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Semra Kocabıyık*

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Key Words: Gentamicin resistance, Resistance plasmids.

Introduction

The excessive and uncontrolled use of aminoglycosides-gentamicin in particular, has led to emergence of resistance to these agents in Gram-negative bacilli.[1-3] The aminoglycoside resistance in clinical strains is usually attributed to the presence of modification enzymes.[4-6] Situation of the structural genes of these enzymes on plasmids and/or transposons has greatly increased their spread throughout the family *Enterobacteriaceae* and *Pseudomonas* species.[7-11]

During 1983 and 1984 we noted an alarming increase of gentamicin resistant *Enterobacteriaceae* and *Pseudomonas* strains at the Hacettepe University Hospital in Ankara, and reported ANT (2″) and AAC (3)-II as the predominating modification enzymes involved.[12, 13] This study was undertaken to analyze the plasmids and cross-resistance patterns of such strains, there by achieving the characterization of the R-plasmids transferred.

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Introduction

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Materials and Methods

Hundred and three gentamicin resistant (MIC $\geqslant$ 8 µg/ml) Gram-negative bacilli included in this study (59 exhibiting ANT (2″) profile and 44 exhibiting AAC (3)-II profile) were recieved at the Hacettepe University Hospital, Ankara (Turkey) from June through September 1984. During the collection period, 50.5 % of the Gram-negative bacilli was recorded to be gentamicin resistant.

Antibiotic susceptibilities of the strains were determined by the disk diffusion method of Bauer *et al.*[14] Minimum Inhibitory Concentration (MIC) determinations were carried out by the conventional tube dilution method.[15]

Aminoglycoside modification enzymes, in crude cell-free preparations were analyzed by the Phosphocellulose Paper Binding Assay as described by Haas and Dowding.[16]

Transferribility of the resistance markers was examined by broth mating.[6] Transfer frequency was expressed as the number of transconjugants per initial donor cell per milliliter after 18 h at 37°C.

Plasmid DNA was isolated by the alkaline lysis method of Takahashi and Nagano[17] and analyzed by agarose gel electrophoresis on an horizontal apparatus. Plasmids from *E. coli* V_{517} (Molecular weights of 35.8; 4.8; 2.6; 1.8 and 1.4 M dal), plasmid R 40 a (96 M dal) and plasmid R_{27} (112 M dal) were used as standards in size estimation.

Plasmid curing experiments were performed by incubation of bacteria at 37°C for 24 h in Nutrient Broth (Oxoid) containing 5 µg/ml mitomycin C (Sigma).

Results

Initial analysis of the plasmid DNA from the resistant isolates, although revealed a heterogeneous plasmid population (sizes ranged between 1.2 to 112 M dal) Table I, three plasmid species (35, 60 and 70 M dal) were more frequently isolated as compared to others. 35 M dal plasmids were usually harbored by the strains possessing AAC (3)-II enzyme, while 60 M dal plasmids were mostly encountered in the strains having ANT (2″) activity. 70 M dal plasmids, on the other hand, were frequently isolated from the strains exhibiting either of the modification enzymes.

Table II documents the resistance patterns, plasmid contents of the parental and transconjugant strains, and the transfer frequencies for the selective marker (gentamicin). Penicillin G (Pen G) /gentamicin

TABLE I

DISTRIBUTION OF THE PLASMIDS OF DIFFERENT MOLECULAR SIZES

Plasmid (Size in Md)	Number (%)[a]		Percent of Strains[b]	
	AAC(3)-II	ANT(2'')	AAC(3)-II	ANT(2'')
1.2	1 (3.1)	–	5.3	–
2.0	1 (3.1)	1 (1.4)	5.3	3.4
2.2	–	1 (1.4)	–	3.4
2.3	–	2 (2.7)	–	6.9
2.6	–	1 (1.4)	–	3.4
2.7	–	3 (4.1)	–	10.3
3.5	1 (3.1)	1 (1.4)	5.3	3.4
3.6	–	1 (1.4)	–	3.4
4.2	1 (3.1)	6 (8.2)	5.3	20.7
4.4	1 (3.1)	4 (5.5)	5.3	13.8
4.6	–	1 (1.4)	–	3.4
4.8	–	2 (2.7)	–	6.9
5.2	1 (3.1)	2 (2.7)	5.3	6.9
7.0	2 (6.3)	–	10.5	–
7.6	–	1 (1.4)	–	3.4
8.0	–	2 (2.7)	–	6.9
9.0	–	1 (1.4)	–	3.4
9.8	–	3 (4.1)	–	10.3
10.5	–	2 (2.7)	–	6.9
12.0	–	2 (2.7)	–	6.9
13.0	1 (3.1)	–	5.3	–
15.0	2 (6.3)	2 (2.7)	10.5	6.9
16.5	1 (3.1)	1 (1.4)	5.3	3.4
19.0	–	2 (2.7)	–	6.9
20.0	–	1 (1.4)	–	3.4
22.0	–	1 (1.4)	–	3.4
26.0	–	1 (1.4)	–	3.4
32.0	1 (3.1)	3 (4.1)	5.3	10.3
35.0	7 (21.9)	3 (4.1)	36.8	10.3
35.8	3 (9.4)	–	15.8	–
46.0	1 (3.1)	2 (2.7)	5.3	6.9
60.0	1 (3.1)	8 (11.0)	5.3	27.6
70.0	6 (18.8)	6 (8.2)	31.6	20.7
80.0	–	3 (4.1)	–	10.3
88.0	1 (3.1)	2 (2.7)	5.3	6.9
112.0	–	2 (2.7)	–	6.9
TOTAL	32 (100.0)	73 (100.0)		

a) % of total plasmid collection of AAC(3)-II AGRP (total 32) or ANT(2'') AGRP (total 73).

b) % of 19 strains exhibiting AAC(3)-II AGRP and 29 strains exhibiting ANT(2'') AGRP, which carry plasmids of the given sizes.

