular adenomas. In their series none of the follicular adenomas (0/9) showed staining with anti-EMA antibody while three of four (75%) follicular carcinomas showed EMA expression and they suggested that EMA expression by follicular carcinomas was useful for differentiating these lesions from follicular adenomas. In contrast, in our study, both follicular adenomas and carcinomas showed a similar expression of EMA. Eighty-eight percent of follicular adenomas (15/17) and 90 percent of follicular carcinomas (9/10) expressed EMA and staining pattern and staining intensity of the lesions were also comparable. We propose that EMA expression can not be used as a marker for differentiating follicular adenomas from follicular carcinomas of the thyroid gland.

Leu-7 antigen is expressed by a wide variety of tumors of both epithelial and nonepithelial origin. Its expression in thyroidal lesions have also been documented (3-5). Ghali et al (3) reported different staining number and intensity between follicular adenomas

and follicular carcinomas. In their study three of 14 follicular adenomas stained weakly and all follicular carcinomas (5/5) stained strongly with anti-Leu-7 antibody and they suggested that Leu-7 monoclonal antibody can be used as a marker for differentiating benign lesions from malign thyroid follicular lesions. However Leu-7 antigen reactivity was found in both follicular adenomas and follicular carcinomas in the present study. Our results are in agreement with the results of Cheifetz et al (5)and Ostrowski et al (4) who also found no difference in the expression of the antigen between malignant and benign follicular lesions. It seems that the presence of Leu-7 antigen is also not useful for making a decision on the nature of the follicular thyroid lesions.

Several reports exist describing intermediate filaments including vimentin in normal thyroid and its neoplasms (10-16). In the present study vimentin was found to be positive in both normal and pathological thyroidal tissues. Most of the studies done on vimentin immunoreactivity also failed to demonstrate a value in differentiating follicular lesions.

In conclusion EMA, Leu-7 antigen and vimentin can not be used as differentiation markers in diagnostic cytology and pathology in differentiation between follicular adenomas and carcinomas.

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A METHOD IN EVALUATING URINARY ERYTHROCYTE MORPHOLOGY: COMPUTER ASSISTED LIGHT MICROSCOPY (CALM)

Çağatay Öktenli* • Mete Kilciler** • Fatih Bulucu*
Abdülgaffar Vural***

SUMMARY

Objective: *We recently suggest a model of a diagnostic system, which markedly improves the quality of the images supplied by computer assisted light microscopy (CALM) for urinary erythrocytes.*

Material and Methods: *Freshly collected, mid-stream urine specimens were obtained from randomly selected 49 patients with hematuria. Twenty three patients had biopsy-proven glomerular disease and the other 26 had urological pathology, causing hematuria. Ten ml of all collected urine samples were centrifuged at 1,500 rpm for five minutes. The specimen was observed carefully by CALM, the proposed computerized system.*

Results: *Morphological analysis of urinary erythrocytes in 49 patients with hematuria disclosed that the erythrocytes were glomerular in 22 patients, nonglomerular in 25 patients and mixed-type in 2 patients. Sensitivity and the specificity of the examination in diagnosing glomerular and nonglomerular bleeding were 95,6-92,3 %, and 92,3-95,6 %, respectively.*

Conclusions: *In conclusion, all available means taken together point to this simple, noninvasive approach in routine algorithms for diagnosis of hematuria.*

Key words: *Computer assisted light microscopy, Hematuria, Urinary erythrocyte morphology*

Birch and Fairley described glomerular bleeding giving rise to a wide range of morphological alterations on erythrocytes, including queer, small, hypochromic, and fragmented "dysmorphic" erythrocytes that have been observed in the urine (1). They also reported that phase-contrast microscope (PCM) was clinically useful tool for detecting glomerular bleeding. The assessment of these changes is difficult with standard bright field microscope because of the lack of contrast of glomerular pattern erythrocytes which often contain little hemoglobin. Classification of urinary erythrocytes under a standard light microscope depends on subjective visual assessment by human eyes, requires more skill, and can vary largely among different examiners and takes much time (2).

PCM is a simple, risk-free and inexpensive technique which can be performed in the outpatient clinic; and the result can be obtained within a few minutes (2). Staining is sometimes used in attempt to improve observation (3). However, these reported methods have some shortcomings, and evaluation of further methods have since been described, including differential interference microscope (4), Scanning electron microscope (SEM) (5) and real-time confocal scanning laser microscope (6). PCM has the disadvantage of nonarchivability and requires rapid examination of urinary sediment (7). Furthermore, there are still a number of uncertainties on the reliability (8) and reproducibility (9) of the results. SEM provides images of excellent quality, but it involves very complicated pretreatment and high expenses. Real-time confocal scanning laser microscope relies on visual assessment by naked eye, besides the utilization of spècial apparatus; and it requires some experience.

The aim of the study was to establish a more simple evaluation method of urinary eryhrocyte morpho-

* Internal Medicine Department Gülhane Military Medical Academy And Faculty Ankara-Turkey
** Urology Department Gülhane Military Medical Academy And Faculty Ankara-Turkey
*** Nephrology Department Gülhane Military Medical Academy And Faculty Ankara-Turkey

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logy and to evaluate the usefulness of this new method for the diagnosis of hematuria. Characteristics of the test were evaluated in 49 patients with definite causes of hematuria.

MATERIALS AND METHODS

Fresh, mid-stream urine specimens were obtained from 49 consecutive in-patient and out-patient subjects with different causes of hematuria, attending the nephrology and urology departments. All samples were examined within 30 to 60 minutes after urination. Criteria for inclusion were the observation of a trace amount or of more hematuria by dipstick and 5 or more red cell per high-power field (hpf) on microscopic analysis of the sediment. Sediments with predominant pyuria were excluded from the study. Twenty three of the patients had biopsy-proven glomerular diseases (18 men and 5 women, mean age of 22 years, ranged between 20-32), including 7 cases of membranoproliferative glomerulonephritis, 5 of lupus nephritis, 5 of membranous nephropathy, 3 cases of Henoch-Schoenlein purpura nephritis, and 3 of focal segmental glomerulosclerosis. Twenty six of the patients were observed to be suffering from urological diseases, based on clinical data, including radiological and/or histological examination (22 men and 4 women, mean age of 43 years, ranged between 20-67). These included 15 cases of urolithiasis, 6 of bladder cancer and 5 of prostate cancer.

Ten ml. of all urine samples were centrifuged at 1,500 rpm for five minutes. After centrifugation, the supernatant was decanted and a drop of sediment was placed on a glass slide with a coverslip. The specimens were observed carefully by light microscope (Nikon Eclipse E 600) with the proposed image-analysis system (IMAGE Analyzer, Vysis USA). CALM, the system developed for the purpose, consisted of a microscope with polarizer and plane and phase contrast objectives, a monochrome (Grundig FA 87 Digital, Germany) CCD of high resolution, a high sensitivity camera head, OS8 based Macintosh 8600/250 system using Quips lab images software enabling adjustment of colour and contrast, proffessional 21" Super VGA colored (1024x768) monitor, a video colour printer (Textronix Phaser 450) using thermal sublimation transfer enabling further retouching of the image in terms of colour and contrast. Three dimensional images similar to scans can be obtained using phase-contrast unit. Even with immersion lenses, good definition with excellent contrast and colour can always be obtained. This can not be regarded merely as the result of photographic enlargement since the sharpness is far superior to that of traditional photographs with x1000 magnification and photographic enlargement. Non-distorded clear images of materials can be observed on the screen and can be stored on Hard Disc digitally. The time required for the examination was less than 10 minutes.

When possible, large numbers of erythrocytes were always inspected; for each patient a percent of glomerular and nonglomerular type erythrocytes was calculated. Dysmorphic erythrocytes are more fragmented with an irregular wavy shaped surface, and there are areas of loss of the membrane, membrane protrusions, irregular deposits of dense cytoplasmic material around the cell membrane, and variations in size (Figure 1). Some erythrocytes appear like doughnuts. Isomorphic erythrocytes had a smooth or crenated outline (Figure 2). Urinary erythrocyte morphology was classified according to the numerical criteria described previously by Fassett et al. (10). If more than 80 % of the erythrocytes in a specimen showed the dysmorphism, indicating a glomerular bleeding, and if more than 80% of the erythrocytes were undistorted and uniform in size and shape, it was recorded as isomorphic, indicating a nonglomerular bleeding. If a more even proportion of the erythrocytes were dysmorphic and isomorphic it was recorded as mixed. At the termination of the study, urinary microscopic findings were compared with the clinical diagnosis.

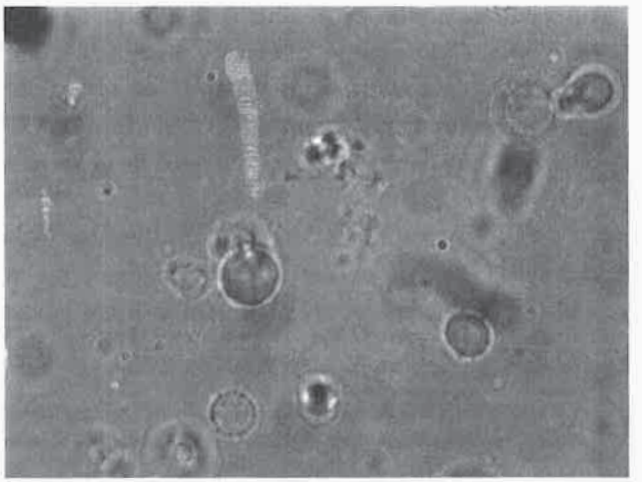

Fig. 1. Dysmorphic erythrocytes with CALM.

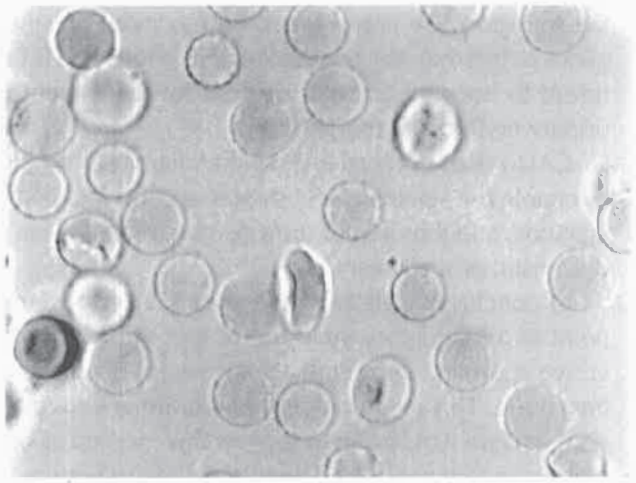

Fig. 2. Isomorphic erythrocytes with CALM

RESULTS

We found that the CALM provided excellent images which facilitated diagnosis, and hence the development of an easier and dependable method in evaluating urinary erythrocyte morphology in patients with hematuria. Morphological analysis of urinary erythrocytes in 49 patients with hematuria disclosed that the erythrocytes were glomerular in 22 (45 %) patients, nonglomerular in 25 (51 %) patients, and mixed-type in 2 (4 %) patients (Table 1). When compared with the clinical findings, the ratios of correct diagnosis was 22/23 (95,6 %) in glomerulonephritis and 24/26 (92,3 %) in urological diseases. Misdiagnosis was made in two renal calculus cases which showed mixed-type urinary erythrocyte morphology in urological diseases and in a membranous nephropathy case which showed nonglomerular morphology in glomerular diseases. According to above mentioned criteria and the suggested microscopic technique, taking mixed-type as diagnostic of glomerular bleeding, the sensitivity and the specificity of the examination in diagnosing glomerular and nonglomerular bleeding were 95,6-92,3 %, and 92,3-95,6 %, respectively.

DISCUSSION

The use of urinary erythrocyte morphology to determine the source of hematuria has been addressed by many researchers with various methods over the recent decade (4-6, 9, 11). This improved urinary assessment has clinical relevance, because it is possible to diagnose hematuria of unknown origin safely, quickly and economically. But diagnostic rate is variable in different reports and a number of questions remain unanswered concerning the general clinical application of urinary morphologic studies (12). This is due to the fact that dysmorphic erythrocytes may be found in the absence of renal diseases (13), the presence of mixed hematuria which many autor indicate glomerular (14, 15) and the hematuria of IgA nephropathy which may be nonglomerular as well as glomerular (16). Glomerular bleeding complicated with a urological one was diagnosed clinically as urological hematuria at pain attack but as glomerular hematuria when asymptomatic. This inconsistency was probably due to the fact that diagnosis was influenced by the dominant bleeding site (17). It seems reasonable to doubt the efficacy of urinary erythrocyte morphological analysis to identify the source of bleeding and is not a reliable procedure to identify the exact origin of the bleeding in view of the lack of correspondence between the clinical findings obtained and the underlying pathology (18).

The contrast between cells and fluid is enhanced by the use of PCM or differential interference microscope (19). These methods have the disadvantage of obligatory immediate diagnosis and non-archivability

Table 1. Urinary erythrocyte morphology and final diagnosis in patients with hematuria by CALM

Final Diagnosis	# of patients	CALM
Membranoproliferative glomerulonephritis	7	Glomerular*
Lupus nephritis	5	Glomerular
Membranous nephropathy	4	Glomerular
Membranous nephropathy	1	Nonglomerular
Henoch-Schoenlein purpura nephritis	3	Glomerular
Focal segmental glomerulosclerosis	3	Glomerular
Urolithiasis	13	Nonglomerular
Urolithiasis	2	Mixed
Bladder cancer	6	Nonglomerular
Prostat cancer	5	Nonglomerular

CALM: Computer assisted light microscopy *Urinary erythrocyte morphology

(20). Another problem associated with the technique is high inter observer variation due mainly to confusion in distinguishing glomerular and nonglomerular urinary erythrocytes (21). For this reason, considerable experience by an interested laboratory technician is required for a consistent interpretation (22).

CALM, a novel system which markedly improves the quality of the images obtained by light microscopy for urinary erythrocytes. It provides objective and reproducible images, to be used in the detection of glomerular bleeding. With this system, it is possible to enlarge, emphasize contrast and vary the colour of the preparation, without any chemical staining. Also, no skill is needed for judgement. Cooperation between the investigators is easy since all the collected data in the software. The present method has more advantageous points than the conventional methods and is believed to become a useful method for assessment of urinary erythrocyte morphology.

CALM does not lead to a definite diagnosis, but does enable the selection of the most appropriate investigations, and thus avoids unnecessary, often invasive, diagnostic procedures.

In conclusion, all available means taken together point to a mandatory inclusion of this simple, noninvasive approach in routine algorithms for diagnosis of hematuria. This method does not require any different skill, and we would like to suggest this method as one of the standard methods. The method seems extremely efficient for routine clinical practice.

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PROSTATITIS AND PROSTATE-SPECIFIC ANTIGEN

Lütfi Tahmaz • Mete Kilciler • Orhan Yalçın • Murat Dayanç
A. Fuat Peker • Doğan Erduran

SUMMARY

Objective: *The objective of this study is to investigate the possible effects of prostatitis on prostate-specific antigen (PSA) concentration.*

Materials and Methods: *PSA levels were measured in 54 selected patients with prostatic infection and no incidence of benign prostatic hyperplasia (BPH) and prostatic cancer.*

Results: *PSA levels were found to increase (over 4 ng/ml) in 4 of 5 (80%) patients with acute prostatitis, in 4 of 19 (21%) patients with chronic bacterial prostatitis and in 3 of 20 (%15) patients with abacterial prostatitis. PSA levels returned to normal by antibiotherapy in 8 patients with acute and chronic bacterial prostatitis and 3 patients with chlamydia infection.*

Conclusion: *When PSA is referred to as a tumor marker, it should be noted that coexisting prostate inflammation may contribute to a rise in PSA levels without any malignancy*

Key words: *Prostatitis, prostate infection, prostate-specific antigen.*

Researchers who identified the existence and characteristics of prostate-specific antigen (PSA) in 1980, after a forty year pursuit of an ideal tumor marker, have also stated that it is a valuable marker for prostatic adenocarcinoma (1,2). PSA, which is a serine protease, is produced by benign and malignant epithelia cells of the prostatic gland. This means that the marker is organ-specific but no cancer specific (3,4).

PSA has a considerably high concentration in the seminal fluid and it facilitates the liquefaction of seminal coagulum after ejaculation. It is a valuable marker for detection, staging and follow-up of prostate carcinoma. The biologic half-life is 2.2-3.2 days and the normal range of PSA in adults is between 0-4ng/ml (5,10). It has been reported that digital rectal examination, prostatic massage, transrectal ultrasonography and ejaculation don't cause any statistically significant changes in serum concentration (11,12).

Prostatitis is inflammation of the prostate gland. Drach et al. Defined prostatitis with the existence of more than 10 leukocytes for each high-power field in the microscopic examination of prostatic secretion and classified 4 types of prostatitis according to symptoms, digital rectal examination findings, microscopic examination of prostatic secretion and bacterial culture documentation; acute bacterial prostatitis, chronic bacterial prostatitis, chronic non-bacterial prostatitis and prostatodynia (13). Although prostatitis is detected in nearly 5 out of 1000 men Per year, the incidence may rise up to 75% in prostate specimens (14). Neal et al. have reported significant increases in serum PSA levels of test animals, 5-7 day after the instillation of infected saline into the urethra of these animals (15).

The purpose of our study is to examine the serum PSA levels in a selected group of patients with prostatitis who have not demonstrated the occurrence of benign prostatic hyperplasia and prostatic carcinoma and to investigate the effects of prostatitis on serum PSA concentrationts.

Gülhane Military Medical Academy Department of Urology Ankara / TURKEY
Fırat University Medical Faculty Department of Urology Elazığ / TURKEY

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Table 1. The type of bacteria causing prostatitis.