TABLE II

CONJUGAL TRANSFER OF ANTIBIOTIC RESISTANCE MARKERS AND R-PLASMIDS FROM THE STRAINS EXHIBITING ANT(2") AND AAC(3)-II ACTIVITIES

Donor Strains	Resistance Patterns of Donors *	Plasmid (s)of Donor Strais * (M dal)	Transfer Frequency for Gm
of AAC(3)-II AGRP			
E.coli			
HT 84159	Pen G, Gm,Tm,Km,Neo,Sm,Nm,Clm,Cep	70	$6x10^{-4}$
Enterobacter spp			
HT 832	Pen G,Gm,Tm,Km,Sm,Nm, Chl,Cep,Tet	70	$1x10^{-5}$
HT 834	Pen G,Gm,Tm,Km,Sm,Nm,Chl,Cep,Tet	46,15,7,4.4	$7x10^{-5}$
HT 8461	Pen G,Gm,Tm,Km,Sm,Nm, Chl,Cep,Tet	70,3.5	$2x10^{-6}$
Klebsiella sp			
HT 8445	Pen G,Gm,Tm,Km,Sm,Nm,Chl,Cep	70	$1x10^{-1}$
Proteus spp			
HT 8443	Pen G,Gm,Tm,Km,Neo,Sm,Nm,Chl,Cep,Tet	35	
HT 8467	Pen G,Gm,Tm,Km,Neo,Sm,Nm,Chl,Cep,Tet	70,35	$8x10^{-4}$
Citrobacter sp			
HT 8434	Pen G,Gm,Tm,Km,Neo,Sm,Nm,Chl,Cep,Tet	70,35	$8x10^{-4}$
of AnT(2")AGRP			
E.coli			
HT 84119	Pen G,Gm,Tm,Km,Sm,Chl,Cep	70,8,4.6,3.6	$1x10^{-6}$
HT 84124	Pen G,Gm,Tm,Km,Neo,Sm,Chl,Cep,Tet	80,60	$3x10^{-4}$
Enterobacter spp.			
HT 8449	Pen G,Gm,Tm,Km,Sm,Chl,Cep	60	$1x10^{-5}$
HT 8465	Pen G,Gm,Tm,Km,Sm,Chl,Cep	60,22,10.5,9.8,4.2,2.3	$5x10^{-6}$
HT 84107	Pen G,Gm,Tm,Km,Sm,Chl,Cep,Tet	80,35,12,8,5.2,4.4,2.7	$3x10^{-6}$
Klebsiella spp.			
HT 8455	Pen G, Gm,Tm,Km,Sm,Chl,Cep	70	$1x10^{-5}$
HT 8456	Pen G,Gm,Tm,Km,Sm,Chl,Cep,Tet	70	$6x10^{-2}$
Proteus spp.			
HT 831	Pen G,Gm,Km,Sm,Chl,Cep,Tet	35,10.5, 5.2, 4.2	
HT 8478	Pen G,Gm,Tm,Km,Neo,Sm,Chl,Cep,Tet	80	$1x10^{-3}$
Citrobacter sp			
HT 8446	Pen G,Gm,Tm,Km,Sm,Chl.Cep,Tet	60	$1x10^{-2}$

Pen G= Penicillin G; Gm= Gentamicin; Tm= Tobramycin; Km= Kanamycin; Neo= Neomycin; Sm= Streptomycin; Chl= Chloramphenicol; Cep= Cephalothin; Tet= Tetracycline; Nm= Netilmicin; Nal= Nalidixic acid.

* Transferred markers and plasmid (s) are underlined.

(Gm)/tobramycin (Tm)/kanamycin (Km)/streptomycin (Sm)/chloramphenicol (Chl)/cephalothin (Cep) resistance was found to be a common resistance profile for the donor strains. Plasmids of 46, 60, 70 and 80 M dal in sizes were conjugative, (Figure 1) and shared the common resistance profile of the population. Transfer of the multiple resistance profile from *E. coli* to *E. coli* and from other genera of *Enterobacteriaceae* to *E. coli* was achieved in most of the crosses made. Transfer frequencies ranged between $1x10^{-1}$ to $1x10^{-6}$. Co-transfer of Tm and Pen G resistances with Gm resistance was intriguing. Neo^r and Tet^r, however, usually segregated from Gm^r in conjugal transfers.

TABLE III

COMPARISON OF MICs FOR FOUR AMINOGLYCOSIDES (Gm, Tm, Ak, Nm) IN PARENTAL AND TRANSCONJUGANT STRAINS

Bacterial Strains	MIC (μg/ml) Gm	Tm	Ak	Nm
Donors are of AAC (3)-II AGRP				
Escherichia coli				
HT 84159	> 64	32	2	64
Enterobacter spp				
HT 832	> 64	> 64	16	32
HT 834	> 64	> 64	4	16
Klebsiella sp.				
HT 8445	> 64	32	2	16
Citrobacter sp				
HT 8434	> 64	64	8	16
Transconjugants				
E. coli K-12 nal^r				
(HT 84159)	> 64	> 64	< 4	16
Enterobacter K-12 nal^r				
(HT 832)	> 64	> 64	< 4	16
(HT 834)	> 64	32	< 4	8
Klebsiella K-12 nal^r				
(HT 8445)	64	< 4	< 4	16
Citrobacter K-12 nal^r				
(HT 8434)	> 64	64	< 4	64
Donors are of ANT (2″) AGRP				
E. coli				
HT 84119	16	32	4	1
HT 84124	> 64	> 64	4	4
Enterobacter spp				
HT 8449	32	16	2	4
HT 8465	32	32	1	0.5
HT 84107	> 64	32	2	2
Klebsiella spp				
HT 8455	32	16	1	1
HT 8456	> 64	64	4	2
Proteus sp				
HT 8478	8	64	16	1
Citrobacter sp				
HT 8446	> 64	> 64	2	4
Transconjugants				
E. coli K-12 nal^r				
(HT 84119)	64	> 64	< 4	< 4
(HT 84124)	> 64	> 64	< 4	4
Enterobacter K-12 nal^r				
(HT 8449)	64	64	< 4	< 4
(HT 8465)	> 64	> 64	< 4	< 4
(HT 84107)	> 64	> 64	< 4	< 4
Klebsiella K-12 nal^r				
(HT 8455)	> 64	> 64	> 4	> 4
(HT 8456)	> 64	64	< 4	16
Proteus K-12 nal^r				
(HT 8478)	64	> 64	< 4	< 4
Citrobacter K-12 nal^r				
(HT 8446)	> 64	> 64	< 4	< 4

Substrate profiles for AAC (3)-II and ANT (2″) AGRPs, are Gm^r Tm^r Ak^s Nm^r and Gm^r Tm^r Ak^s Nm^s, respectively, MIC break point for Gm, Tm and Nm is 8μg/ml, or Ak is 32μg/ml.