	E. Coli	K. Pneumonia	E. Faecalis	Staf. Aureus
Acute Bacterial Prostatitis	3	1	1	-
Chronic Bacterial Prostatitis	11	1	2	5

MATERIALS AND METHODS

Between January 1995 and October 1996, 54 patients ranged between 21-52 years old (mean 37) and together with symptoms of prostatitis were included in the study. They were suffering from acute or recurrent pelvic, scrotal and perineal pain. Dysuria, pollakiuria, nocturia, and urgency were not evident. Digital rectal examination (DRE), transrectal ultrasonography (TRUS), microscopic examination and bacterial culture documentation of prostatic secretion were performed according to Stamey and Meares (16). In view of this results, prostatitis was determined according to Drech et al. (13). Serum PSA concentrations were measured with monoclonal radiometric immunoassay at the time of diagnosis, before physical examination and 6-8 weeks after antibiotic treatment of the patients with bacterial prostatitis. Enzyme immunoassay (EIA) test revealed Chlamydia trachomatis in the prostatic secretion of 14 of 20 (70%) patients with non-bacterial prostatitis. These patients were treated with doxycycline or ofloxacine for 4 weeks. Two of six patients, who were suspected of having prostate carcinoma, underwent transrectal needle biopsy and tru-cut biopsy was performed for the other four.

RESULTS

The type of prostatitis and bacteria responsible for infection was shown in table-1. Increased PSA levels (over 4 ng/ml) were found in 4 of 5 patients (80%) with acute bacterial prostatitis and 4 of 19 patients (21%) with chronic bacterial prostatitis and 3 of 20 patients (15%) with non-bacterial prostatitis. PSA levels were below 4 ng/ml in all the patients with prostatodynia (table-2). Histopathological examination of 6 patients who had undergone prostate biopsy because of suspicious digital rectal examination or TRUS has revealed the existence of chronic inflammatory changes and no carcinoma. Prostate secretion cultures became sterile in 22 of 24 patients with acute or chronic bacterial prostatitis and 12 of 14 patients with chlamydia after the treatment of these patients with effective antibiotics for four weeks. Serum levels of PSA returned to normal values (0.5, 0.9,1.7, 2.3 ng/ml in acute bacterial prostatitis, 0.4, 1.7, 1.9, 2.5 ng/ml in chronic bacterial prostatitis and 0.8, 2.1, 2.4 ng/ml in abacterial prostatitis respectively) 6-8 weeks after the end of antibiotic treatment.

DISCUSSION

Beside prostate carcinoma, serum PSA levels may also exhibit an increase due to various manipulations like cystoscopy, prostate biopsy and as a result of non-malignant diseases such as acute urinary retention, benign prostate hyperplasia (BPH) and prostatitis (16-21). PSA may rise in case of any disruption in the prostatic basal cells, the epithelial basal membrane, the prostatic stroma, the capillary basal membrane and the capillary endothelial membrane (22). Palou et al. have reported a 24% incidence of acute bacterial prostatitis and 3.3% incidence of chronic bacterial prostatitis in patients with elevated PSA values (20). However, they did not evaluated the existence of benign or malignant diseases and they were not in specific age limit. So it was difficult to achieve a clear differentiation. Prostatitis can probably increase vascular permeability and lead to cellular death which may in turn facilitate the diffusion PSA into the bloodstream (22). In a study in which histopathological examination of non-selective autopsy specimens was carried out, prostatitis was found in 6.3% of the cases (20). Kohen et al. have identified a very high incidence of

Table 2. PSA levels of patients with prostatitis

	Ac.Bac.Prost.	Chr.Bac.Prost.	Abac.Prost.	Prostatodynia
Patients, n	5	19	20	10
Mean PSA	7.6	1.7	1.4	1.2
Range	2.9-28	0.3-37	0.2-21	0.3-3.9
Increased PSA	5.5,6.3,10.9,28	7.9,9.6,14.9,37	6.9,14.3,21	-
PSA; (2.5-4ng/ml)	2.9	2.8,3.2,3.5,3.6	2.9,3.1,3.4,3.7,3.8,3.9	2.7,3.9

Table 3. The results of prostatic fluid culture after antibiotherapy

	Culture (+)	Culture (-)
Ac.Bacterial Prostatitis (n=5)	-	5
Chr.Bacterial Prostatitis (n=19)	2	17
Chr.Abacterial Prostatitis (n=14)	2	12

(98%) inflammatory changes after the histopathological examination of the specimens from the patients with BPH and who had gone through prostate resection (23). Chronic prostatitis may coexist in 60% of the patients with BPH and PSA levels may exceed 10 ng/ml (24,25). Braver et al. have reported that 11 of 35 patients who underwent prostatectomy for BPH were seen to have PSA values above 4 ng/ml and they have concluded that the underlying reason was the inflammation of the gland (26).

There is a significant relationship between PSA levels and prostate inflammation in both acute and chronic prostatitis (27). In addition to this, during the digital rectal examination, confusion of prostatitis with malignant prostate diseases is more common that confusion with benign diseases (28). In their study covering 72 cases with prostatitis and 50 years of age, Pansadora et al. have reported elevated serum PSA levels (above 4 ng/ml) in five out of 7 (71%) patients with acute prostatitis, in two out of 13 (15%) patients with chronic prostatitis in two out of 32 (6%) patients with non-bacterial prostatitis (29).

In our study, there were 54 patients with no BPH and carcinoma. Increases in PSA were measured in 80%, 21% and 15% of the patients with acute prostatitis, chronic bacterial prostatitis and chronic non-bacterial prostatitis respectively. When these results and similar findings in the literature are evaluated, it can be inferred that prostatitis induces PSA increment and this effect is more pronounced in acute prostatitis. When we take into account that the mean age of the patients in our study group was 37 (only one man 52 years old, the others below 50), we may consider the reference range of 0-4 ng/ml PSA too high for the patients under 50. Oesterling et al. have determined the normal age-specific upper limit of PSA for a healthy population to be 2.5 ng/ml between 20-29 ages (mean 26), 2.6 ng/ml was measured as the normal upper limit for PSA (10).

In this study, PSA values between 2.5 and 4 ng/ml were found in one patient with acute bacterial prostatitis, 3 patients with chronic bacterial prostatitis, 6 patients with abacterial prostatitis and 4 patients with prostatodynia. When we re-evaluate our results with respect to age-specific normal values, we find increased PSA in 5 of 5 (100%) patients with acute bacterial prostatitis, in 8 of 19 (42%) patients with chronic bacterial prostatitis, in 9 of 20 (45%) with abacterial prostatitis and in 2 of 10 (20%) patients with prostatodynia (Table-2). The fact that serum PSA was increased in significant number of cases (in a selected group of patients with no BPH or carcinoma) and it returned to normal values after an effective antibiotherapy. These findings supported the literature findings that the underlying reason is the inflammation of the gland.

As a conclusion; prostatitis can cause high PSA levels and this effect more prominent in patients with acute bacterial prostatitis. Prostate inflammation may accompany prostate carcinoma in most of the patients. For these reasons, when using PSA as a tumor marker, we believe that it will eliminate possible misdiagnosis if the existence of prostate inflammation is evaluated.

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THE EFFECT OF ETODOLAC ON THE MICROVASCULAR PATENCY RATES

İbrahim Aşkar* • Kutlu Sevin* • Aydın Saray** • Babür Küçük***
Bizden Tavil Sabuncuoğlu****

SUMMARY

Many investigators have attempted to enhance the patency rate of microvascular arterial anastomosis using pharmacological agents. In twenty male New Zealand white rabbits, femoral artery was transected, crushed or injured or cut and anastomosed. There were ten rabbits in the control group and ten other in the etodolac group. The patency rates were evaluated by the standard "milking test" and blood flow of the vessel at 10 min, 1 day, and 7 days after the anastomoses. Histopatological examination was performed at the 7th postoperative day after the patency test was performed. The analysis revealed progressive endothelial damage on the arterial intima and focal hemorrhages in arterial media in control group, whereas minimal endothelial damage was seen on intima and focal hemorrhages in media in the etodolac group. Etodolac was found to be effectively decreasing the cellular injury on the vessels.

Keywords: *Microvascular anastomosis, etodolac, patency rate*

Microsurgical arterial repairs are usually done on an emergency basis, for example, in digital replantation or revascularizations. Patency rates exceeding 90 percent can be expected in such case (1). Although advanced techniques have been developed in microvascular surgery, some skin flaps still fail to survive. This may be due to a vascular injury and can be attributed to the detrimental effects of cellular swelling, intravascular thrombosis, and leakage of intravascular fluid into the interstitial space. So far, many pharmacological agents have been used to enhance the survival of ischemic experimental skin flap (2). The anti-inflammatory agents, etodolac have an important role in the synthesis of prostaglandin, thromboxane and leukotriene, by modifying metabolism of arachidonic acid (3). Prostaglandin and thromboxane have many effects on the formation of inflammation, fever, edema, chemotaxis of leukocyte, and platelet aggregation (4). In this experimental study, the effect of etodolac on vessel patency was investigated by using a standard anastomosis model on femoral artery in rabbits (5).

MATERIALS AND METHODS

In this study, 20 male New Zealand white rabbits (3500 to 4000 gm) were used. Two main groups; a control group and etodolac group were formed. Antibiotic prophylaxis against wound infection was made by one dose of intramuscular crystallized penicilline G 400.000 Units, 30 minutes before operation. All rabbits were anesthetized by intramuscular injection of ketamine (35 mg/kg) and xylazine (5 mg/kg) (6). In each rabbit, a standard crush injury was made with a clamp along 2 mm of both femoral arteries. The standard injury was achieved using the same clamp for all vessels, squeezing 1 tooth, for 1 second. Then, the injured site of femoral artery was cut and anastomosed using standard microsurgical technique with multiple interrupted sutures of 10-0 nylon (Fig.1). A total of forty anastomoses were made, since two anastomoses were done in each rabbit. The control group received no agent postoperatively, while the experimental gro-

* Ankara University, Medical School, Department of Plastic and Reconstructive Surgery, Ankara, TURKEY.
** Sevgi Hospital, Department of Plastic and Reconstructive Surgery, Ankara, TURKEY
*** Ankara University, Medical School, Department of Otorhinolaryngology, Ankara, TURKEY
**** Ankara University, Medical School, Department of Histology and Embryology, Ankara, TURKEY

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Table 1. Comparison of the patency rates at 10 minutes after the anastomose.

No.	1	2	3	4	5	6	7	8	9	10
Control	P,P	P,P	P,P	P,P	P,P	P,P	P,P	P,P	P,P	P,P
Etodolac	P,P	P,P	P,P	P,P	P,P	P,P	P,P	P,P	P,P	P,P

P: patent (right and left patency rates are shown respectively)

up was given 10 mg/kg/day etodolac* orally. This dose was adjusted due to experiment which was previously performed (3). Arterial blood flow the femoral arteries were examined and assessed as either patent (P), slow flow (SF), no flow (NF) and thrombosis (T) (Table 1, 2, 3). Anastomoses were observed at 10 min, 1 day, and 7 days postoperatively. The patency rates were determined by the standard "milking test" using two jeweler's forceps. All anastomoses were resected en bloc with particular care to avoid direct trauma to the site at the 7^{th} postoperative day. The specimens were immediately fixed in 10 percent buffered formalin, dehydrated, embedded in paraffin. Serial 4 to 5 mm-thick sections were prepared for each specimen and stained with haematoxylin and eosin. The cross-sections were examined under light microscope. Results were analyzed by the Fisher's exact test. Differences with a probability of $p < 0.05$ were considered significant.

RESULTS

The comparison of the patency rates at 10 minute, 1 day, and 7 days evaluations were given in the Table 1, 2 and 3 respectively. While analysis of the patency rates at 10 minute, and 1 day, revealed no significant statistical difference between both groups' patency rates. However, those at 7 days evaluations revealed a significant difference between these two groups' patency rate ($p < 0.05$).

In the control group, histopatological examination suggested a time related, progressive damage to the arterial intima, media, and adventitia. On the first postoperative day, minimal endothelial damage in intima, no or minimal inflammation in adventitia was observed in both groups. On the postoperative seventh day, in the control group, moderate to severe endothelial damage in intima, focal hemorrhages in media, and mild to moderate inflammation in adventitia was observed (Fig 2). In the etodolac group, minimal endothelial damage in intima, focal hemorrhages in media, and minimal inflammation in adventitia were observed (Fig 3).

DISCUSSION

Many studies have demonstrated poor survival rates after free tissue transfers and replanted tissues subjected to prolonged warm ischemia (7,8,9). Various factors such as cellular swelling, acidosis, arteriovenous shunting, and alterations in the clotting system were blamed for the etiology (9,10,11). Moncada et al. have linked the collapse of skin flap microcapillary system as a result of the disruption of physiological balance of prostacyclin (PGI-2) and thromboxane (TXA-2) that maintains vessel patency (12,13). PGI-2 is a very potent vasodilator and inhibitor of platelet aggregation generated by vascular endothelium. PGI-2 is opposed by TXA-2, a powerful vasoconstrictor and platelet-aggregating agent that is formed by platelets. When ischemia and reperfusion damage on the endothelium of the skin flap microcapillary system occurs, the exposed subendothelial collagen encourages platelets to aggregate and release TXA-2 (11,14,15). This causes the disturbance of the homeostatic balance that normally exists between PGI-2 and TXA-2, and leads to further platelet aggregation and vasoconstriction.

Table 2. Comparison of the patency rates at 1 day after the anastomose.

No.	1	2	3	4	5	6	7	8	9	10
Control	P,P	P,T	P,P	T,P	P,P	P,P	P,SF	P,P	SF,P	P,P
Etodolac	P,P	P,P	SF,P	P,P	P,P	SF,SF	P,P	P,SF	P,P	P,P

P: patent SF: Slow Flow T: Thrombosed (right and left patency rates are shown respectively)

* Edolar, Mustafa Nevzat, İstanbul

Table 3. Comparison of the patency rates at 7 days after the anastomose.

No.	1	2	3	4	5	6	7	8	9	10
Control	P,P	T,T	T,P	P,T	T,P	T,T	P,T	P,P	P,T	T,P
Etodolac	P,P	SF,P	SF,P	SF,P	P,P	P,SF	P,T	P,P	T,P	P,P

P: patent SF: Slow Flow T: Thrombosed (right and left patency rates are shown respectively)

Zachary et al. managed to improve flap survival by nonspecifically blocking the formation of arachidonic acid metabolites, both prostaglandin and thromboxane (16). Sasaki and Pang demonstrated that island skin flaps treated with prostaglandin synthesis inhibitors and exogenous PGE-2 had significantly increased skin viability (17). Both Emerson and Zykes and Zachary et al. used exogenous PGI-2 to improve flap survival (18,19). Reus et al. demonstrated a diphasic response to continuous intra-arterial infusion of PGI-2 in pig axial skin-flap survival; low dose PGI-2 improved flap survival and high-dose PGI-2 has the opposite effect (20).

Under some experimental conditions, other actions presumed not to be related to inhibition of prostaglandin synthesis may be involved in the effects of anti-inflammatory agents, although the studies suggesting these possibilities have uncertain applicability to human tissues in vivo. These are as follows: (i) scavenging oxygen radicals, (ii) altering cyclic nucleotide levels, (iii) altering protein kinase activity, (iv) altering ion (Ca++, K+) flux, (v) altering enzyme activity, (vi) inhibit organic anion transport or binding, (vii) altering heterologous receptors, and (viii) inhibit leukocyte migration, lysosome breakdown, lysozyme release (21).

Nonsteroidal anti-inflammatory agents have been shown to regulate upward the number of prostaglandin receptors (the expected consequence of prostaglandin synthesis inhibition). Metz et al. have observed that some biologic effects of exogenous prostaglandin are magnified or can only be detected after tissues have been pre-treated with a prostaglandin synthesis inhibitor to inhibit endogenous prostaglandin synthesis. Suggesting that such upward regulation of prostaglandin receptor number may have important effects qualitatively as well as quantitatively. However, this paradoxical effect of prostaglandin synthesis inhibitors could be shown only on liver cells. It requires new advanced studies for other tissue (21). Nonsteroidal anti-inflammatory agents affect response to circulatory prostaglandin in ischemic skin flaps via the same mechanism.

Other studies demonstrate that platelet aggregation, and occlusive emboli consisting of cellular blebs and trapped leukocytes is noteworthy in ischemic microvasculature, and capillary narrowing secondary to interstitial edema is observable. The inhibitory action of nonsteroidal anti-inflammatory agents on leukocyte migration and adherence may protect capillary patency. Decreased levels of prostaglandin synthesis may result in less edema formation, and sta-

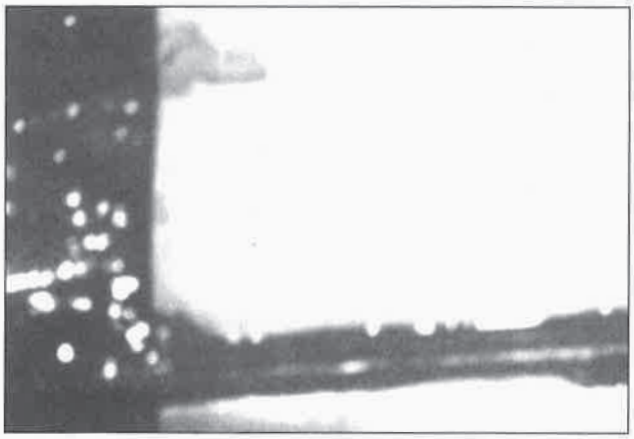

Figure 1. Anastomosis of femoral artery under microscope.

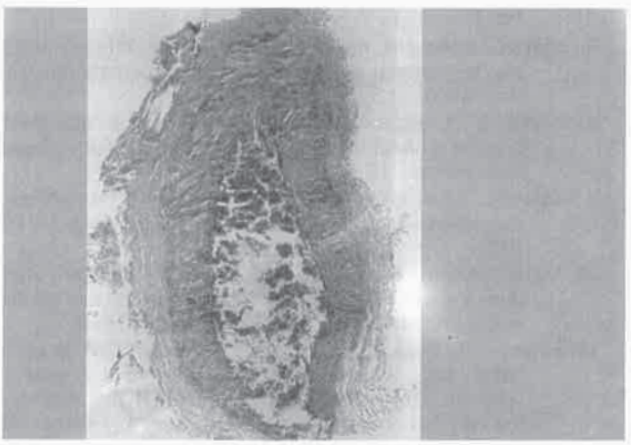

Figure 3. In the etodolac group, minimal endothelial damage in intima, focal hemorrhages in media, and minimal inflammation in adventitia were observed (HE, x25).

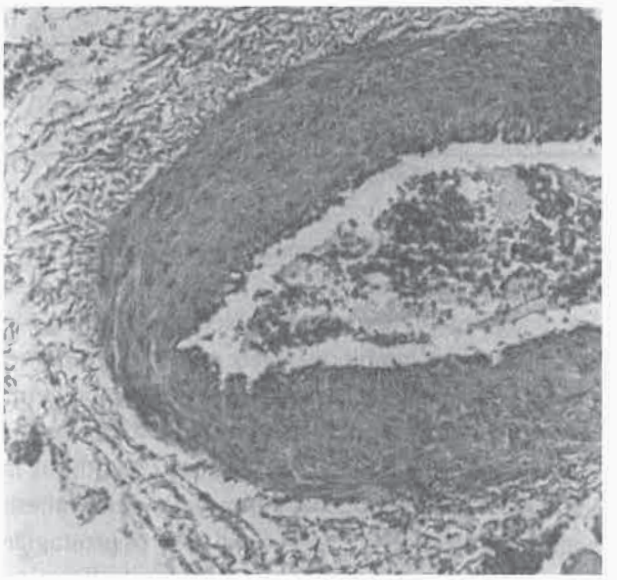

Figure 2. On the seventh postoperative day, moderate to severe endothelial damage in intima, focal hemorrhages in media, and mild to moderate inflammation in adventitia was observed in the control group (HE, x25).

bilization of cellular membranes by nonsteroidal anti-inflammatory agents may decrease the incidence of cellular blebbing and endothelial cell disruption (22,23,24). Single daily dose is easy to administer. Since pH of ischemic tissues is low, the concentration and the effect of any drug can not be clearly determined. So, single dose may be helpful.

In this experimental study, we have observed that etodolac increases patency rates after microvascular anastomosis. Postoperative administration of etodolac in clinical doses significantly ($p<0.05$) increased patency rates of microvascular anastomoses in rabbits. We have also observed that this effect continues during postoperative seven days. We suggest that nonsteroidal anti-inflammatory agents as structurally complex, agents increase patency rates by in hibiting prostaglandin synthesis, decreasing edema, or other mechanisms beyond their anti-inflammatory action.

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DEFICIENCY OF ANTIOXIDANT DEFENCE IN SPONTANEOUS PNEUMOTHORAX*

Sema Yavuzer** • Adem Güngör*** • Gülriz Ersöz**
Hakan Fıçıcılar** • Şinasi Yavuzer***

SUMMARY

Spontaneous pneumothorax (SP) is one of the most common clinical problems encountered by thoracic surgeons. More than 20% of patients with SP relapse within a year and require surgery for recurrence. SP is caused by rupture of a subpleural bleb or emphysematous bullae, most often found in the apex of the lung. The pathophysiologic mechanism of these lesions is not clear. Cigarette smoking that leads exposure of tremendous amounts of oxidant agents is an important factor. The other contributing factors may be congenital pulmonary-pleural defects and defective antioxidant defence. Previous studies in our department revealed that there have been defective antioxidant enzyme activities accompanied with altered platelet function in patients with chronic obstructive pulmonary disease namely in chronic bronchitis and emphysema. In addition, it has been shown that supportive treatment of glutathione system normalises platelet response to agonists in these patients.

In the present study both activities of erythrocyte antioxidant enzymes; superoxide dismutase (SOD), catalase (CAT), and ADP, collagen-induced platelet aggregation in whole blood were evaluated in 12 SP patients and 12 healthy volunteers. In the patient group, SOD activity and ADP-induced platelet aggregation response were found significantly lower than those of the controls ($p<0.05$). CAT activity, collagen-induced platelet aggregation and platelet count were not significantly different between the two groups. Our results suggest that defective antioxidant defence and oxidative stress may play an important role in the pathogenesis of SP and it is thought that supportive antioxidant therapy, combined with surgery, may be beneficial in prevention of recurrences.

Key words: *Antioxidants, free radicals, pneumothorax*

Spontaneous pneumothorax (SP) is one of the most common clinical problems encountered by thoracic surgeons. More than 20% of patients with SP relapse within a year and require surgery for recurrence. SP is caused by rupture of subpleural bleb or emphysematous bullae, most often found in the apex of the lung. The exact mechanism of this entity is unclear. Smoking habit which results in oxidant exposure is one of the important factors among others such as congenital pulmonary-pleural defects and defective antioxidant defence mechanism (1).

Our previous studies showed that there have been defective antioxidant enzyme activities accompanied with altered platelet function in patients with chronic obstructive pulmonary disease eg:chronic bronchitis, emphysema. Platelet functions were normalised by 3 months of N-acteyl cystein therapy in these patients (2).

In the present study it was aimed to investigate the antioxidant status and platelet aggregation of the patients with SP.

MATERIALS AND METHODS

The study was carried out with twelve male SP patients in Ankara University, Faculty of Medicine Department of Thoracic Surgery. Out of twelve, ten patients were within the age range 22-38, two patients were 51 and 66-year-old. On physical examination, there was no evidence of Marfan syndrome, Ehlers-Danlos syndrome or any other connective tissue disorder. There was no sharpness of the first or the second rib or any important pulmonary pathology according to the chest X Ray. An age-matched group of twelve healthy male volunteer consisted the control group. All of the patients and 9 (75%) of the controls have been smoking 10-20 cigarettes per day.

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** Ankara University Medical School, Department of Physiology.
*** Ankara University Medical School, Department of Thoracic Surgery

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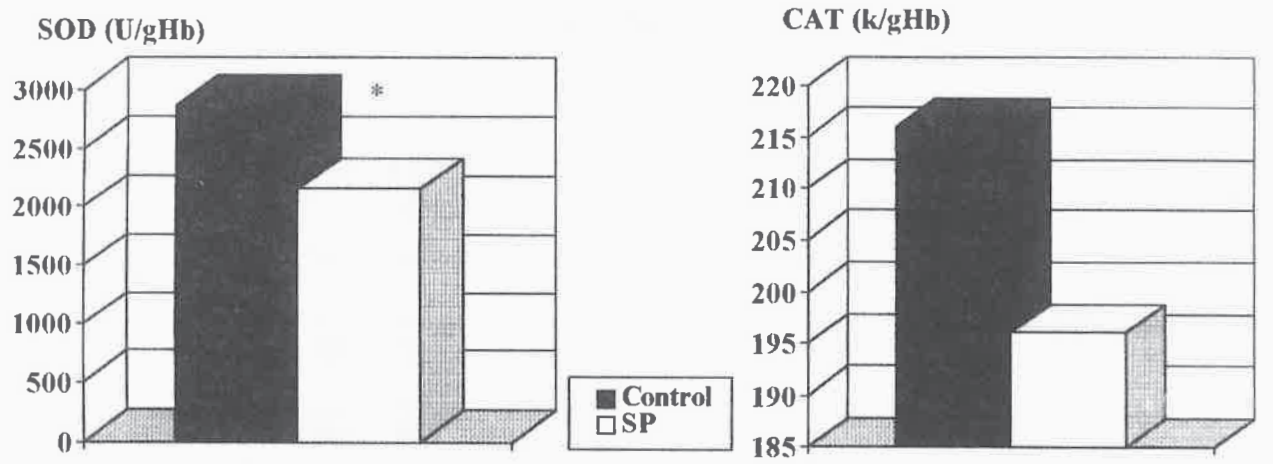

Fig. 1. Erythrocyte SOD and CAT enzyme activities in the control and the spontaneous pneumothorax (* $p< 0.05$)

Venous blood samples were taken from the fasting patients and controls. Erythrocyte superoxide dismutase (SOD) and catalase (CAT) activities were determined in the heparinised blood samples obtained from the subjects. After separating plasma from the blood samples, erythrocytes were washed twicely with saline and were hemolised by adding 1.5 volume distilled water. Then the etanol-chloroform extracts were prepared, and the enzyme activities were spectrophotometrically determined. SOD activity was measured by the method that depends on the ability of the enzyme to inhibit the reduction of nitroblue tetrazolium (NBT) by superoxide, which is generated by the reaction of photoreduced riboflavin and oxygen. Results were expressed as units of superoxide dismutase per gram of hemoglobin. 1 unit is defined for a particular system as that amount of enzyme causing half the maximum inhibition of NBT reduction (3). The determination of CAT activity was performed by the method that based on the decrease of optical density of H_2O_2 at 240 mμ due to enzymatic decomposition of H_2O_2. In order to express CAT activity, the velocity constant k was related to hemoglobin content in blood. k is the velocity constant of the reaction step in which the primary enzyme-substrat complex (=compound I) forms (4). The chemicals were obtained from Sigma Chemical Co. and Hitachi Model 100-20 spectrophotometer was used for enzyme assays.

For evaluation of platelet aggregation 4.5 ml of blood samples were placed into siliconized tubes containing trisodium citrate (1:9), and 1-2 ml were placed into the tubes that were containing EDTA for platelet count. ADP (10μM) and collagen (2μg/ml) induced platelet aggregation in ten patients and ten controls were measured by electrical impedance technique, using Chronolog 560 WB Aggregometer (5). Two platinium electrodes were placed in the blood samples, ADP and collagen were added to the samples for in vitro activation of platelets. Increase in impedance between the electrodes due to the adhesion and the aggregation of platelets on the electrodes were recorded. Maximal aggregation intensity and rate was calculated on the aggregation curve. Platelet counts were performed on Medonic Cell Analyser 610. The chemicals were obtained from Chrono-Log Coorp.

Mann Whitney U test was used for statistical evaluation. $p<0.05$ was regarded as statistically significant.

RESULTS

Mean Cu-Zn SOD activity of the patients with SP was 2155.97(±53.09) U/grHb, of the controls was 2859.88(±216.28) U/grHb. SOD activity of the patients was significantly lower than that of the controls ($p<0.05$) (Figure 1). Mean erythrocyte CAT activity of the patients was 196.33(±33.55)k/grHb, of the controls was 216.48(±11.98) k/grHb. The difference between CAT activities of the two groups was not statistically significant.

Mean maximal intensity of ADP-induced platelet aggregation of the patients was 11.35(±2.7) ohm, of the controls was 22.85(±4.38) ohm (Figure 2). Mean maximal rate of ADP-induced platelet aggregation of

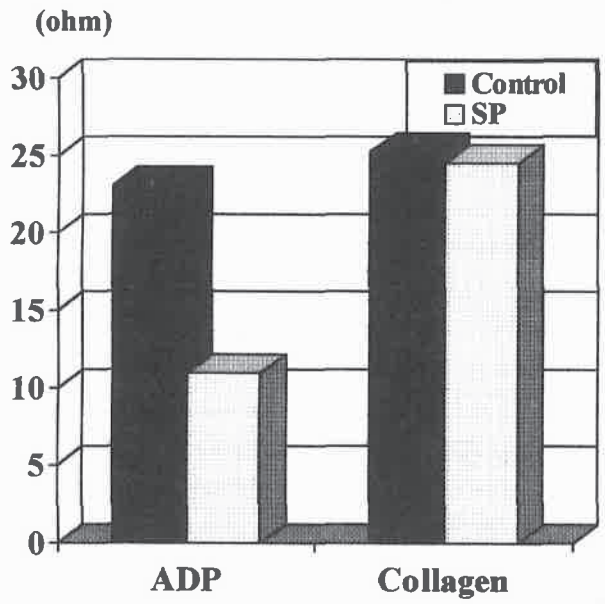

Fig. 2. Maximal intensity of ADP and collagen-inducedplatelet aggregation in the control and the SP groups (*p=0.05

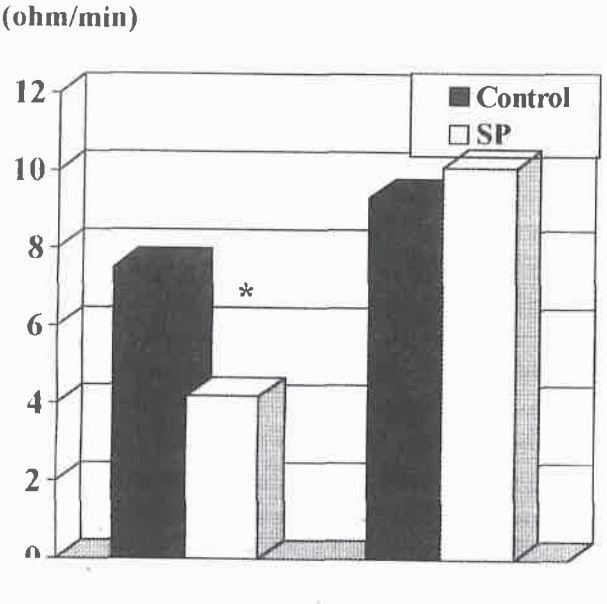

Fig. 3. Maximal rate of ADP and collagen-inducedplatelet aggregation in the control and the SP groups (*p< 0.05)

the patients was 4.22(±0.83) ohm/min, of the controls was 7.55(±0.92) ohm/min (Figure 3). Maximal intensity (p=0.05) and maximal rate (p<0.05) of ADP-induced platelet aggregation of the patients were significantly lower than those of the controls. Mean maximal intensity of collagen-induced platelet aggregation of the patients was 25.17(±2.74) ohm, of the controls was 24.55(±3.56) ohm (Figure 2). Mean maximal rate of collagen-induced platelet aggregation of the patients was 9.28(±1.23) ohm/min, of the controls was 10.05(±0.93) ohm/min (Figure 3). The maximal intensity and the maximal rate of collagen-induced platelet aggregation were not significantly different between the two groups.

Platelet count of the patients was 244100(±50200)/mm^3 and of the controls was 253800(±53600)/mm^3. There were no significant difference between the two groups.

DISCUSSION

Primary spontaneous pneumothorax (PSP) is predominantly a disease of young adults (the age of 34 or under). The incidence of PSP falls in third decade and, males are affected predominantly (6). This pathological manifestation is frequently caused by the rupture of pulmonary bullae or blebs into pleural cavity. Blebs and bullae generally arise as a result of a congenital or acquired weakness of the connective tissue of subpleural alveoli. Blebs frequently occur at the lung apices. It has been suggested that the relative ischemia at the apex of the lung make this area more susceptible to infections.

Additionally there have been several case reports about familial PSP. It has been suggested that familial PSP is one of the clinical features of some other Mendelian genetic diseases such as α_1 anti-trypsine (α_1 AT) deficiency, Marfan syndrome, Ehlers-Danlos syndrome, other connective tissue disorders (7). Emphysema is the most common cause of pneumothorax in patients whose ages are over 40. Emphysematous bullae are frequent in these patients.

On the other hand a high prevalence of tobacco smoking has been reported in series of PSP. Smoking has been implicated as an important contributing factor in etiology of respiratory diseases. Cigarette smoke contains a large variety of compounds including many oxidants and free oxygen radicals that are capable of initiating or promoting oxidative damage in lung (8). So the antioxidant status of the patients has great importance. In the present study most of the patients are young adults (ten of them were aged between 22-38,

two of them were 51 and 66 years old). All of them are males and smokers. Pryor and associates (9) identified a quinone/hydroquinone complex in cigarette smoke and it was shown that this radical was capable of reducing molecular oxygen to superoxide radicals. Thus SOD has a crucial importance in detoxification of superoxide radicals.

In the present study in order to evaluate the antioxidant status, erythrocyte SOD and CAT activities were measured because it has been suggested that erythrocytes represented a potential intracellular antioxidant defence system (10). Erythrocyte SOD activity of the patients was significantly lower than that of the controls. Therefore it seems that the first stage of antioxidant defence is defective and detoxification of superoxide anion is insufficient. Oxidants are also produced endogenously by activation of inflammatory cells such as neutrophils and alveolar macrophages. It results in increased formation of superoxide radicals (11). So oxidative stress may play an essential role in pathogenesis of SP.

In addition there is also increase in production of nitric oxide in respiratory disorders. When there is insufficient detoxification of $O_2^{\cdot-}$, nitric oxide (NO) reacts with $O_2^{\cdot-}$ rapidly to form peroxynitrite anion. It is currently believed that tissue injury that is caused by NO overproduction takes place particularly in an oxidant- rich environment, due to the formation of toxic peroxynitrites (12).

Oxidants may contribute to the pathophysiological processes in SP by several ways, including inactivation of antiproteases, particularly α_1AT, potentiation of elastase activity, stimulation of neutrophyl and macrophage activities. Thus proteinase and antiproteinase balance favors proteolytic activity (11).