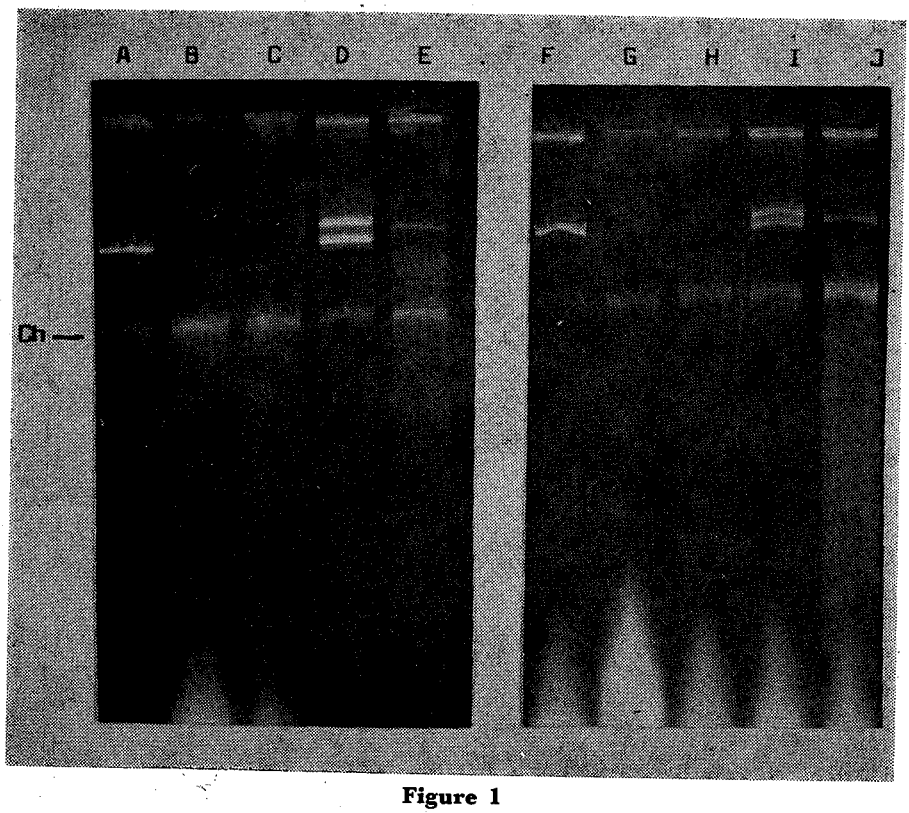

Figure 1

Representative results of R-plasmid transfer studies. Lanes (A and F), 55 Md plasmid of recipient *E. coli* K-12 nal^r; (B and C), marker plasmid R 27 (112 Md); (D) Nal^r Gm^r transconjugants containing a 80 Md plasmid from Gm^r donor; (E), Donor *Proteus* HT 8478 with a 80 Md plasmid; (G), *E. coli* C 600 (plasmidless); (H), marker plasmid R40a (96.0 Md); (I), Nal^r Gmr transconjugants containing a 60 Md plasmid from Gm^r donor; (J), Gmr donor *Klebsiella* HT 84101 with a 60 Md plasmid. Ch: Chromosomal DNA.

Neither the transfer nor the mobilization of the 35 M dal plasmids and low molecular weight plasmids ($\leqslant$ 15 M dal) was achieved under the experimental conditions.

As well as the substrate profiles, enzymatic activities [ANT (2″) or AAC (3)-II] of the donor strains were almost always sustained in the respective transconjugants Table III.

The loss of the R-plasmids, upon curing, usually accompanied with the loss of enzyme activities. However, 3 plasmidless strains (out of 50) still displayed the modification activities of the original strains.

Discussion

In Turkey, various *in-vitro* susceptibility studies of the antibiotic resistance in clinical isolates have been performed by disk-diffusion method and practically no data is available for their plasmids and transfer properties.[12, 13] In the present study, data regarding the plasmid isolations conducted together with the conjugation experiments suggested that the gentamicin resistance is mediated by a variety of physically distinct plasmids (Table II). Among these, specific emphasis was given to a 70 M dal plasmid since it was the most frequent one among the other R-plasmids, and was harbored by the strains possessing either ANT (2″) or AAC (3)-II enzymes.

The results, although indicated that R-plasmid associated modification plays a significant role in dissemination and establishment of the gentamicin resistance under study, there is evidence for the chromosomal location(s) specifying the resistance: that is, after plasmid curing gentamicin resistance could still be retained. The possibility that the determinants may be either chromosomal or plasmid-linked further suggests that the gentamicin resistance under study could be transposon associated. Moreover, diversity in the molecular weights of the gentamicin resistance plasmids that I have isolated and those reported so far[18-20] supports this notion.

REFERENCES

1. Cross AS, Opal S. Progressive increase in antibiotic resistance of Gram-negative bacterial isolates. Arch Intern Med. 1983; 143: 2075-80.
2. Houovinen D, Gronroos P, Herva E, et al. Aminoglycoside resistance among blood culture isolates. J Clin Pathol. 1984; 20: 65-9.
3. Kramery V, Janouskova J, Calpas S, et al. Computer monitoring of gentamicin resistance in Chechoslovakia from 1972 to 1982. Eur J Clin Microbiol. 1984; 3: 42-3.
4. Davies J, Smith DI. Plasmid-determined resistance to antimicrobial agents. Ann Rev Biochem. 1978; 32: 496-518.
5. Minshew BH, Holmes RK, Sonforn JP, et al. Transferrable resistance to tobramycin in Klebsiella pneumoniae and Enterobacter cloaceae associated with enzymatic acetylation of tobramycin. Antimicrob Agents Chemother. 1974; 6: 492-7.
6. Mendazo MC, Blance MG, Mendez FJ, et al. Evalution de la resistance aux aminoside chezdes souches hospitalieres de Serratia. Path Bio. 1984; 32: 750-4.
7. Courvailin P, Carlier C. Resistance towards aminoglycoside-aminocyclitol antibiotics in bacteria. Antimicrob Agents Chemother. 1981; 8: 57-9.
8. Mazodier P, Graud E, Gasser F. Genetic analysis of the streptomycin resistance encoded by Tn 5. Mol Gen Genet. 1983; 192: 155-62.