In the present study, ADP-induced platelet aggregation of the patients was lower than that of the controls. Oxidants may affect platelet functions. Hydrogen peroxide (H_2O_2) in low concentration generally inhibits platelet aggregation. Incubation of platelet rich plasma with H_2O_2 inhibits platelet aggregation by interfering with platelet energy metabolism (13, 14). In our study SOD activity of the patients is defective, so dismutation of $O_2^{\cdot-}$ to H_2O_2 is insufficient.

$O_2^{\cdot-}$ increase both adhesion and aggregation of platelets. But peroxynitrite, derived from $O_2^{\cdot-}$ and NO, inhibits platelet aggregation via c-GMP in platelets. c-GMP inhibits binding of fibrinogen to GPIIb/IIIa receptors and receptor-mediated Ca^{2+} influx. In addition NO and prostacyclin (PGI_2) synergise with each other as inhibitors of platelet aggregation (12). So the decrease in platelet aggregation of the patients with SP may due to inhibition by NO and peroxynitrite using the pathways mentioned above.

In conclusion, our results suggest that defective antioxidant defence and oxidative stress may play an important role in pathogenesis of SP and it is thought that supportive antioxidant therapy, combined with surgery, may be beneficial in prevention of recurrences.

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POST-POLIOMYELITIS SYNDROME AND ITS MANAGEMENT

Meltem Dalyan* • Diana D. Cardenas**

SUMMARY

Patients who have been affected by acute poliomyelitis (APP) may develop new symptoms such as muscle weakness, muscle atrophy, fatigue, and pain several decades after the onset of their APP. This condition which is now known as post-poliomyelitis syndrome (PPS) has created a considerable amount of confusion and anxiety because the effects after APP were assumed to represent a stable condition. The occurrence of new health problems in poliomyelitis survivors might increase the impairments and disability of these individuals. The aim of this review article is to familiarize physicians with PPS. Acute infection, frequency, definition and diagnosis, clinical features, differential diagnosis, pathophysiology, and prognosis of PPS are explained. Emphasis is given to the current management of PPS and the future approaches to the PPS are conveyed as regard in the literature.

Key words: *Post-polio syndrome, Disability, Rehabilitation, Treatment*

Acute poliomyelitis (APP) occurs as a result of a generalized viral infection that has an affinity for motor neurons (1). The virus is a single-stranded RNA enterovirus and is comprised of three antigenically distinguishable viruses (Type 1, 2, or 3) (1,2). A person infected with one of the types is still at risk from either of the two remaining types. Infection with the polio virus occurs by the fecal/oral route (3).

The virus replicates in the lymphoid tissues of the pharynx and the intestine and then a viremia can follow which is the most accepted mechanism for the direct nervous system exposure to the virus (3). APP can begin with the symptoms characteristic of minor illness, followed by high fever, headache, vomiting, neck and back stiffness, and paralysis. Although the polio virus is an extremely infectious agent the disease progresses to central nervous system involvement and paresis or paralysis in 1% to 2% of the cases (1,4). The infection occurs as inapparent in 90% to 95% of the cases and in 4% to 8% of cases only a nonspecific illness is noted (1). In fatal cases, lesions are also found in the cerebral cortex, primarily in the precentral gyrus, hypothalamus, thalamus, motor nuclei of the brain stem, reticular formation, vestibuler nuclei and cerebellum (4). Mortality is usually the result of bulbar or respiratory involvement (4).

APP is primarily a disease of the motor unit and the reason for this selective vulnerability of the motor neurons to the virus is unknown but it is speculated that it could be related to specific receptors on the cell membranes of motor neurons (1). Motor neuron invasion by the virus results in either motor neuron lysis or injury, with partial or complete recovery. The mechanisms of recovery include the occurrence of collateral innervation through sprouting from remaining motor neurons or by muscle hypertrophy of innervated muscle (5).

Dramatic epidemics of APP occurred in the 1940s and 1950s. With the development of the Sabin vaccine in 1955 and the Salk vaccine in 1961, the incidence of new cases dropped significantly in the United States and Canada and APP is currently a very rare disease in these countries (5). The annual incidence of APP since 1965 in United States has been less than

* Ankara Physical Medicine and Rehabilitation Center, Ankara
** University of Washington, Department of Rehabilitation Medicine, Seattle, WA, USA
Professor, Head of Northwest Spinal Cord Injury Model System

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0.01 per 100,000 (4). APP now occurs as a rare complication of the Sabin live virus vaccine (1 case per 9.5 million doses of distributed vaccine in recipients, and 1 case per 3.2 million distributed doses in contacts of recipients) (6). However, APP is still a problem in less developed parts of the world especially in the countries with poor health care delivery systems. It was estimated that 116,000 new cases of APP occurred worldwide in 1990 (6). World Health Organization (WHO) has a commitment to eradicate poliomyelitis globally by the year 2000 and as a result the number of new cases worldwide dropped to 6241 in 1994 (6,7,8). In Turkey expanded immunization programs were started with the cooperation of the Ministry of Health, WHO, UNICEF, and voluntary organizations in 1985 (9). In 1987, 74% of the targeted population were vaccinated and this ratio increased to 88% in 1996 (10). The immunization programs in Turkey have been successful since the number of APP cases have been decreased; there were 219 and 19 new cases in 1982 and in 1996, respectively (11,12). Also, the number of poliomyelitis patients presenting annually to the rehabilitation medicine departments have been decreased in the recent years (11).

Although APP is uncommon in the developed countries and is rapidly declining worldwide and hopefully will be eradicated by the new century, a large group of polio survivors are still present. In United States, a National Health Interview Survey conducted by the National Center for Health Statistics in 1987 showed that there were approximately 640,000 survivors of APP (13). Individuals recovered from APP may develop new difficulties later in life that are directly or indirectly related to the original motor neuron destruction by the poliovirus. The late onset of new weakness, fatigue, and atrophy in APP survivors which is now known as post-poliomyelitis syndrome (PPS) was first reported in 1875 in Paris and more than a century later there were several reports about the stable post-polio patients (5). Wiechers and Hubbell found the evidence of diffuse neuromuscular junction transmission abnormalities and very large motor units even in normal or grade 4 muscles (14). Dalakas and coworkers confirmed evidence of above findings, and also found signs of chronic and new denervation (15). Cashman and colleagues found clear evidence of active and ongoing denervation in the newly weakened and clinically stable muscles in post-polio patients by electromyography (EMG), single fiber electromyography (SFEMG), muscle biopsy, and immunohistochemical analysis (16).

Mulder et al first proposed clinical criteria for the onset of new weakness developing many years after APP and this was followed by a recent practical criteria for PPS that was proposed by Halstead (1,17).

Definition and diagnosis: PPS is actually a clinical diagnosis by exclusion and a good definition of this syndrome has been given by Halstead and Rossi which is based on five criteria (1): (1) A confirmed history of paralytic polio; (2) partial to fairly complete neurologic and functional recovery; (3) a period of neurologic and functional stability of at least 15 years of duration; (4) the onset of two or more of the following health problems since achieving a period of stability: unaccustomed fatigue, muscle and/or joint pain, new weakness in muscles previously affected and/or unaffected, functional loss cold intolerance, new atrophy; and (5) no other medical diagnosis to explain these health problems.

In diagnosis of PPS, it is thought that EMG studies should be reserved for the patients who have an unclear history of past APP, patients who may not have obvious signs of past APP such as weakness, atrophy, decreased reflexes on physical examination, or for the patients who may have other superimposed neurologic disease (5).

Pathophysiology: Although there have been theories about the exact pathomechanism of PPS remains incompletely understood. The most widely accepted model of PPS and the related symptoms is "peripheral disintegration" of motor units which was originally proposed by Wiechers and Hubbell (14). They proposed that the compensatory enlargement of motor units after APP is not indefinitely stable, and that terminal axonal sprouts degenerate over time and this process causes new weakness that is irreversible. The evidence of this hypothesis was provided by SFEMG and muscle biopsy studies of patients with PPS. SFEMG studies on these patients demonstrated that many of them have neuromuscular junction (NMJ) transmission defects and evidence of increased jitter as a sign of inconsistent conduction among the branches of a motor axon. NMJ transmission abnormalities and defective synthesis and release of acetylcholine is thought to

be related with the muscle fatiguability and generalized fatigue. Besides increased jitter in SFEMG studies, decrement in repetetive stimulation and sensitivity of post-polio patients to non-depolarizing muscle relaxants are evidences of NMJ transmission defects in PPS (5). It is possible that the surviving motor units are subject to chronic excessive metabolic demand so they become progressively dysfunctional and some of the terminal sprouts drop off leaving the muscle fibers denervated. This terminal axon drop out is associated with muscle biopsy samples that show isolated angulated muscle fibers and this was also confirmed by immunuhistochemical studies (5).

Immunologic mechanisms, persistence of poliovirus, premature death of anterior horn cells, and an atypical form of amyotrophic lateral sclerosis are the other several proposed theories of PPS pathomechanism (2).

Frequency, clinical features, differential diagnosis, and prognosis: There have been several population based studies about the frequency of PPS and it is estimated from these reports that it is between 20% and 40% (1). PPS mostly occurs 30 to 40 years after the initial illness. A review of several studies has noted that the time range between the APP and the onset of new symptoms is 8 to 71 years and mean interval is approximately 35 years (5). Symptoms are thought to occur in persons with more severe polio at the onset however some persons with relatively mild polio at onset could also be symptomatic. Aging, older age at the time of APP, bulbar involvement and history of respiratory support, good functional recovery after APP, increased recent physical activity, a recent weight gain, muscle pain especially associated with exercise, and joint pain are the factors that are thought to correlate with the development of PPS (18,19). These associations might imply that overuse is a major factor in the onset of weakness and functional problems. But it is still unclear that some of the above factors such as weight gain, muscle pain, and joint pain are whether the true risk factors or simply the consequences of disease process. Although the role of physical activity has been studied before, the results are contradictory. Klingman et al (18) found that increased recent physical activity was a predictive factor for PPS but this was not confirmed in Trojan's and Ramlow's study (19,20). It is thought that the role of physical activity needs to be further studied.

Several patterns of clinical onset of PPS can be observed. Most often, functional decline is insidious. However, new functional problems may begin abruptly after a minor illness, weight gain, or forced bed rest because of an unrelated accident, medical illness, or surgery. The most prevalent new health related complaints are fatigue, muscle or joint pain, and weakness. In Halstead's study the most frequently reported symptoms of PPS were fatigue (89%), muscle pain (71%), joint pain (71%), weakness in previously affected muscles (69%), weakness in previously unaffected muscles (50%) (21). New muscle atrophy, increased sleep requirement, new or increased deformity, decreased mobility, new difficulties in walking and stair climbing, increased need for ambulatory aids, increased need for personal assistance, increased difficulty in dressing, and a change or cessation of occupation are the other signs and symptoms of PPS (21,22).

The diagnosis of PPS is clinically based. Diseases of almost all systems must be considered in the differential diagnosis (2,5). Especially the musculoskeletal conditions such as osteoarthritis, repetetive injury syndromes, tendinitis, bursitis, and biomechanical deficits in gait (e.g., genu recurvatum) may be precipitated or accelerated by poliomyelitis but not constitute a true PPS. Several neurologic diseases such as adult spinal muscular atrophy, amyotrophic lateral sclerosis, multifocal conduction motor block, multiple sclerosis, myastenia gravis, radiculopathy, fatigue syndromes, and fibromyalgia syndrome might be mistaken for PPS.

PPS has a slow course and the general level of functioning is mostly effected and only severe dysphagia or respiratory weakness might be life threatening. Muscular strength usually shows a slow decline (15).

Clinical management: Besides a through medical and neurologic examination, in suspected PPS; routine laboratory tests, erythrocyte sedimentation rate, thyroid hormone levels, serum protein electrophoresis, EMG studies, and imaging studies might be performed for the evaluation or differential diagnosis.

Weakness is one of the most frequently encountered symptoms of PPS. These patients should receive a reasonable strengthening and areobic exercise prog-

ram, stretching and education in the avoidance of muscular overuse. Exercise in PPS has been a controversial topic but in the recent years there have been reports on this subject which used objective criteria such as isokinetic strength measurements or SFEMG and macro-EMG (23,24,25). It might be concluded from these studies that PPS patients can benefit from a judicious non-fatiguing, long-term exercise prescriptions but it is usually recommended that muscle testing should be performed regularly to avoid overuse. It was also reported that PPS patients showed significant improvements in cardiovascular fitness after an aerobic exercise program (23,27). Swimming and walking are recommended but overuse is an important issue that has to be monitored during all types of exercise programs in these patients. In addition to regular muscle testing it was stated that creatine kinase levels could be a good marker of overuse (28).

Orthotic management, usage of assistive devices, and the modification of the present orthoses should be considered. Appropriate orthoses in conjunction exercise programs in the management of biomechanical deficits such as inadequate dorsoflexion in swing, genu recurvatum, genu valgum, and mediolateral ankle instability can increase the ability to walk, and reduce pain. Waring and coworkers found that 78% of their PPS patients had improvement in walking, safer ambulation, and decrease in pain with the orthotic management (29). It was reported that the inappropriate use of lower extremity orthoses can contribute to muscle disuse and/or injury in postpolio patients and both the regular follow-up and the importance of the modifications in orthototic management were emphasized (30).

Excessive fatigue in PPS patients can be managed with the use of energy conservation techiques, pacing, life style changes, and taking regular rest periods. This approach for the management of fatigue was objectively shown by Agre and Rodriquez (31). They reported that symptomatic PPS patients had less local muscle fatigue, increased work capacity, and improved recovery of strength after an activity if they were allowed to take regular rest periods during the activity.

Pain is a common symptom in PPS and the chronic overstress of muscles and joints is the most likely etiology (31). A study evaluating pain in postpolio patients showed that the most frequent locations were knees and back (32). Clinical studies of symptomatic patients have noted the significant association of location of pain with the methods of ambulation (2,5). Ambulatory patients have a high incidence of pain in the lower extremities and lower back and the patients using wheelchairs or crutches have more pain in upper extremities. The management of such the pain is based on reducing the chronic stresses placed on muscles and joints. This type of pain usually occurs at the end of the day and aggravated by activity. A combination of interventions including reduction of activity, pacing, life style modifications, education in good body mechanics, bracing, NSAIDS, TENS, and use of moist heat and stretching is frequently helpful (5). Amitriptyline, cyclobenzaprine, and aerobic exercise can be helpful if the patient has fibromyalgia (5).

Degenerative joint disease is the result of chronic biomechanical stresses and residual muscle weakness around weight bearing joints is another cause of pain in PPS (33). The tendons, bursae, and the ligamants might also be subject to injury. An increased risk of nerve compression syndromes is also reported in these patients (34). Treatments include modification of extremity use, physical modalities such as superficial heat, ultrasound, TENS, strengthening and stretching, orthotic management and assistive devices with special modifications if necessary, NSAIDS, and rarely steroid injections or surgery (2,5).

Dysphagia is reported to occur in 10% to 20% of PPS patients (35). Swallowing evaluation by videofluoroscopy is recommended if the patient presents with a serious history of aspiration and episodes of aspiration of pneumonia (2). Patients should also be screened to rule out any structural lesions such as stricture, Zenker's diverticulum, and pharyngeal pouches. Dysphagia is managed by diet changes, special breathing and swallowing techniques, and avoidance of eating when fatigued (5,35).

In addition to the symptoms and functional problems described above PPS patients may also experience pulmonary dysfunction many years after the stabilization. This problem has the potential for lifethreatening complications. Pulmonary compromise mostly occurs in those individuals who required ventilation at the time of APP. Scoliosis and kyphosis, obesity, smoking, other cardiopulmonary diseases, and sleep apnea are the other contributing factors of pulmonary dysfunction (5). Initial baseline assessment should consist of pulmonary function tests including vital ca-

pacity and FEV1 and blood gases if CO2 or O2 desaturation is suspected. Non-invasive methods are preferred if ventilatory assistance is needed. Glossopharyngeal breathing can be taught to the patients and intermittent positive pressure ventilation, continuous positive airway pressure, and bi-level positive airway pressure are frequently used for treatment (36). Smoking and weight gain should be avoided. Patients with pulmonary dysfunction or a history of frequent infections should receive annual influenza vaccination and pneumococcal vaccine at least once (36).

Post-polio patients when given the diagnosis of PPS may feel that they are experiencing poliomyelitis a second time and difficulties in adjustment to this second and unexpected disability are inevitable. Psychological distress and depression can be seen (37,38). It is well known that most of the poliomyelitis survivors have had come to terms with their disability and they tend to be educated, employed and have more achievements when compared with the individuals with other physical impairments and disability. Type A personality is also common in survivors and it was reported that this type of personality could contribute to PPS; it was suggested the Type A behavior should be decreased in order to increase patients' compliance with the PPS management programs (39). Psychosocial and emotional problems are best managed with an interdisciplinary approach which include obtaining help from psychologist, psychiatrists, and support groups.

Pharmacological treatments: Several pharmacological treatments have recently been assessed in PPS. These include amantadine, prednisone, human growth hormon, bromocriptine, selegiline, insulin-like growth factor-1(IGF-1), and pyridostigmine. Stein and colleagues evaluated the effect of amantadine 100 mg BID in 25 PPS patients in a randomized, placebo controlled trial and they did not find any statistically significant difference between two treatment groups; although 54% of amantadine patients reported improvement in fatigue when compared to 43% of the placebo patients (40). Dinsmore and coworkers assessed high dose prednisone (80 mg per day for 28 days, followed by a gradual reduction) in 17 PPS patients in a randomized, placebo- controlled trial and they reported no significant improvement in muscle strength or fatigue (41). Human growth hormone has been evaluated by Gupta and colleagues in an open trial in 5 PPS patients and little or no improvement were found in muscle strength (42). Bruno and coworkers have done a placebo controlled, cross-over trial of bromocriptine 12.5 mg per day in 5 PPS patients and an improvement in subjective fatigue symptoms were found in 3 patients, however there were also significant side effects (43). IGF-1 which is a nerve growth factor was used in 22 patients and an improvement in recovery after exercise was noted without any change in strength or fatigue (44). Selegiline, in a report of two cases, was found to produce an improvement in PPS symptoms that ceased with discontinuation of the drug (45).

Pyridostigmine (Mestinon) which is normally used for the treatment of myastenia gravis has been evaluated in small clinical trials in PPS and encouraging results have been accomplished. Pyridostigmine is an anticholinesterase that inhibits the hydrolysis of acetylcholine and prolong its survival and effect in the NMJ (5). The NJM transmission dysfunction observed in PPS has led pyridostigmine usage as a treatment for this disorder. Trojan and colleagues reported that 9 of 17 PPS patients in an open trial of pyridostigmine had improvements in fatigue; stimulation SFEMG was used as an objective criteria in this study (46,47). In addition, Seizert and coworkers have found improvements in some objective and subjective measures of fatigue with pyridostigmine 180 mg per day in a double-blind, placebo controlled, crossover trial in 27 PPS patients (48).

Pyridostigmine might have several possible beneficial effects in PPS (49). These might be acute improvement in fatigue and strength by amelioration NMJ transmission. Additionally it may produce chronic improvement of muscle bulk and strength, and axonal sprout maintenance by trophic or IGF-1 induced effects. Increase of IGF-1 by pyridostigmine could provide a further therapeutic benefit.

In the view of encouraging results with pyridostigmine so far the North American Post-Poliomyelitis Pyridostigmine Study (NAPPS) has been started (49). As stated, this multi-center, randomized, placebo-controlled trial of a 6 months course of pyridostigmine 60 mg three times per day in 126 patients is aiming to determine the clinical and functional effects of this medication. It is anticipated that NAPPS will provide more objective information about the clinical efficacy

and the potential use of pyridostigmine in PPS in the near future.

It has to be noted that there are medications that should be avoided in persons with a history of paralytic polio (49). Depolarizing anesthetics, beta-blockers, benzodiazepines, some antibiotics (e.g. tetracycline, aminoglycosides), some anticonvulsants (e.g. phenytoin), certain antipsychotics such as lithium and phenothiazines, and barbiturates. These medications can produce an increase the NMJ transmission dysfunction and augment fatigue and other symptoms of PPS. Additionally, benzodiazepines and barbiturates might be contraindicated in postpolio patients with respiratory insufficiency.

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THE POTENTIAL APPLICATION OF PHOTODYNAMIC THERAPY IN GYNECOLOGIC DISORDERS

Mete Güngör* • Sevgi Tezcan**

SUMMARY

Photodynamic therapy (PDT) is an experimental cancer treatment modality that selectively destroys cancer cells by an interaction between absorbed light and a retained photosensitizing agent and is a rapidly emerging field with potential applications in gynecologic benign disorders. This review summarizes the principles of photodynamic activity and clinical applications in gynecology.

Key words: *Photodynamic therapy, gynecology, cancer*

In several countries, the efficacy of PDT is being studied in phase I and II clinical studies (1). PDT is based on the photoactivation of a light absorbing dye that selectively concentrates in target tissue (2). The activated dye generates cytotoxic products that cause necrosis and ultimately tumor death (2). There is some controversy regarding the mechanism of tumor cell kill during and after photodynamic therapy. Singlet oxygen, a reactive and short-lived excited state of oxygen, release during PDT results in damage to such cellular components as mitochondria (3), lysosomes (4), the endoplasmic reticulum ,and the nuclear membrane (5). The outcome of this damage is loss of cell integrity. Opposing the views that tumor destruction is a result of direct tumor cell kill are theories that postulate that PDT causes tumor cell death by vascular stasis and ensuing hypoxia (6). The vascular effects may be mediated by release of inflammatory agents and cytokines induced by PDT (7). Thus, Henderson has found that PGE2 is readily released from tumor cells undergoing PDT in vitro and is inversely related to cellular survival. The administration of indomethacine, a cyclooxygenase inhibitor, before light treatment has been shown to block microvascular effects of PDT (8). Also, Nseyo et al, in preliminary studies of patients undergoing PDT for bladder cancer has detected the local release of immunomodulators IL-2, IL-1β and TNF-alfa for as long as 59 days following a single PDT treatment (9). Tissues undergoing PDT ultimately become infiltrated by lymphocytes, plasma cells and histiocytes, again consistent with a possible local immunological response (10).

The photosensitizer must be non-toxic for normal human tissues, highly tissue selective and tumor toxic specific (11). Additionally, its effective phase must be well-defined, simple to activate and reliable.

The tissue photosensitizers that are commonly used clinically are hematoporphyrin derivative (a complex mixture of several different types of porphyrin monomers, dimers and polymers) and photofrin II (a semipurified version of hematoporphyrin derivative that contain an increased concentration of dihematoporphyrin esters (12). Both can be photoactivated by light at wavelengths around 630 nm (red light) and are retained in neoplastic tissue after IV administration (13). Retention of porphyrin photosensitizer also has been reported in liver, spleen, kidneys, skin, embryonic tissue and fresh scar tissue. The retention of the photosensitizers in these tissue may persist for 4 to 6 weeks. Because of their retention in skin, the patient must avoid exposure to sunlight to avoid severe phototoxic damage (14).

* Fellow, Ankara University, Medical School Department of Obstetrics and Gynecology
** Professor, Ankara University, Medical School Department of Obstetrics and Gynecology

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Currently interest is directed toward the second-generation photosensitizers, including Monoaspartyl-e6 (Mace), benzoporphyrin monoacid (BPD MA), disulfonated aluminum phthalacyanine (ALS 2Pc), meta-tetrahydroxypheylchlorin (m-THPC) and 5-aminolevulinic acid (5-ALA) (2). 5-ALA is a precursor of protoporphyrin IX (Pp IX) in the biosynthetic pathway for heme. Under normal biologic conditions, the synthesis of heme regulates the synthesis of ALA via feedback control (15). The step of converting Pp IX into heme is a relatively slow process. Therefore, the administration of exogenous ALA bypasses the feedback effect of heme upon the synthesis of ALA and induces the accumulation of Pp IX. An excessive accumulation of Pp IX causes tissue photosensitivity. However, unlike those other photosensitizers, Pp IX does not persist in the skin for >24 hours after either systemic or localized administration of 5-ALA. Moreover, it is very tissue specific, with low concentration in muscle, blood vessels and dermis and higher, clinically useful concentrations in epidermis and endometrium (12).

Light penetration varies among different tissues as well as within different areas of a single tissue type (16,17,18). Consideration of tissue and light characteristics clearly demonstrate that the ideal photosensitizer for treatment of more penetrating tumors should have an absorbance maximum at wavelengths > 630 nm (13). Any source of light with the appropriate spectrum can be used for photodynamic therapy. The photosensitizer is most effectively activated by laser light. A frequently used system for PDT is the argon-pumped dye laser (2).

Experimental and Potential Clinical Applications of PDT.

1. Diagnosis and Treatment of Gynecologic cancers
2. Endometriosis
3. Endometrial Ablation
4. Ectopic pregnancy and early pregnancy termination .

Gynecologic Cancers

Large, multifocal, and higher grade lesions frequently require more extensive surgical procedures because of invasive potential and recurrence outside of the treated area. Exenterative surgical treatment of recurrences is unacceptable for many candidates because of perioperative risk. For this reason, PDT has been used to treat both vaginal and epidermal recurrences of gynecologic tumors.

Rettenmaier et al, have reported treatment of six patients with complete response in two cases, partial responses in three and a single case with no response (19). Corti et al, reported five local complete responses and two partial responses in seven patients with vaginal vault recurrences from gynecological and colorectal primary lesions (20).

The National Cancer institute (NCI) reported on a phase I study of PDT with Photofrin II for disseminated intraperitoneal neoplasm. Twenty three patients were injected with photofrin 48-72 hr prior to laparotomy and debulking surgery to leave behind neoplastic nodules < 5 mm in diameter. Treatment with 630 nm laser light was given intraoperatively using a dilute lipid suspension (0.02-0.05 % Intralipid) to enhance light diffusion. Eighteen patients with ovarian Ca, 8 with sarcoma and 2 with pseudomyxoma peritonei, underwent intra-operative PDT and 5/8 patients cleared positive peritoneal cytologies after treatment. 6 patients removed free of disease for up to 18 months (21).

In two clinical trials with disseminated intraperitoneal malignant neoplasms, small bowel perforations were seen in three of the patients (21,22). In a rat study, utilizing the photosensitizers, photofrin or meso-tetrahydroxyphenyclorin (m-THPC), intestinal organs were the most photosensitive intraabdominal structures and intestinal perforation was the most common cause of death after PDT (23). Therefore, PDT of the peritoneal cavity may be feasible if the intestinal tract can be protected during treatment. Atilla et al, presented no significant conversion of Pp IX occurred in the submucosal and muscular layers of the intestine, as evidenced by minimal fluorescence. The fact that microscopic tumor on the serosal surface of the peritoneum and of the small bowel showed photosensitizer conversion may lead to improvement of adjuvant treatment of intraperitoneal (IP) micrometastatic disease.

Selective ALA-induced Pp IX production in intraperitoneal ovarian cancer micrometastases can be achieved because of a higher intratumoral conversion rate of ALA to Pp IX compared to the normal surrounding tissues (24). It may provide an in vivo diagnostic aid to improve visualization of micrometastatic ovari-

an cancer spread in the peritoneal cavity and it may serve as adjuvant photodynamic therapy for the treatment of micrometastatic (small volume) intraperitoneal disease. Major et al, reported that in vivo fluorescence detection of Pp IX can be used to identify IP micrometastases of epithelial ovarian carcinoma after application of 5-ALA. They have reported of its use as a diagnostic aid in ovarian cancer second-look laparotomy procedures in an animal model. Considering the large surface area of the human peritoneal cavity, increasing the diagnostic efficiency may be best achieved using fluorescence-based visualization techniques (25).

Wierrani et al, reported promising results in a study of 8 patients with recurrent gynecologic tumors. They used m-THPC as a photosensitizer. Their results indicate that terminal disease can be mildly treated and their life expectancy can be extended without compromising its quality (2).

Endometriosis

The potential for clinical use of PDT modality in the treatment of endometriosis is intriguing. Manyak et al evaluated the potential of PDT for endometriosis in 15 female virgin New Zealand white rabbits. They reported complete or nearly complete destruction of endometrial epithelium in 23 of 26 transplants (88%). Aggressive intraperitoneal use of PDT would be tampered by injury potential to other organs systems involved by endometriosis. It is encouraging that a recent report of three patients treated for ovarian carcinomatosus with IP PDT using a light-diffusing medium had no demonstrable damage to other abdominal organs (26).

Endometrial Ablation

Yang et al, investigated the potential application of PDT for endometrial ablation in a rat model. 5-ALA induced fluorescence specific to the endometrium in rat uterine horns and subsequent exposure to photoactivating light resulted in selective endometrial ablation. Histologic examination of uterine horns shows complete destruction of the endometrium and the inner part of the circular layer of myometrium. Because myometrium does not convert 5-ALA into Pp IX, the destruction of myometrium adjacent to endometrium may be though a non-photodynamic mechanism. One possibility is that necrotic endometrium releases substances that may be toxic to the adjacent myometrium. They concluded that PDT with 5-ALA induces a persistent disruption of endometrium in the animal models (12). These studies have provided important information about the development of an alternative, simpler and safer method for achieving endometrial ablation in patients with menorrhagia.

Ectopic and early pregnancy

Yang et al, have evaluated the efficacy of PDT in ablation of early pregnancies in a rat model. They demonstrated destruction of the early rat pregnancies due to photodynamic effects of ALA (27). There are at least two possible mechanism responsible for the demise of early pregnancies during PDT. First, the fetus because of its rapid proliferation may develop a high concentration of protoporphyrin IX, thus making it very susceptible to photoactivating light. Alternatively resorption of pregnancies could be secondary to damage to the adjacent desidua and endometrium upon which the early pregnancy depends for survival. Reduced blood supply because of constriction of blood vessels could explain the effects of PDT. Because of these results, we postulated that PDT may have a potential role in the treatment of Ectopic pregnancy and early pregnancy termination. The rebreeding experiments demonstrate that ALA at a dose sufficient to achieve the desired interruption of pregnancy did not irreversibly compromise endometrial function in 66.7% animals. However, based on limited data, we are unable to conclude that uterine function was uniformly normal.

With technological development and improvement of photosensitizers, PDT is going to be an alternative treatment modality of malignant and benign gynecological diseases.

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ANEURYSM OF THE MAİN PULMONARY ARTERY: SURGICAL TREATMENT BY ANEURYSMORRHAPHY AND CLOSURE OF THE ASSOCIATED VENTRICULAR SEPTAL DEFECT, ATRIAL SEPTAL DEFECT AND PATENT DUCTUS ARTERIOSUS

Haldun Özberrak* • Adnan Uysalel* • Semra Atalay** • Refik Taşoz*
H. Ercan Tutar** • Hakkı Akalın*

SUMMARY

Dilatation of pulmonary artery rarely reaches to aneurysmal proportions. Once pulmonary artery aneurysm occurs, it carries an additional risk due to the associated pulmonary hypertension.

A twelve year old girl with pulmonary aneurysm secondary to pulmonary hypertension and increased flow into the pulmonary vascular bed due to ventricular septal defect (VSD), atrial septal defect (ASD) and patent ductus arteriosus (PDA) was treated by aneurysmorrhaphy and closure of the associated VSD, ASD, and PDA. The etiology, diagnostic investigation and surgical management of pulmonary artery aneurysms are discussed in the present report.

Key words: *Pulmonary artery aneurysm, surgical treatment*

Aneurysm of the pulmonary artery is a rare entity. Most reports in the literature deal with an incidental finding at autopsy after a rapid and unexplained death caused by rupture of the aneurysm (1,2,). Deterling and Clagett found only 1 case of aneurysm among 17,545 necropsies (3).

In general these lesions fall into two categories ; central aneurysms involving the pulmonary trunk , right and left main pulmonary arteries (70 %) and peripheral aneurysms that arise from segmental or intrapulmonary arterial branches (30 %) (4).

This report describes the etiology, diagnostic investigation and surgical management of the main pulmonary artery aneurysm in a young girl.

CASE REPORT:

A 12 year old girl was admitted to Ibn-i Sina Hospital in February 1996 with a chief complaint of dyspnea and upper respiratory tract infection . She was noncyanotic, extremities were normal and proportional, growth retardation was present (3%). Her blood pressure was 110/70 mmHg., pulse was 124/min and respirations were 35 per minute. The left hemithorax was more prominent than the right and the biventricular lift could be felt over the precordium. A pansystolic grade 5/6 murmur over the fourth intercostal space , early diastolic murmur over the second left intercostal space and a systolic ejection click at apex was heard. No physical finding that correlate with Behçet's or Marfan's syndrome were detected. Laboratory analysis was normal. Chest roentgenograms demonstrated bilaterally enlarged hiler structures with a large mass in the left hemithorax (Fig1). Echocardiogram revealed a large malalaignment VSD and a secundum ASD . Pulmonary artery and branches were massively enlarged . Ascendan aortic diameter was measured as 23mm (PA/AO diameter>2). Right -sided chambers and left atrium were dilated. Normal left ventricular function was detected (Table 1). Doppler study sho-

Table 1. Echocardiographic evaluation data

Year	Diameter (mm) 1994	Diameter (mm) 1996
Main pulmonary artery	28	51
Left pulmonary artery	27	30
Right pulmonary artery	21	23
Ascendan aorta	23	23

MPA /AO < 2 (1994)
MPA /AO > 2 (1996)

MPA: Main pulmonary artery
AO: Ascendan aorta

* Departments of Cardiovascular Surgery, Faculty of Medicine University of Ankara, Turkey.
** Pediatric Cardiology, Faculty of Medicine University of Ankara, Turkey

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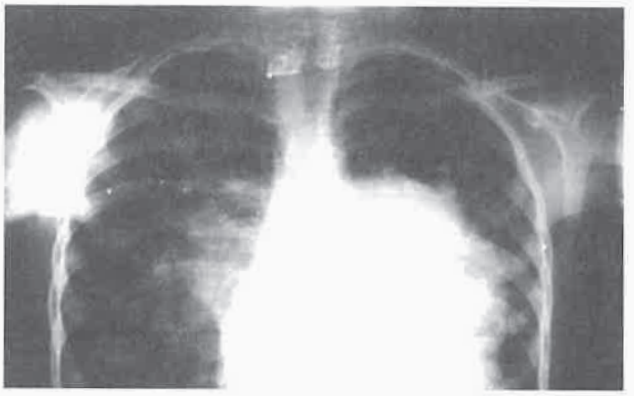

Fig. 1. Chest roentgenogram showing cardiomegaly and a large rounded mass in the left hemithorax in the frontal view

wed moderate pulmonary and tricuspit regurgitation. She had to had two cardiac catheterization one in 1994 and the other in 1996 (Table 2). Following the first catheterization operative correction was decided , but her parents refused the operation. Cardiac catheterization was diagnostic of a left to right shunt at the atrial and ventricular level and pulmonary hypertension. A large aneurysm was demonstrated that confirmed on MRI (Fig 2) and echocardiogram.The patient underwent surgical correction on March 5 1996. Operational findings; a) Cardiomegalia b) Pulmonary artery aneurysm e) VSD f) ASD g) PDA

Procedure

Under cardiopulmonary bypass the patient cooled down to 28 C°, the aorta was cross-clamped for 63 minutes. The cold cyristalloid cardioplegic and topical cooling was utilised as an additional measure of myocardial preservation. The aneurysm was entered and a large portion of its wall excised from 1 cm. above the pulmonary valve to 2.5 cm behind the pulmonary artery bifurcation. PDA was seen which has not been detected by preoperative evaluation and sutured through the inside of the pulmonary artery. The walls of the pulmonary artery were approximated with a continuous 4/0 polyproplene suture. The VSD closed through a vertical right ventriculotomy with a patch of Gore-tex (0.6mm). This was inserted with interrupted pledgetted sutures of 4/0 prolene inferoposteriorly, with a runnig 4/0 prolene on the rest of the circumference of the defect. The secundum atrial septal defect was closed primarily. After bypass was discontinued RV/LV pressures were 35/92 mmHg.