9. Brau B, Pilz U, Piepersberg W. Genes for gentamicin (3)-N-Acetyltransferases III and IV: 1. Nucleotide sequences of the AAC(3)-IV gene and possible involvement of an IS 140 element in its expression. Mol Gen Genet. 1984; 193: 179-87.
10. Townsend DE, Ashdown N, Greed LC, et al. Transposition of gentamicin resistance to cationic agents. J Antimicrob Chemother. 1984; 14: 115-24.
11. Kotarski SF, Merriwether TL, Tkalcevic GT, et al. Genetic studies of kanamycin resistance in Champlyobacter jejuni. Antimicrob Agents Chemother. 1986; 30: 225-30.
12. Akalın HE, Lolans V. Comparison of enzyme mediated aminoglycoside resistance in Gram-negative bacilli isolated in Turkey and the United States. J Infect Dis. 1983; 148: 1128-31.
13. Kocabıyık S, Akalın E, Alaeddinoğlu NG. Aminoglycoside resistance profiles of gentamicin resistant strains of Enterobacteriaceae and Pseudomonas. 15th International Congress of Chemotherapy. Abstract No. 451, Istanbul, 1987.
14. Bauer AW, Kirby WM, Sherris JC, et al. Antibiotic susceptibility testing by standardized single disk method. Am J Clin Pathol. 1966; 45: 493-6.
15. National Committe for Clinical Laboratory Standards. Methods for dilution antimicrobial susceptibility test for bacteria that grow aerobically. NCCLS: Villanova PA, 1985.
16. Haas DJ, Dowding JE. Aminoglycoside modifying enzymes. Methods in Enzymology. 1975; 43: 611-28.
17. Takahashi S, Nagano Y. Rapid procedure for isolation of plasmid DNA and application to epidemiological analysis. J Clin Microbiol. 1984; 20: 608-13.
18. Townsend EE, Grubb WB, Ashdown N. Gentamicin resistance in methicillin-resistant Staphylococcus aureus. Patholgy. 1983; 15: 169-74.
19. Jaffe HW, Sweeney HM, Nathan C. Identity and interspecific transfer of gentamicin-resistance plasmids in Staphylococcus aureus and Staphylococcus epidermidis. J Infec Dis. 1980; 141: 738-47.
20. Zervos MJ, Mikesell TS, Schaberg DR. Heterogeneity of plasmids determining high-level resistance to gentamicin in clinical isolates of Streptococcus faecalis. Antimicrob Agents Chemother. 1986; 30: 78-81.

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Effect of 50 % Proximal Small Bowel Resection on Gastric Prostaglandin-E Like Activity in Rats

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Summary

The effect of 50 % proximal small bowel resection on prostaglandin E_2(PGE_2) like activity was determined in rat gastric mucosa. This study was performed in 30 rats divided into three groups: Group I, control; group II, sham operation and group III, 50 % proximal small bowel resection. The PGE like activity in the rat gastric mucosa decreased ($p < 0.01$) and the total gastric acidity increased significantly ($p < 0.001$) with 50 % proximal small bowel resection when compared to the control and sham operation groups. The results suggest that endogenous prostaglandin synthesis may play a role in gastric hyperacidity after 50 % proximal small bowel resection.

Key Words: Small bowel resection, Gastric hypersecretion, endogenous prostaglandins.

Introduction

It has been demonstrated both in clinical and experimental studies that gastric acid secretion increases with massive small bowel resection.[1-4] The impairment of an intestinal inhibitory mechanism has been most frequently suggested to explain this hypersecretion.[5-7] The role of endogenous prostaglandins is not established.

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Prostaglandins are found in high concentration in the gastric mucosa and gastric juice and a variety of its pharmacological actions have been demonstrated. Thus, prostaglandins have been shown to alter smooth muscle activity, intestinal and gastric secretion.[8,9] The physiological role of prostaglandins is still being elucidated.

It is considered that the prostaglandins can be affected indirectly by small bowel resection and may alter gastric acidity. The aim of this study was to determine the effect of 50 % proximal small bowel resection on gastric prostaglandin-E_2(PGE_2) like activity in rats.

Materials and Methods

Thirty Swiss-Albino rats of both sexes, weighing 100 to 200 g were studied. Animals were divided into three groups. The first group served as unoperated controls, the second group was sham operated and comprised the second series of control animals, and the third group underwent a 50 % resection of the proximal small intestine.

Twelve hours before surgery, animals were weighed and then deprived of food. After anesthetizing with intraperitoneal sodium pentobarbital (5 mg/100 g b.w.), the rats were subjected to the operative procedures using a midline laparotomy. The entire small bowel from the ligament of Treitz to the ileocecal junction was exteriorized, and the length of the jejunum and ileum was measured using slight tension. The rats in the first group did not have any surgery and served as unoperated controls. In the second group sham operation consisted of transection and reanastomosis of the small bowel at the distance of 2 cm from the ligament of Treitz. In the third group 50 % of the small intestine was resected beginning 2 cm distal to the ligament of Treitz. The remaining intestine was anastomosed by an end-to-end entero-enterostomy. After surgery, the animals were allowed water; however, they were fasted for an additional 24 hr and then fed a standard rat chow diet ad libitum.

A fifteen day recovery period was permitted following the operations, since the amount and type of gastric secretion fluctuates considerably in the early postoperative days.[6] After this period all animals had gastric secretory studies performed by the Shay and Sun pylorus ligation technique.[10] Total gastric acid was measured in the collected gastric juice by titration with 0.1 N NaOH using phenol red as an indicator. Following storage at -20°C of gastric fundus, prostaglandin extraction was performed using the method previously described by Coceani and co-workers.[11] The PGE_2 like activity was determined in each gastric sample by a standard bioassay method.[12]

The significance of the data was evaluated using the Student's t-test.

TABLE I
TOTAL GASTRIC ACIDITY AND THE PGE_2 LIKE ACTIVITY OF THE GASTRIC MUCOSA

	Total gastric acidity (mEq/L)	PGE_2 like activity (ng/g tissue)
Control (n: 10)	16.40 ± 1.55*	2.04 ± 0.27
Sham (n: 10)	14.10 ± 2.15	1.63 ± 0.16
Resected (n: 10)	67.90 ± 5.72	1.04 ± 0.09
Resected vs. control	$p < 0.001$	$p < 0.01$
Resected vs. sham	$p < 0.001$	$p < 0.01$
Control vs. sham	NS**	NS

* Values are means ± SEM ** NS, not significant

Results

Total gastric acidity (mEq/L): The total gastric acidity increased significantly with 50 % proximal small bowel resection when compared to the control and sham operation ($p < 0.001$). There was no significant difference in total gastric acidity between the control and sham operation groups ($p > 0.05$).