A postoperative control echocardiogram revealed main pulmonary artery of 20.2 mm in diameter. Right and left pulmonary artery diameters were measured as 16.9 mm and 15.3 mm respectively. No patency was detected through closed VSD , ASD or ductus arteriosus. Pulmonary valve was competent.

Postoperative pathological evaluation of pulmonary arterial specimen demonstrated leukocytoclastic changes localised to vaso vasorum in the adventitia and no specific histologic change was detected in the pulmonary artery itself. She was discharged on the seventh postoperative day. Even though the postoperative period was uneventful, due to her cardiomegaly she was receiving digoxin and ACE inhibitor at the time of discharge, which she has been put on two years ago, after first catheterization.

Table 2. Cardiac Catheterization Data

Year	Pressure 1994	Pressure 1996
Right atrium	3	3
Right ventricle	64 / 0-5	64 / 0-5
Main pulmonary artery	65 / 35 (45)	65 / 35 (45)
Left ventricle	95 / 0-5	95 / 0-5
Ascending aorta	95 / 56 (69)	95 / 56 (69)

Qp / Qs : 3.7 (1994)

Qp / Qs : 4.4 (1996)

COMMENT

The most frequent cause of pulmonary artery aneurysms is congenital heart diseases with left to right shunting (1,2). Among these, the most common associated lesion is PDA (2,3). There are few reports in the

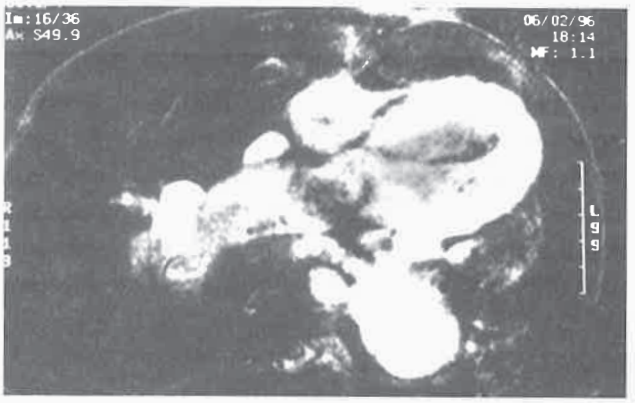

Fig. 2. Magnetic resonans imaging of the anaurysmal dilatatior of the pulmonary trunk

literature about main pulmonary artery aneurysms due to absent pulmonary valve syndrome, pulmonic valve stenosis, VSD or ASD (3,5). The acquired aneurysms often result from bacterial endocarditis (1,5,6). Other important causes are pulmonary hypertension, direct damage or degeneration of the arterial wall (atherosclerosis, tuberculosis, syphilis, Marfan's syndrome, Behçet's syndrome, trauma) and idiopathic (3,4,6).

Central pulmonary artery aneurysms are usually associated with congenital heart diseases and thought to be caused by congenital arterial wall weakness (2,3). In the present case VSD, ASD and PDA were the associated lesions. We are unaware of any previous report describing pulmonary artery aneurysm associated with ASD, VSD and PDA together. Maehara et al., were the first group that described the histological changes in the wall of the aneurysm. They mentioned basic abnormalities as ; mucoid degeneration of the media and fragmentation of the elastic fibers (3). There are also reports about pulmonary artery aneurysms due to a developmental defect in pulmonary elastic tissue (3). In our case pathological evaluation showed leukocytoclasis which usually associates with hypersensitivity angiitis that are caused by certain autoimmun and neoplastic disorders, drug reactions, bacterial infections, serum sickness, subacute bacterial endocarditis,chronic active hepatitis, ulcerative colitis, Sjögren's syndrome, Good posture syndrome (7). In the present case the major cause of leukocytoclastic changes localised to vaso vasorum was believed to be infective which was correlated with the clinical status of the patient.

Preoperative diagnosis of pulmonary artery aneurysm is rare and most reports in the literature deal with incidental finding at necropsy (1,5,6). In the present case two dimensional echocardiogram revealed massively dilated main pulmonary trunk and major branches. The main pulmonary artery/ ascendan aorta diameter ratio was greater than 2 which in case correlated with pulmonary artery aneurysm.

In our case, PDA could not be imaged in parasternal short axis view of 2D echocardiogram, because of aneurysmatically dilated pulmonary artery. Turbulent flow through ductus arteriosus to pulmonary artery was not detected with color doppler and continuous doppler echocardiography. We know that all signs of PDA on doppler mapping become obfuscated in the presence of severe pulmonary hypertension with little or no left to right shunting (8). Aortogram was performed in left lateral position and no shunt was detected due to patent ductus arteriosus. In cardiac catheterization, the oxygen saturations in the right ventricle and pulmonary artery were the same, which supported the result of aortogram. In fact, when we considered the case postoperatively; PDA could be detected by venous contrast echocardiography and also, aortography should be performed in more than one position.

The rate of enlargement of the aneurysm does not correlate with the level of pulmonary artery pressure (3). In our case, echocardiographic evaluation in 1994 revealed pulmonary artery dilatation, where as echocardiography prior to the operation in 1996 showed pulmonary artery aneurysm. Even though the size of the pulmonary artery progressed to aneurysmal proportions ,no significant change in the pressure of pulmonary artery was detected in the past two years. Therefore, we think that although the effect of significant pulmonary hypertension on the development of pulmonary anerysm is clear enough, left to right shunts appear to be the basic predisposing factor.

The first group, that reported surgical correction of a main pulmonary artery aneurysm by aneurysmectomy and Dacron graft replacement were Williams and associates in 1971 (4). Following this report , a few other reports have been published (3,4). Excision of the aneurysm and implantation of a pulmonary homograft or repair by aneurysmorrhaphy are the other techniques reported (2,5)

In our case,due to rapid increase in main pulmonary arterial diameter and heart failure, surgical treatment was mandatory. Pulmonary reconstruction was performed by using the nondilated apparently uninvolved posterior wall of the aneurysm to size similar to the ascending aorta. Aneurysmorrhaphy was performed since closing the VSD, ASD, PDA reduced pulmonary artery pressure and flow. By decreasing turbulent flow and pressure, the possibility of aneurysm recurrens would be reduced.

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PARAMEDIAN DIENCEPHALIC SYNDROME (CASE REPORT*)

Canan Işıkay** • Ayşe Bingöl*** • Canan Yücesan** • Aytaç Yiğit**
Nermin Mutluer** • Aylin Öcal** • Yasemin Akarsan***

SUMMARY

Paramedian diencephalic syndrome as the result of bilateral thalamic infarction is a rare cause of the amnestic syndrome with sudden onset. It consists of hypersomnolent apathy, amnestic syndrome and abnormal vertical gaze. We report a case of paramedian diencephalic syndrome persistent verbal and visual short-term memory deficits with an acute onset.

Key words: *Amnestic syndrome, paramedian diencephalic syndrome, paramedian thalamic artery, thalamic infarction*

Paramedian diencephalic syndrome consists of hypersomnolence with apathy, amnestic syndrome and vertical gaze palsy (1). It is a rare cause of amnestic syndrome with sudden onset. Acute presentation is important for differential diagnosis.

CASE REPORT

A 43-year-old right-handed woman presented with complaints of forgetting whatever she heard or saw in a few minutes, slowness in motion and speech, lack of initiative, lack of interest and withdrawal. One month prior to admission, she had developed acute decrease of the level of consciousness and upward deviation of the right eye. Her blood pressure was moderately high. On the neurological examination she was disoriented to time, place, people and to herself. A computed cranial tomography (CT) revealed bilateral thalamic hypodensities compatible with infarction. One week later she began to recognize her family and remembered some of her autobiographical information. The complaints listed above became appearant as consciousness cleared. Her medical and family histories were unremarkable.

Neurological examination revealed apathy, disorientation to time and place, psychomotor slowing, decrease in spontaneous activities and anterograde and retrograde verbal and visual amnesia. The rest of the neurological examination was unremarkable.

Fasting blood glucose (126 mg/dl), triglyceride (284 mg/dl), HDL (32 mg/dl), platelet (390000/mm^3), fibrinogen (605 mg/dl) and oral glucose tolerance test were the only abnormal laboratory findings. Cerebral MRI revealed hyperintense lesions on the T_2-weighted images situated bilaterally in the anterior thalamic regions (Fig.1). Bilateral carotid artery Doppler ultrasonography (DUS) showed intimal thickening and unevenness of the lumen in bilateral common carotid and internal carotid arteries. 4-vessel cerebral digital subtraction angiography (DSA) showed unevenness of the lumen and delayed filling in the left posterior cerebral artery. Cerebral single photon emmission computed tomography (SPECT) revealed hypoperfusion in the right basal ganglia. Transthoracal echocardiography and bilateral vertebral artery DUS were normal.

On neuropsychological evaluation there was moderate disability in higher cortical functions globally (more specifically in orientation to time, retrieval pro-

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** Department of Neurology, İbn-i Sina Hospital, Ankara Medical School, Ankara University, Ankara, Turkey
*** Neurologist, T.C.D.D. Hospital, Ankara, Turkey

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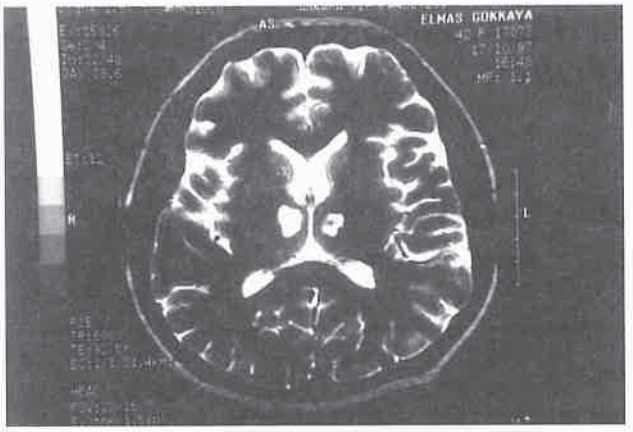

Fig 1. Bilateral anterior thalamic hyperintense lesions on T_2-weighted MRI compatible with ischemia.

cess of short-term verbal memory, complex mental tracking, mental flexibility and constructional praxia) and severe disability in mental processing speed, verbal fluency, verbal memory span, storage processes of short-term verbal and visual memory, sequencing process of short-term visual memory and motor praxia.

The patient had mild hypertension, latent diabetes mellitus, hypertriglyceridemia and atherosclerosis of the cerebral vessels as ischemic stroke risk factors. She was discharged on an appropriate diet and antihypertensive and antiaggregant treatment. Six months later she could do her daily house work independently and her interest about environment had improved. Vertical gaze palsy and retrograde amnesia had disappeared but anterograde amnesia still persisted. A control cerebral MRI revealed that bilateral thalamic lesions, although smaller, still persisted.

DISCUSSION

We report a case of bilateral anterior thalamic infarctions with persistent verbal and visual short-term memory deficits with an acute onset. The most striking deficit of the patient is associated with short-term verbal and visual memory. This points to bilateral limbic lesions and is compatible with the patient's bilateral anterior thalamic infarctions. All thalamic lesions do not lead to amnesia. Lesions that localize in the posterior parts and affect only the dorsomedial nuclei do not cause overt and persistent amnesia. In contrast, the disruption of the ventroamigdalofugal and mamillothalamic fibres which are situated anteriorly and go to dorsomedial nucleus causes severe and chronic amnesia (1). Thalamic amnesia seems to be a disconnection syndrome due to the intrathalamic white matter lesions rather than to the nuclear grey matter lesions (2). Our patient's memory deficits with anteriorly situated lesions are compatible with the literature.

The second problem is associated with frontal cortex functions. The deficits in these functions (e.g. time disorientation, slow mental processing speed, mental rigidity, complex mental tracking inability) can result partially from memory deficits and disruption of thalamocortical fibres (1, 3). Thalamic lesions can cause changes in personality and mood, apathy, confabulation and decrease in spontaneousness (3). Personality changes resemble closely to those seen in focal frontal or frontal-limbic system dysfunction (3). Personality changes relate to the localisation of the lesion. Anterior thalamic lesions, by disrupting the connections to the cingulate gyrus, can cause akinesia and withdrawal (3) and this explains some of our patient's symptoms (lack of spontaneousness, loss of interest and withdrawal). In contrast, dorsomedial lesions, by disrupting the frontal connections, cause euphoria and loss of insight (3).

It is well known that bilateral thalamic or even unilateral thalamic lesions can lead to dementia (3, 4). Global moderate dysfunction of the higher cortical functions of our patient is compatible with this information. This may be attributable to ipsilateral cortical hypometabolism observed in unilateral thalamic lesions (4) which in our case is expected to be bilateral.

Motor and constructional apraxia can be seen with subcortical lesions (3), they can also be viewed as a part of the global cortical dysfunction due to cortical hypometabolism.

Thalamic lesions cause decrease of arousal and consciousness especially in the acute phase. This may be due to disruption of the pathways in the subthalamic region, ascending noradrenergic pathways and/or reticular activating system and mesencephalic-diencephalic junction (3).

How can one accident cause bilateral symmetric infarctions? The vascularization of the thalamus is complex and highly variable (5). The perforating endvessels that arise from the arterial segment that lies between the basilar artery bifurcation and posterior cerebral artery are responsible for the vascularization of the thalamus (5, 6); this arterial segment is called "mesencephalic artery" or "basilar communicating ar-

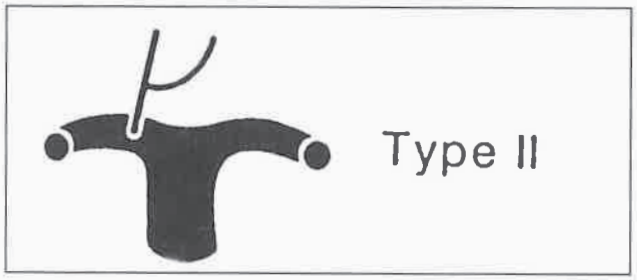

Fig 2. Type II variation of the arterial pattern of origin of the paramedian thalamic arteries.

tery" (6). Ventral thalamic region is vascularized by paramedian thalamic and polar arteries. Polar artery that arises from the posterior communicating artery is responsible for 60-70% of the total vascularization and mainly of the anterior region including mamillothalamic tractus (2, 6). In cases in which polar artery does not exist, vascularization of the anterior region is mediated by paramedian thalamic arteries. Paramedian thalamic arteries arise from the basilar communicating artery and show many variations; in Type II variation they arise as one stem from the posterior cerebral artery and then bifurcate (5) (Fig. 2). Our patient's cerebral DSA demonstrated uneven lumen and delayed filling of the left posterior cerebral artery and we speculate that our patient has Type II variation of paramedian thalamic arteries which can explain bilateral thalamic infarcts with a single ischemic accident.

Vertical gaze palsy is also attributable to the vascular distribution of paramedian thalamic arteries which besides the medial thalamus also supply the rostral interstitial nucleus of the medial longitudinal fasciculus and posterior commissure whose lesions cause vertical gaze palsy (6).

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CAUSE AND EFFECT OF TREATMENT IN LYMPHOEDEMA OF THE LEFT LOWER EXTREMITY: A CASE REPORT

İ. Haluk Gökçora • Sevgi Gözdaşoğlu* • Belgin Can** • Meral Barlas
Betül Ulukol* • Serdar Gültan*** • Meral Tekelioğlu**

SUMMARY

*A female child received a laparotomy with a subtotal resection of a yolk-sac tumour, extending from her left groin to her left lower abdominal quadrant, the perianal, left labial and sacrococcygeal regions, presenting as stage III disease, at age three. She had abnormal venous engorgement of the left labial region, groin and lower abdominal wall apart from the huge tumour mass. Further to the surgical treatment she received vincristine 1.5 mg/m²/week, actinomycin-D 15 mcg/kg/day*5, cyclophosphomide 500 mg/m²/week chemotherapy for six cycles to be followed by 3300 cGy pelvic, 5500 cGy upper left femoral irradiation. This resulted in the disappearance of the tumour but her pelvic bony structures failed to grow with her age, along with a necrosed femoral head, hip dislocation and a massive lymphoedema of the left lower extremity thus crippling her to wheelchair status. She had failed to show up at the outpatients clinic for the next decade, but did appear at our unit one day with gross lower extremity lymphoedema, at age thirteen. Her main complaint at the time of admission was being unable to lift up her left leg and walk without aid. Though the other portions of her body had grown normally, her pelvis was extremely small, measuring only 20 centimeters in diameter. Her left leg was twice the diameter of her contralateral side with enhanced lymphoedema distal to the upper one-third of left femoral region.*

Medical imaging techniques and radiocontrast roentgenography failed to show any lymphatic structure. The same patient at sixteen, is presently able to walk properly and wear nylon stockings and skirt for the first time in her life, after extensive excision of her lymphoedematous left lower limb skin and subcutaneous tissue, and application of split-thickness skin grafting in three separate operative sessions. After some psycho and physiotherapy she is presently able to attend her formal secondary education; much more attentative in her physical activities and enjoys a better self-esteem.

Key words: *Child, lymphoedema, electron microscopy*

Lymphoedema of an extremity is in reality "an interstitial oedema of lymphatic origin". While lymphoedema is rich in protein, the oedema of heart and kidney failure, in contrast, has a low protein content. The causes of lymphoedema may be primary (congenital or acquired deficiency of the lymphatics or dilatation and incompetence of the lymphatics) or secondary (neoplastic infiltration of lymph nodes, infective or iatrogenic). The main complaint remains as a slowly progressive swelling of the limb or genitalia. While in primary lymphoedema the swelling takes years to develop, secondary lesions may appear within a few weeks and progress rapidly. The swelling is not painful and there is no discomfort in the swollen limb appart from that caused by the increased weight and any mechanical disability. Vesicles may appear on the skin which leak clear-coloured fluid. These can not be compressed or emptied. The lymphoedema of the lower limb affects the toes much more than other forms of oedema and if it has been present for years the toes get squashed together and become squared-off revealing an odd shape. This hardly ever occurs with venous, cardiac or renal oedema.

* Departments of Paediatric Surgery , Paediatrics University of Ankara, School of Medicine; Ankara, Turkey
** (Haematology and Oncology Research Unit), Histology and Embryology University of Ankara, School of Medicine; Ankara, Turkey
*** Plastic & Reconstructive Surgery University of Ankara, School of Medicine; Ankara, Turkey

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CASE REPORT

The skin of a lymphoedematous leg gets thick and hyperkeratotic. Such were the findings when the present case (Fig .1) was presented by her family when she was thirteen.

This female child received a laparotomy with a near to total resection of a yolk-sac tumour, extending from her left groin to her left lower abdominal quadrant, the perianal, left labial and sacrococcygeal regions, presenting as stage III disease, when she was three. She had abnormal venous engorgement of her left labial region, groin and lower abdominal wall apart from the huge tumour mass which had covered almost halve of her abdomen at the time. Further to the surgical treatment she received vincristine 1.5 mg/m²/week, actinomycin-D 15 mcg/kg/day*5, cyclophosphomide 500 mg/m²/week chemotherapy for six cycles. This was followed by 3300 cGy pelvic, 5500 cGy upper left femoral irradiation. The result was the disappearance of the tumour but her pelvic bony structures had failed to grow with her age, a necrosed femoral head, a dislocated hip and a massive lymphoedema of the left lower extremity crippled her to wheelchair status. She had failed to show up at the outpatients clinic for the next decade, but did appear one day with gross lower extremity lymphoedema. Her main complaint at the time of admission was being unable to lift up her left leg and walk without aid. Though the other portions of her body had grown normally, her pelvis was extremely small, only 20 centimeters in diameter. Her left leg was twice the diameter of her contralateral side with enhanced lymphoedema distal to the upper one-third of left femoral region.

Fig 1. Preoperative photograph of the child: note extremely small pelvis and apparent difference between the lower extremities

Medical imaging techniques and radiocontrast roentgenography failed to show any lymphatic structure. She received debulking treatment by massive excision the skin and subcutaneous tissues down to the muscle fascia. followed by split thickness skin grafting in there different sessions: from the knee to the ankle, the foot and the knee/lower twoqthirds of the thigh. The same patient now fifteen, is able to walk much better and wear nylon stockings and a short skirt the first time in her life. Following psycho and physiotherapy she has been able to attend her formal secondary education and is much more attentative in her physical activities, thus enjoys a better self-esteem. (Fig. 2)

The processed biopsy material taken from the lymphoedematous leg was examined by light and electron microscopy. Four to six micron sized microtome speciemens were stained with hematoxylen-eosin, Masson's trichrome and Mallory Azan for light microscopy. Semi-thin processed sections were stained with Toluidin blue-Azur II and examined with Zeiss axioscope photomicroscope. Thin sections stained with uranyl acetate and lead citrate and examined with Jeol 100 electron microscope (7).

The most striking finding revealed by light microscope was the thickening and increase of collagen fibres, connective tissue cells (especially fibroblasts) and macrophages (Fig. 3). Electron microscopy revealed widened lymphatics full of lipid cells which were also present among collagen fibres. A typical macrophage with irregular outline (Fig. 4) and greatly increased collagen fibres are further distinguished by transmission electron microscopy.

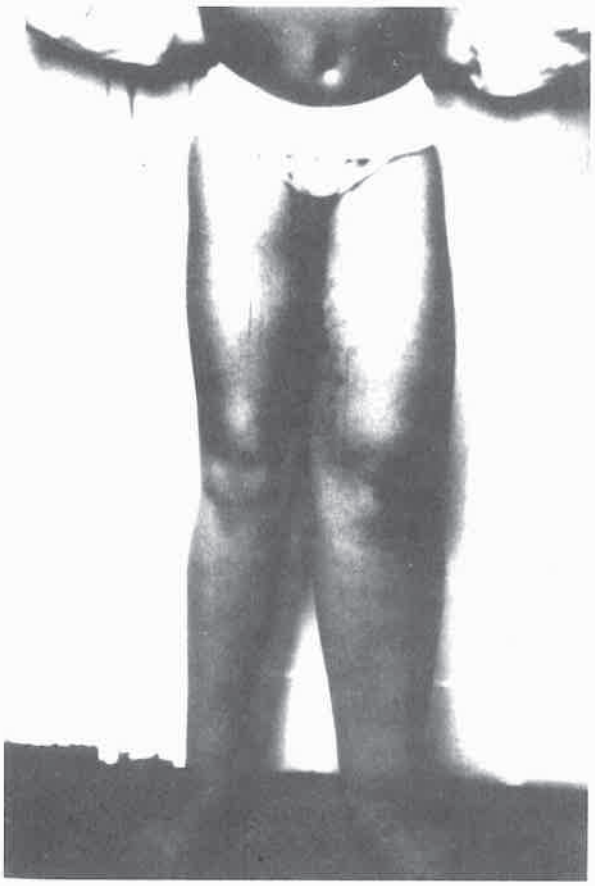

Fig 2. Postoperative apperance of the lower extremities.

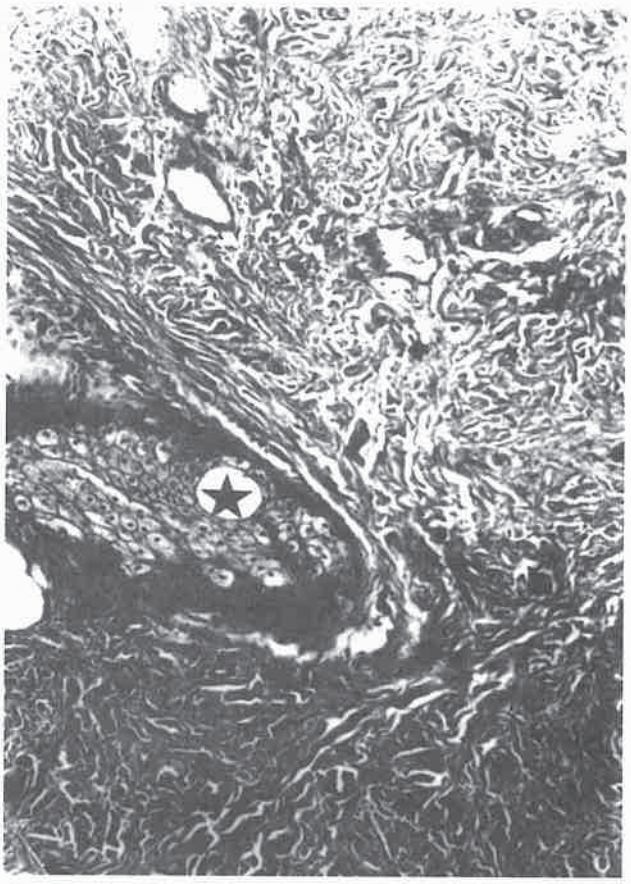

Fig 3. Light microscopy: * 25
Dermis: thickening and increasing of the collagen fibres (arrow), hair follicle (star).

DISCUSSION

Multidisciplinary approach for the treatment malignant diseases have enabled a 60-65 % full remission and well being in the paediatric age group (1,2). Longer life expectancy, late effects of cancer treatment and hence such concepts as quality of life have surfaced among oncological disciplines with success and the cure of such diseases at hand. Late effects of cancer treatment may be encountered in almost all organs and systems (3.4).

The underlying mechanism in the present case's lymphoedema was the impairment of the flow of lymph from the concerned extremity either as a result of non-inflammatory obstruction (eg: surgical excision) of the lymph channels and because of resulting malformations of the lymph vessels by high-dose irradiation. Secondary dilatation of the vessels lead to incompetence of the valve system, disrupting the orderly flow along the lymph vessels. This inturn results in progressive stasis of a protein-rich fluid with secon-

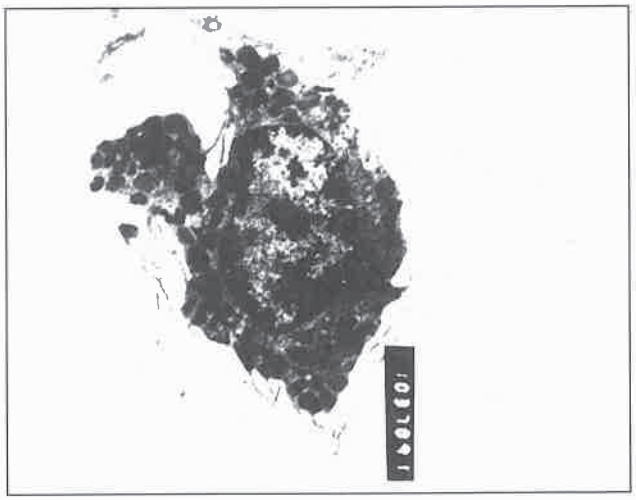

Fig 4. Transmission electron microscopy: * 10 000
Typical macrophage exibiting numerous cytoplasmic infoldings, collagen fibres are also seen in the extracellular matrix (arrows) nucleus of the macrophage (star). (Uranyl acetate - lead citrate)

dary fibrosis leading to the hypertrophy of the limb with markedly thickened/fibrotic skin/subcutaneous tissue and the diminution of the adipose tissue. Altered proteins in the tissues cause chronic inflammation which result in chronic lymphoedema. Macrophages, fibroblasts and to a lesser extent lymphocytes increase greatly in numbers and relative volumes. Collagen and fat cells also greatly increase in relative volume. The lengths of blood vessels and initial lymphatics are much greater in the injured tissue. The numbers of small vesicles and vacuoles rise greatly in both types of vessels (8). The findings in the present case have revealed such changes.

Lymphography has been in clinical use in clarifying the primary lymphoedemas into hyperplastic and hypoplastic varieties. We have not been able to demostrate preoperatively any lymphatics in the left lower limb or groin in the present case.

Extraction of lymph nodes during radical operations and radiation fibrosis have been indicated as the most important factors in the aetiology of lymphoedema. Irradiation for malignancies may further provoke or acccelerate a chronically oedematous condition (8,11,12).

Though surgical management depends on multiple aetiological factors, *there is no perfect treatment of lymphoedema*. Debulking or cytoreductive surgery for the excess fibrous and lymphatic stagnation in the region is known as *Charles' procedure*. Surgical excision of strips of skin and oedematous subcutaneous tissue down to the fascia in staged procedures or even an extensive excision and grafting procedure, which took over a year-and-a-halve in the present case, can be considered in the very chronic and severe forms. Cosmetic and functional results are desired and elastic leg supports will be necessary

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A NEW METHOD FOR RECONSTRUCTION OF CRANIAL BONY DEFECTS: Technical note with illustrative case

Çağlar Berk* • Gülşah Bademci* • Ertekin Arasıl**

SUMMARY

Major defects of the skull may become necessary to repair regardless of its aetiology. Aesthetic considerations dominate at most of the times, so we define a new, two staged technique for cranioplasty using methyl methacrylate shaped on a pre-modelled plaster cast. The technique is simple, cost-effective and gives excellent cosmetic result.

Key words: *Cranioplasty, Methyl methacrylate, Surgical technique*

Major bony defects of the cranium are most often the result of trauma or extripation for tumor (1). Regardless of its aetiology cranioplasty may become necessary when primary repair or bone replacement was not possible at the time of injury. As is true of acute craniomaxillofacial reconstruction, the reconstructive goal in cranioplasty is to provide protection of the brain and restore the preinjury appearance (2).

Skull defects of greater than 2 or 3 cm should be considered for repair. However, this decision varies with location. Even small defects in the frontal area can be disturbing to the patient and therefore can be considered for repair. As the defect size increases, it becomes more difficult to make an aesthetically acceptable reconstruction (3).

We define a new technique for the reconstruction of large skull defects using methyl methacrylate shaped on a pre-modelled cast; that is simple to apply and gives excellent cosmetic result.

METHOD AND TECHNIQUE

The neurocranium, resembling a half-cut sphere, is practically symmetrical at both sides along the curves passing through nasion, a given point and inion; like the global meridians (Fig. 1a). A bony defect may be contoured accurately with a pliable material if this is shaped along a defined curve on the intact side and than carried to the similar coordinates on the defective side. Using pliable steel Kirschner wires of 1.2 mm diameter, the skull defect is contoured in a grid-like fashion and this 'skeleton' is fixed to the scalp on the defect area using pieces of adhesive tape (Fig. 1b). The skeletonised defect area is covered with layers of adhesive dressing retension sheet (Hypafix, #4210, Smith&Nephew) gently without impressing (Fig. 1c). The the head is wrapped first with a thin layer of gauze dressing and than with plaster cast (Scotchcast, 3M) completely and waited till the cast hardens (Fig. 1d). The cast is removed from the head by cutting with a power instrument and trimmed to a size slightly greater than the defect area. The finished cast is sterilised with Ethylene Oxide gas and becomes ready to use in the operation.

During the operation the scalp flap is removed carefully from the underlying dura and brain. Meticulous effort should be exercised to keep the dura intact or repair it in a watertight fashion to prevent further problems related to CSF leakage. The freed bone edge is saucerized by removal of the outer table with a high-speed burr and this lip prevents the implant from slipping into the defect. Any of the commercially availab-

* M.D., Resident in Neurosurgery. Department of Neurosurgery, Ankara University Faculty of Medicine, Avicenna Medical Center, Ankara, Turkey

** M.D., Professor and Chairmar. Department of Neurosurgery, Ankara University Faculty of Medicine, Avicenna Medical Center, Ankara, Turkey

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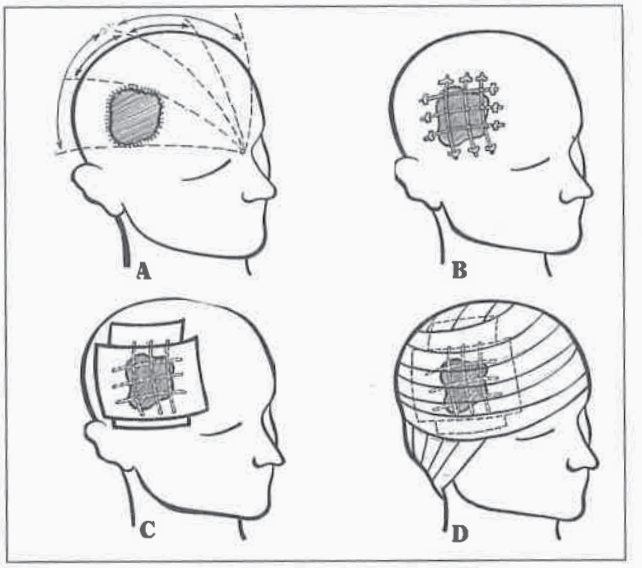

Fig. 1(a-d). Rationale and steps for pre-operative defect moulding.

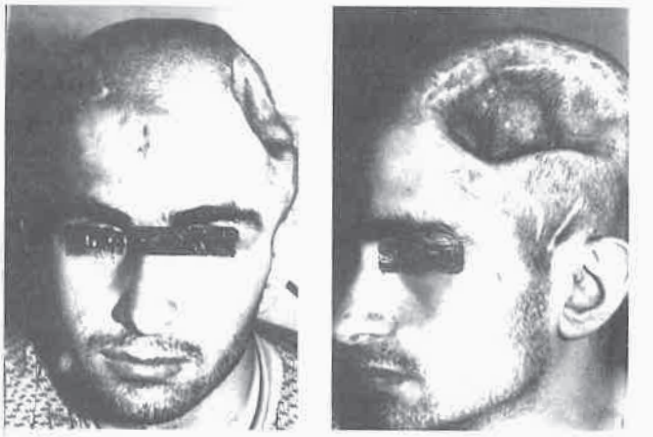

Fig. 2 (a-b). Pre-operative views of the patient.

le cranioplasty kits containing methyl methacrylate may be used. The elements are mixed and doughed. Shaping of the plastic implant is performed in the nylon sleeve provided in the cranioplasty kit, on the pre-modelled sterile plaster cast. After the exhothermic polymerization process takes place away from the surgical field, the implant is placed over the defect and trimmed to final shape with a high speed drill (Midas Rex Pneumatic Tools, Fort Worth, Tx., USA) and craniotome attachement. The finished implant can be easily fixed using microplates or simpyl steel wires.