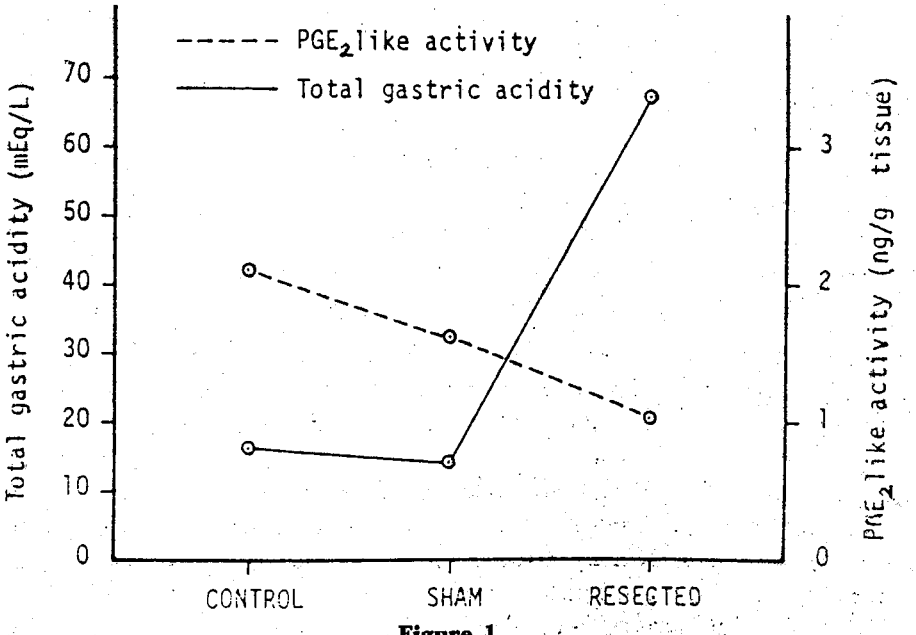

Figure 1
Comparisons between total gastric acidity and PGE like activity of the gastric mucosa.

Prostaglandin-E_2 like activity (ng/g tissue): The prostaglandin E like activity in rat gastric mucosa decreased significantly with 50 % proximal small bowel resection when compared to the control and sham operation ($p < 0.01$). The difference between the control and sham operation groups was not statistically significant ($p > 0.05$).

The results are summarized in Table I. Comparisons between total gastric acidity and prostaglandin E_2 like activity in the groups of rats are presented in Figure 1.

Discussion

Many investigators have studied gastric acid hypersecretion which is frequently observed after extensive small bowel resection, but the mechanism remains unclear. Several groups of investigators have shown that the degree of gastric acid hypersecretion can be related directly to the amount of small intestine resected.[1, 7] Controversy exists over which segment of the intestine, when removed, produces the more pronounced gastric acid hypersecretion. A greater increase in gastric acid secretion was reported after resection of the proximal small intestine compared with the distal small intestine,[6] whereas others have obtained controversial results.[2]

It has been suggested that gastric acid hypersecretion after massive intestinal resection may result from the removal or reduction of the hormones normally contained in the small intestine which are capable of inhibitory gastric acid secretion.[5, 6, 13]

The role of endogenous prostaglandins is not established after small bowel resection. Prostaglandins are not circulating hormones; and there is ample evidence that these compounds may act physiologically as local regulators of celluler and tissue functions.[9] Several prostaglandins have been shown to inhibit gastric acid secretion which may be caused by a variety of secretory stimuli in animals and man.[8, 9, 14] The precise mechanism of acid inhibition is unknown. Proposed mechanisms include direct action on oxyntic cells, inhibition of gastrin release, alteration in cyclic AMP production, reduction in mucosal blood flow, and stimulation of non-parietal cell secretion.[8]

In our study the PGE_2 like activity in rat gastric mucosa decreased ($p < 0.01$) and the total gastric acidity increased significantly ($p < 0.001$ with 50 % proximal small bowel resection when compared to the control group. The PGE_2 like activity and the gastric acid secretion did not change significantly ($p > 0.05$) with sham operation, demonstrating a specific effect of 50 % proximal small bowel resection. The increase in

gastric mucosa. The work of Soll on isolated parietal cells[15, 16] suggests that PGE_2 decreases histamine-stimulated accumulation of cyclic AMP, as well as secretory activity. This inhibitory effect of prostaglandins on histamine-stimulated acid secretion probably reflects the role of endogenous prostaglandins.[8] Histaminase has been shown to be absent in the gastric mucosa, but occurs in high concentration in small bowel mucosa. A major site of histaminase production is removed by small bowel resection so that there is more histamine available to stimulate the oxyntic cells.[17] The increased levels of histamine caused by lack of histaminase-producing tissue besides the decrease in prostaglandins, which are able to block the effect of histamine on cyclic AMP synthesis, may play a role in gastric hypersecretion after small bowel resection.

The mechanism of the decrease in PGE_2 like activity can not be explained with this study. A substance secreted from the proximal small bowel may well be controlling the endogenous PGE_2 synthesis. With resection of the proximal small bowel the substance may be eliminated which in turn leads to decrease PG synthesis and stimulate gastric acid secretion. The determination of such substance is beyond this study.

These results suggest the involvement of gastric mucosal prostaglandins in the mechanism of gastric hypersecretion which is observed after small bowel resection. The decrease in prostaglandins may be one of the factors involved in this mechanism. Further studies are required to explain the effect of small bowel resection on endogenous prostaglandin secretion.

REFERENCES

1. Frederick PL, Sizer JS, Osborne MP. Relation of massive bowel resection to gastric secretion. N Engl J Med. 1965; 272: 509-14.
2. Osborne MP, Frederick PL, Sizer JS, et al. Mechanism of gastric hypersecretion following massive intestinal resection. Clinical and experimental observations. Ann Surg. 1966; 164: 622-34.
3. Windsor CWO, Fejtar J, Woodward DAK. Gastric secretion after massive small bowel resection. Gut. 1969; 10: 779-86.
4. Landor JH, Baker WK. Gastric hypersecretion produced by massive small bowel resection in dogs. J Surg Res. 1964; 4: 518-22.
5. Ruderman RL, Kamel I. Intestinal control of gastric hyperacidity. Surg Gynecol Obstet. 1972; 134: 637-9.
6. Santillana M, Wise L, Schuck M, Ballinger WF. Changes in gastric acid secretion following resection or exclusion of different segments of the small intestine. Surgery. 1969; 65: 777-82.
7. Buxton B. Small bowel resection and gastric acid hypersecretion. Gut. 1974; 15: 229-38.