ILLUSTRATIVE CASE

A 20-year-old man was referred for cranioplasty (Fig 2a, b). The patient had undergone a ventriculoperitoneal shunt operation at the age of 11 for the treatment of post-traumatic hydrocephalus. Three months later a left frontoparietal subdural haematoma was encountered due to overshunting and evacuated through a left frontoparietal craniectomy. He than had four unsuccessfull cranioplasty operations, using alloplastic material and autogenous bone, each ending up with a greater bony defect. The patient had no neurologic symptoms, and the preoperative axial (Fig.3a) and coronal (Fig.3b) MR images showed large bony defect with sequestered bone graft and porencephalic areas underneath. The patient was operated, sequestered rib

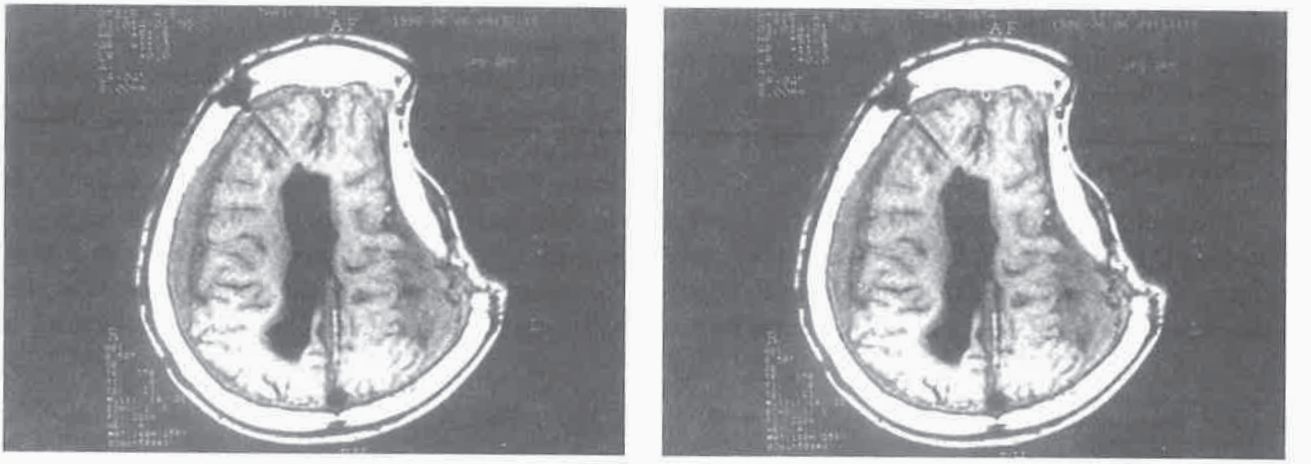

Fig. 3(a-b). Pre-operative contrast enhanced axial and coronal MRI demonstrate large cranial defect area with sunken split rib graft cranioplasty and porencephalic area underneath.

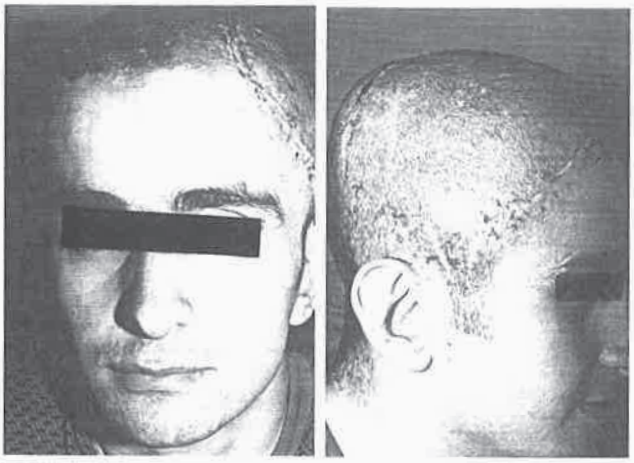

Fig. 4(a-b). Post-operative views of the patient with excellent cosmetic result.

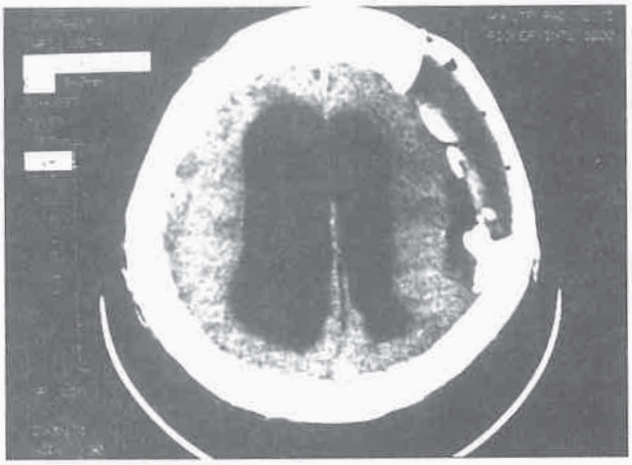

Fig. 5. Post-operative CT demonstrating precisely fitting cranioplasty.

grafts were removed and cranioplasty was performed using the described technique. Excellent cosmetic result was achieved (Fig 4a,b) and the patient was discharged in the first post-operative week. CT scan at the first post-operative month demonstrates the precise fitting cranioplasty with natural looking curvature (Fig.5).

DISCUSSION

The indications, timing, material of choice and operative approach for cranioplasty is beyond the scope of this article. We decsribe a two-staged operative procedure that is simple, cost effective and gives excellent cosmetic results. All of the materials used throughout the procedure can be easily obtained in a standart hospital setting. The first stage of the procedure, that is pre-operative moulding, takes about an hour. This, at the end, gives the opportunity and advantage of pre-wieving the final post-operative cosmetic result and enables the surgeon to modify the plaster cast if needed. During the operation, the surgeon can work relaxed and confident of the result as he will have the pre-modelled and checked plaster cast available. The polymerisation stage of methylmetharcrylate will take place on the plaster cast, away from the surgical field, so the patient is protected from its deleterious effects (4). After trimming, the finished implant may be fixed using micro-plates or steel wires that does not interfere with CT or MRI in the follow-up.

CONCLUSION

Cranioplasty using the here described, two staged, technique is simple, safe, yet effective and can be advocated for the reconstruction of large and difficult cranial bony defects.

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A CASE REPORT: URETERAL TRIPLICATION SEEN ALONG WITH IPSILATERAL URETEROCELE

Talat Yurdakul* • Giray Karalezli* • Kadir Karabacak**

SUMMARY

The fourth case of ureteral triplication associated with ipsilateral ureterocele is reported. Weigert-Meyer law was not valid for this case.

Key words: *Congenital anomaly, Surgery, Ureterocele, Ureteral triplication*

Ureteral triplication is a rare anomaly of the urogenital system. It is frequently seen with other congenital anomalies. Calculus formation, urinary infection and incontinence predisposition may also be peresent(1). We are presenting a case in which ureteral triplication is seen along with ipsilateral ureterocele.

CASE REPORT

A 6 year old girl applied to our urology department with complaints of recurrent urinary infections and occasional prolapsus of ureterocele from the urethra.

IVP revealed a duplex kidney image on the left. The upper segment had no function. The lower segment showed ureterohydronephrosis (Fig la). The right kidney and ureter were normal. Renal ultrasound confirmed the duplex kidney. Ureterocele in the left trigone with 4x4 cm dimensions was seen in cystoscopy. Ureteral orifices could not be seen clearly during cystoscopy because of the mass of the ureterocele and mucosal edema. There was a filling defect on the left, showing ureterocele in retrograd cystography (Fig 2). There was no reflux during retrograde cystography. No other congenital anomalies was found on further examinations.

Ureteroneocystostomy operation was performed individually to both ureters without changing their po-

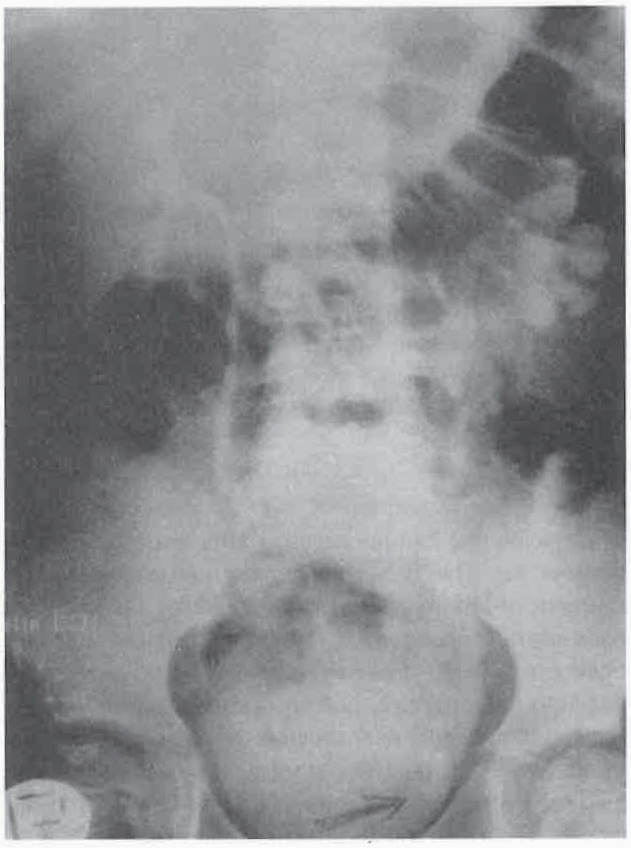

Fig. 1a. Plain graphy 2 weeks postoperatively shows the position of the ureteral stents. This film reveals Wegert-Meyer Law is not valid in this case.

* Associate Professor in Urology, University of Selçuk, Schooll of Medicine, Department of Urology
** Resident in Urology, University of Selçuk, School of Medicine, Department of Urology

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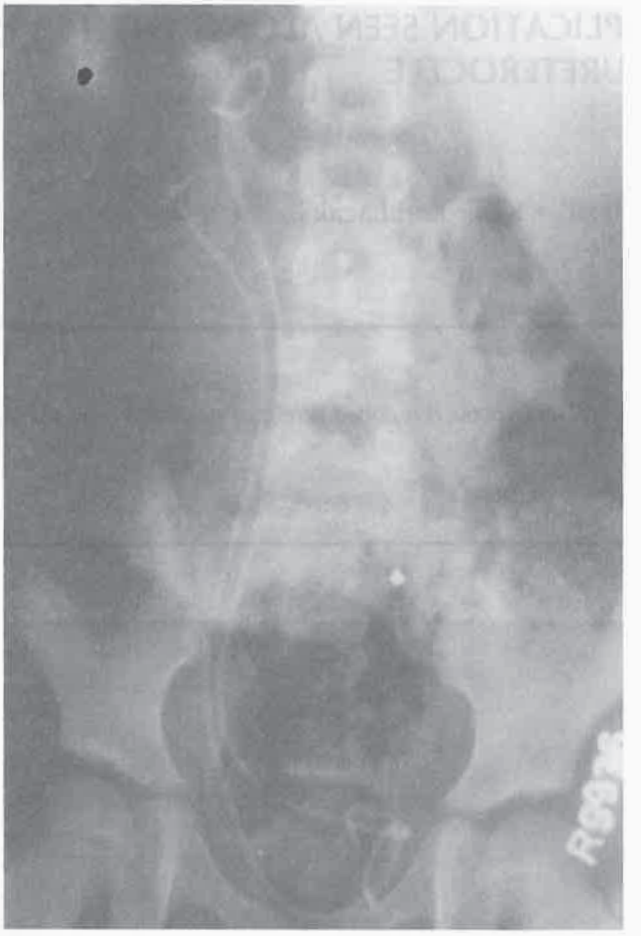

Fig. 1b. IVP shows dilated lower segment and ureteral dilatation of this segment.

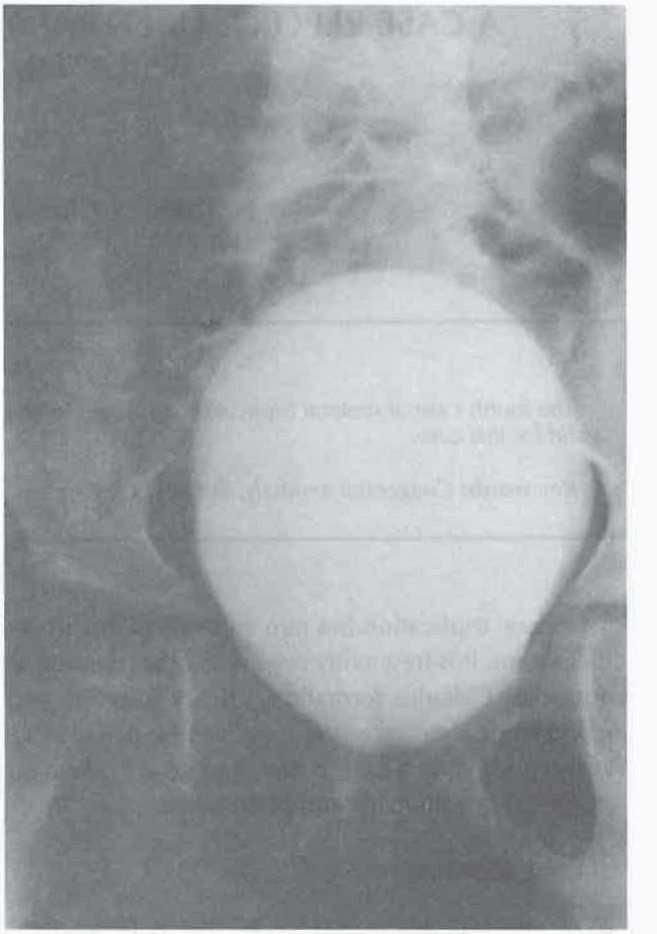

Fig. 2. Cystography showjs the filling defect of ureterocele on the left.

sition with the Paquin method after excision of the ureterocele. The ureterocele belonged to the lower segment of kidney ureter in the bladder. During preparation of this ureter a thin tubular structure was noticed on it. A 3F ureteral catheter was advanced 20 cm. into the structure, but no urine came out (Fig 3). For histopathologic examination one centimeter of the ureter was excised. Histopathologic examination revealed uroepithelium and muscular layers similar to ureter (Fig 4). On the postoperative plain graphy position of the ureter catheters revealed Weigert-Meyer law was not valid for this case (Fig 1b).

DISCUSSION

Smith described four different type ureteral triplications (2).

1. 3 ureters and 3 ureter orifices (ureteral triplications)
2. 3 ureters and 2 ureteral orifices (double ureter one of which is a bifide)
3. 3 ureters and 1 ureteral orifice (tripide ureter)
4. 2 ureters and 3 ureteral orifices (double ureter which shows inverse Y bifurcation)

Although we were not able to observe the third ureteral orifice due to the size of the ureterocele. This case may be classified as type I or type II along with ipsilateral ectopic ureterocele. There are also some triplication cases with blind end ureters in the literature(3). Altough a retrograd pyelography wasn't done during the operation, the third ureter might belong to either an aplastic or a very highly dysplastic kidney.

Among 75 ureteral triplication cases, contralateral duplication was the most common anomaly (22 cases). Ectopic ureter (18 cases) and renal dysplasia (5

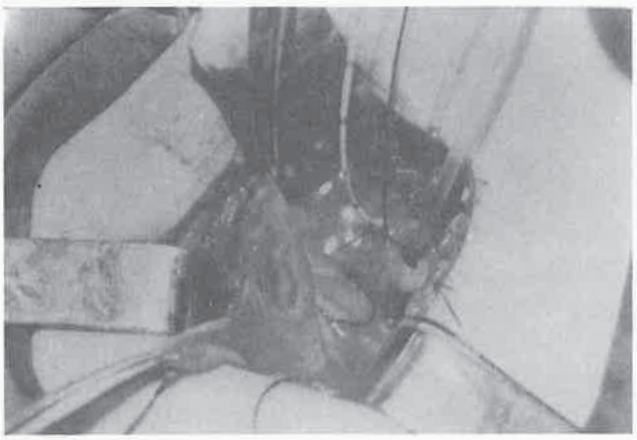

Fig. 3. The photography which was taken during the operation showing triple ureters associated with ureterocele

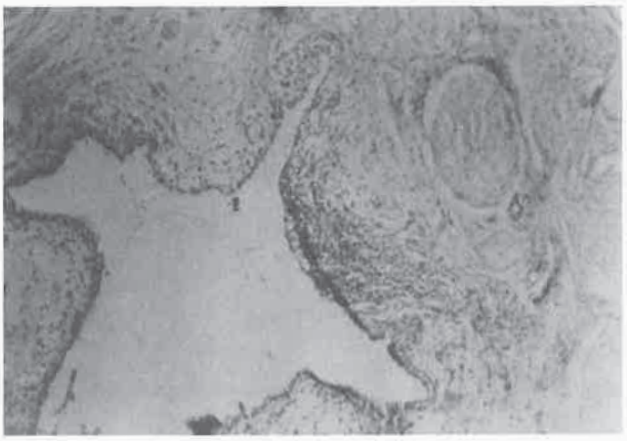

Fig. 4. Transitional epitelium covering the ureteral lumen and ureteral mucles (x100)

cases) followed(4). In following years, bilateral amastia and VACTERL syndrome were published with triplication (5, 6). In Perkins' study in which 60 cases were evaluated, only one ureterocele case was reported with triplication. Contralateral ureterocele was stated with type 3 triplication. In the same study 5 cases were found not to be consistent with Weigert-Meyer law(1). The same situation was also valid for Rich's case(5). Similary, Weigert-Meyer law is not valid for our case.

Rich reported an ipsilateral ureterocele with triplication showing otozomal dominant transmission of bilateral amastia(5). Ipsilateral ureterocele is also present in the triplication phenomenia reported by Verdu(7). In both cases, the 3rd ureter belonged to the dysplastic segment. In another case, ipsilateral ureterocele was observed in combination with complete ureteral triplication(8). We are reporting the 4th ipsilateral ureterocele case which is seen in combination with ureter triplication.

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