8. Cohen MM. Role of endogenous prostaglandins in gastric secretion and mucosal defense. Clin Invest Med. 1987; 10: 226-31.
9. Wilson DE, Kaymakçalan H. Prostaglandins: Gastrointestinal effects and peptic ulcer disease. Med Clin North Am. 1981; 65: 773-87.
10. Shay H, Sun DCH, Gruenstein M. A quantitative method for measuring spontaneous gastric secretion in the rat. Gastroenterology. 1954; 26: 906-13.
11. Coceani F, Pace-Asciak C, Volta F, Wolfe LS. Effect of nerve stimulation on prostaglandin formation and release from the rat stomach. Am J Physiol. 1967; 213: 1056-64.
12. Bennett A, Friedmann CA, Vane JR. Release of prostaglandin E_1 from the rat stomach. Nature. 1967; 216: 873-6.
13. Johnson LR, Grossamn ML. Intestinal hormones as inhibitors of gastric secretion. Gastroenterology. 1971; 60: 120-44.
14. Fung WP. Effect of naturel and synthetic prostaglandins on gastric function and peptic ulcer healing. Aust NZ J Med. 1980; 10: 678-81.
15. Soll AH, Wollin A. Histamine and cyclic AMP in isolated canine parietal cells. Am J Physiol. 1979; 237: 444-50.
16. Soll AH. Prostaglandin inhibition of histamine-stimulated aminopyrine uptake and cyclic AMP generation by isolated canine parietal cells. Gastroenterology. 1978; 74: 1146.
17. Caridis DT, Roberts M, Smith G. The effect of small bowel resection on gastric acid secretion in the rat. Surgery. 1969; 65: 292-7.

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The Effects of Nicardipine on Renal Functions

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Summary

18 patients, 4 men, 14 women, aged 33-59 years, with WHO Class I or II essential hypertension were given placebo for the first two weeks and nicardipine, 20 mg t.i.d. orally, for the following four weeks. Nicardipine was compared to placebo. Although supine and standing blood pressures displayed significant decreases, no statistically relevant changes occured in the 24-hour urinary volume, urine biochemistry, clearances of creatinine, calcium and phosphorus and tubular reabsorption of phosphate values at the end of the nicardipine period. A slight rise of the serum uric acid level, which fell within the normal range of the reference laboratory constituted the only difference in blood biochemistry encountered after nicardipine. We conclude that nicardipine has no mentionable effect on renal functions during chronic oral therapy and that its antihypertensive efficacy can not be partially attributed to a diuretic action.

Key Words: Nicardipine, renal functions, 1,4-dihydropyridines, calcium antagonists.

Introduction

Nicardipine is a new 1,4-dihydropyridine calcium antagonist with well-documented antihypertensive efficacy.[1,2] Its potent direct vasodilatory action results in a decrease of the tonus of all arteriolar resistance

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vessels.[3] Studies concerning its renal effects are few and have given debatable results. Abe *et al.*[4] has reported that the intrarenal infusion of nicardipine produces significant increases in renal blood flow and glomerular filtration rate while lowering renovascular resistance in dogs. Rosenkranz *et al.*[5] has described similar changes and a diuretic and natriuretic effect in rabbits. The diuresis, natriuresis and kaliuresis observed in animals with nicardipine has been associated with an increase of glomerular filtration rate, a decrease of tubular sodium reabsorption and alterations in intrarenal hemodynamics.[4] In human trials, an elevation of the glomerular filtration rate has also been claimed in hypertensive[6] as well as normotensive[7] subjects. On the contrary, Chaignon *et al.*[8] has observed no significant differences in renal blood flow or glomerular filtration rate with nicardipine. Young *et al.*[9] has suggested a disparity between the renal consequences of acute and chronic nicardipine administration. Surprisingly, we found no data regarding its impact on the renal excretion of calcium and phosphorus. This trial was planned with the aim of contributing to the understanding of the renal effects of oral nicardipine therapy, including a possible change in urinary calcium and phosphorus levels in patients with mild to moderate essential hypertension.

Materials and Methods

18 patients, 4 men, 14 women, with WHO Class I (10 patients) and II (8 patients) essential hypertension, aged 33-59 (average 48.3) years, hypertensive for 1-180 (average 35.5) months, without metabolic, endocrinologic or systemic disease or any cardiovascular disorder other than hypertension were chosen. Eligibility for inclusion into the study group depended on a supine resting blood pressure value of 140/95 mm Hg or greater and a diastolic pressure between 95-115 mm Hg on three separate occasions. Secondary hypertension was excluded by routine screening (blood urea nitrogen, serum electrolytes and creatinine, urine analysis, abdominal ultrasonography and intravenous pyelography and endocrinologic tests when considered necessary).

11 patients had previously used an antihypertensive drug; 7 patients had not. Clinical characteristics of the participants are presented in Table I. The average age of the patients was 48.3 $\pm$ 1.8 years and they had been recognized as hypertensive for 35.5 $\pm$ 11.1 months; 10 had WHO Class I, 8 had WHO Class II essential hypertension.

All patients gave informed consent. The study was designed as a placebo controlled, single blind trial. All medication was stopped two weeks prior to entrance into the group. No diet restriction was imposed but avoidance from irregularities in diet content was requested. The patients

received a placebo for the first two weeks and nicardipine 20 mg for the following four weeks; each at 8 hour intervals. At the beginning and end of the placebo and at the end of the nicardipine period, blood pressures were measured in the supine and standing state with a standard mercury sphygmomanometer. Pulse rates were counted. 24-hour urine samples were collected with an equal amount of fluid intake (1500 ml/24 hours) and venous blood samples were obtained in the fasting state, two hours after the first morning dose of placebo or nicardipine. 24-hour urine volumes were measured. Urine and serum or blood creatinine, urea, uric acid, calcium, phosphorus, sodium and potassium levels were determined with a biochemical analyzer (Dacos Coulter Electronics Inc. discrete analyzer, Florida, USA).

TABLE I
CLINICAL CHARACTERISTICS OF PATIENTS (n= 18)

Characteristic	
Sex (Male / Female)	4 / 14
Age (Below 45 / Equal to or above 45)	5 / 13
WHO Class of hypertension (I/II)	10 / 8
Duration of hypertension (months)	35.5 ± 11.1 (Range : 1–180)
Age (years)	48.3 ± 1.8 (Range : 33–59)
Weight (kg)	76.3 ± 2.6 (Range : 50.8–94.3)
Height (cm)	157.5 ± 1.7 (Range : 145–176)

Values are the mean ± s.e. of mean.

Clearances of creatinine, calcium and phosphorus and tubular reabsorption of phosphate (TRP) values were calculated using standard formulae. All results were expressed as mean ± standard error. Comparisons between paired data were tested using Student's t-test; a p value less than 0.05 was accepted as significant.

Results

Data obtained during the study are summarized in Table II and III. No statistically relevant change was observed in any parameter with placebo. Although supine blood pressure (mm Hg) fell from 161.9 ± 3.9/104.6 ± 1.7 to 131.3 ± 2.4/88.6 ± 1.5 ($p < 0.001$) and standing blood pressure (mm Hg) decreased from 161.4 ± 3.2/105.8 ± 1.3 to 134.0 ± 2.4/91.4 ± 1.5 ($p<0.001$) at the end of the nicardipine period when compared to the last day of placebo, the pulse rate in any state and the urine parameters did not change with nicardipine.

A slight rise of serum uric acid from 4.41 ± 0.28 to 4.55 ± 0.29 mg/dl($p < 0.05$) was observed after nicardipine but fell within the normal range of the reference laboratory and was accepted as clinically insignificant; the other blood para meters did not display meaningful change with nicardipine.

TABLE II

EFFECTS OF NICARDIPINE ON THE WEIGHT, BLOOD PRESSURE, PULSE RATE AND CERTAIN BLOOD AND SERUM PARAMETERS OF THE PATIENTS (n= 18)

Parameter	First day Placebo	Last day Placebo	Last day Nicardipine	Normal Range of Laboratory
Body weight (kg)	76.3 ± 2.6	75.9 ± 3.2	76.1 ± 2.5 NS	–
Supine systolic blood pressure (mm Hg)	160.9 ± 3.8	161.9 ± 3.9	131.3 ± 2.4**	–
diastolic blood pressure (mm Hg)	103.6 ± 1.7	104.6 ± 1.7	88.6 ± 1.5**	–
pulse rate (beats min^{-1})	76.8 ± 3.1	72.3 ± 2.4	72.2 ± 1.9 NS	–
Standing systolic blood pressure (mm Hg)	160.7 ± 3.3	161.4 ± 3.2	134.0 ± 2.4**	–
diastolic blood pressure (mm Hg)	105.1 ± 1.4	105.8 ± 1.3	91.4 ± 1.5**	–
pulse rate (beats min^{-1})	83.6 ± 3.1	79.2 ± 2.3	80.2 ± 2.1 NS	–
Blood urea nitrogen (mg/dl)	13.6 ± 0.8	12.9 ± 2.9	13.7 ± 0.7 NS	7 – 21
Serum creatinine (mg/dl)	0.91 ± 0.06	0.94 ± 0.03	0.96 ± 0.03 NS	0.6 – 1.8
uric acid (mg/dl)	4.38 ± 0.26	4.41 ± 0.28	4.55 ± 0.29*	3 – 8
calcium (mg/dl)	9.26 ± 0.55	9.71 ± 0.09	9.80 ± 0.14 NS	8.8 – 10.5
phosphorus (mg/dl)	3.38 ± 0.08	3.46 ± 0.10	3.52 ± 0.10 NS	2.2 – 4.5
sodium (mmol/L)	141.7 ± 1.0	142.6 ± 1.1	140.3 ± 1.1 NS	135 – 150
potassium (mmol/L)	4.52 ± 0.08	4.67 ± 0.08	4.52 ± 0.09 NS	3.5 – 5.3

Values are the mean ± s.e. of mean. Levels of significance relate to differences from end-placebo values.
*$P < 0.05$ **$P < 0.001$ NS: non-significant

TABLE III

EFFECTS OF NICARDIPINE ON RENAL PARAMETERS (n= 18)

Parameter	First day Placebo	Last day Placebo	Last day Nicardipine	
24-hour urine volume (ml)	1041.1 ± 12.5	1037.8 ± 14.5	1061.6 ± 11.5	NS
urea (mg/dl)	790.0 ± 56.7	813.0 ± 56.2	804.5 ± 51.4	NS
creatinine (mg/dl)	111.3 ± 8.7	111.9 ± 8.5	113.4 ± 8.9	NS
uric acid (mg/dl)	35.5 ± 3.7	36.8 ± 3.2	39.2 ± 3.6	NS
calcium (mg/dl)	19.8 ± 2.8	20.1 ± 2.4	19.3 ± 2.4	NS
phosphorus (mg/dl)	62.1 ± 4.1	62.9 ± 4.5	61.0 ± 4.0	NS
sodium (mmol/L)	131.0 ± 12.1	129.1 ± 12.0	129.9 ± 13.8	NS
potassium (mmol/L)	33.2 ± 3.5	36.3 ± 2.6	32.4 ± 2.2	NS
Creatinine clearance (ml/min)	84.2 ± 4.2	85.6 ± 5.6	86.1 ± 5.3	NS
Phosphorus clearance (ml/min)	13.6 ± 1.2	13.6 ± 1.0	13.3 ± 1.0	NS
Calcium clearance (ml/min)	1.53 ± 0.21	1.48 ± 0.18	1.46 ± 0.19	NS
Tubular reabsorption of phosphate (TRP) (%)	83.1 ± 1.4	83.5 ± 1.4	84.0 ± 1.4	NS

Values are the mean ± s.e. of mean. Levels of significance relate to differences from end-placebo findings. NS : non-significant.

Discussion

A diuretic, natriuretic and kaliuretic effect of nicardipine has been demonstrated in animal trials.[4, 5] A short lasting and moderate diuretic and natriuretic action has also been observed in humans; Van Schaik *et al.*[7] has stated that after 1 week of oral nicardipine at a dose of 20 mg 3 times daily, the urine volume and urinary sodium excretion during water loading measured 2 hours after nicardipine administration increased significantly, compared to placebo, in both normotensive volunteers and in mild to moderate essential hypertensive patients, and that natriuresis was caused by a decrease of the fractional proximal and distal reabsorption of sodium in the normotensive group, and by an increase of the glomerular filtration rate (GFR) and a slight distal effect in the hypertensive group. Yokoyama and Kaburagi[10] demonstrated that IV infusion of nicardipine (33 µg/minute) resulted in a strong diuretic and natriuretic action and an increase of GFR in essential hypertensive patients, while patients with glomerulonephritis had absent (GFR) or less pronounced (sodium excretion and urinary volume) responses. These results suggest that the renal effects of nicardipine may differ with respect to renal pathophysiology and may be more prominent in essential hypertension. But, Baba *et al.*[6] have demonstrated that even though IV (intravenous) nicardipine (0.5 mg) caused an augmentation of renal blood flow, GFR and urinary sodium excretion in patients with mild to moderate essential hypertension, the urinary volume did not change significantly. Also, Van Schaik *et al.*[7] stated that despite the natriuretic and diuretic action observed 2 hours after an oral dose, the decrease in body weight was only 0.2 kg in the normotensive and 1 kg in the hypertensive group at the end of 1 week nicardipine administration; they concluded that the natriuretic effect of nicardipine is short-lasting and partially compensated within 24 hours. Similarly, Young *et al.*[9] have shown that while a natriuretic effect is seen after an acute dose of nicardipine, chronic therapy is not accompanied by a significant diuresis or natriuresis. Our results are in accordance with this last finding; even though 4 patients complained of polyuria during nicardipine treatment, the 24-hour urine volume and sodium, potassium excretion at the end of 4 weeks did not show statistically relevant differences compared to placebo. Most studies have revealed an increase of the plasma renin level after nicardipine[4, 6, 7]; but no change or a slight decrease of plasma aldosterone has been demonstrated.[7, 11] This supports our findings and indicates that nicardipine does not alter the fluid and electrolyte regulating mechanisms of the kidney either by a direct or an aldosterone-mediated effect. This is a superior property in comparison to thiazide diuretics.

We noted no mentionable weight change after nicardipine therapy and decided that nicardipine does not cause sodium and fluid retention, which is a serious problem encountered during the use of many other vasodilators.

We present, to our knowledge, the first data concerning nicardipine's effect on renal calcium and phosphorus excretion. Theoretically, a change of renal calcium excretion could be expected with nicardipine due to inhibition of calcium entry into renal vascular (and perhaps tubular?) cells or in association with its acute natriuretic action; but we found no significant difference in the urinary calcium and phosphorus levels between placebo and nicardipine. Our results, together with the data presented by previous workers, show that nicardipine is an effective antihypertensive agent which may exert a short lasting and moderate diuretic and natriuretic action after an acute dose but does not cause important changes in the renal elimination processes during chronic oral therapy.

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REFERENCES

1. Takabatake T, Ohta H, Yamamoto Y, et al. Antihypertensive effect of nicardipine hydrochloride in essential hypertension. Int J Clin Pharmacol Ther Toxicol. 1982; 20: 346-52.
2. Bellet M, Loria Y, Lallemand A. First-step treatment of mild to moderate uncomplicated essential hypertension by a new calcium antagonist: Nicardipine. J Cardiovasc Pharmacol. 1985; 7: 1149-53.
3. Takenaka T, Nomura T, Sado T, Usuda T, Maeno H. Vasodilator profile of a new 1,4 dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-[2-(N-benzyl-N-methylamino)] ethyl ester 5-methyl ester hydrochloride (YC-93) Arzneimittel Forsch. 1976; 26: 2172-8.
4. Abe Y, Komori T, Miura K, et al. Effects of the calcium antagonist nicardipine on renal function and renin release in dogs. J Cardiovasc Pharmacol. 1983; 5: 254-9.
5. Rosenkranz RP, McClelland DL, Roszkowski AP. Nicardipine and nifedipine: effects on diuresis and serum aldosterone levels in spontaneously hypertensive rats. Proc West Pharm Soc. 1985; 28: 87-91.
6. Baba T, Boku A, Ishizaki T, Sone K, Takebe K. Renal effects of nicardipine in patients with mild to moderate essential hypertension. Am Heart J. 1986; 111: 552-7.
7. Van Schaik BAM, van Nistelrooy AEJ, Geyskes GG. Antihypertensive and renal effects of nicardipine. Br J Clin Pharmacol. 1984; 18: 57-63.
8. Chaignon M, Bellet M, Lucsko M, Rapoud C, Guedon J. Acute and chronic effects of a new calcium inhibitor, on renal haemodynamics in hypertension. J Hypertension. 1985; 3: 535.

9. Young MA, Watson RDS, Stallard TJ, Littler WA: Calcium channel blockers-are they diuretics? Br J Clin Pharmacol. 1985; 20 (Suppl 1): 95S-98S.
10. Yokoyama S, Kaburagi T. Effects of intravenous nicardipine hydrochloride (YC-93), a calium antagonist, on renal function. Jap J Nephrol. 1981; 23: 1143-51.
11. Van Schaik BAM, Hene RJ, Geyskes GG. Influence of nicardipine on blood pressure, renal function and plasma aldosterone in normotensive volunteers. Br J Clin Pharmacol. 1985; 20 (Suppl 1): 88S-94S.

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Coronary Artery Disease in Young Adults

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Summary

Coronary artery disease is an important cause of mortality and morbidity in the young adults. In order to determine the risk factors, early complications and coronary anatomy in patients under 40 years of age, we evaluated 113 patients (105 men and 8 women) with a mean age of 34 who were hospitalized in our coronary care unit between January 1975 and November 1986. We found the major risk factor to be smoking (85 percent), followed by a family history of coronary artery disease (35.4 percent) and hypertension (13.2 percent).

During the coronary care unit phase, 11.5 percent of patients developed congestive heart failure and 5.3 percent ventricular fibrillation. Only 3 died of heart failure.

Of these patients 41.6 percent were evaluated by coronary angiography. According to coronary angiographic anatomy most patients had single vessel disease (44.7 percent) with the left anterior descending artery being the most affected artery.

We conclude that the reversible risk factors should be determined and eliminated in the young age group and invasive revascularization measures be taken early in the course of the disease.

Introduction

Ischemic heart disease continues to be the primary cause of death in industrialized countries. The morbidity and loss of manpower as a consequence of this disease is especially striking at younger age groups.

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It is known that the incidence of myocardial infarction increases with age. Recent studies have shown that the incidence of myocardial infarction in the younger age group is escalating and this has been attributed to stress, smoking, high cholesterol diets and oral contraceptive drugs.[1-6] However, the occurrence of the disease in young people has not been determined precisely yet especially in the developing countries. It has been suggested that the risk factors as well as the occurrence of coronary artery disease varies greatly in different countries.[7]

We therefore reviewed the records of our coronary care unit population and analyzed the data related to 113 patients under 40 years of age in terms of risk factors, complications and coronary angiographic anatomy as a substrate for prevention, treatment and follow up.

Materials and Methods

The patient group consisted of 105 men and 8 women under 40 years of age who had been hospitalized between January 1975 and November 1986 at the Hacettepe University Hospital Coronary Care Unit for chest pain.

The mean age was 34 with a range of 23-39. Ninety seven (86 percent) of the patients presenting with a chest pain were diagnosed to have acute transmural myocardial infarction (diagnosed by WHO criteria including the history of typical chest pain, ECG and serum enzyme changes). The rest of the patients had nontransmural (non-q wave) myocardial infarction or ischemia. A coronary cineangiography was performed in 47 (41.6 percent) of the patients within 6 months following hospitalization for coronary artery disease.

The following parameters were evaluated from the hospital records:

Smoking history, blood pressure, duration of hypertension if it existed, family history, previous history of chest pain prior to the myocardial infarction, weight, height, the wall involved in myocardial infarction according to the ECG changes, fasting blood sugar, cholesterol, triglyceride levels, the immediate complications following the myocardial infarction, aneurysm formation and the results of the coronary angiography.

Results

Eighy-nine (78.7 percent) of the patients denied any chest pain prior to the episode requiring their hospitalization. When the risk factors were questioned it was found that 98 (86.7 percent) patients were smokers of whom 14 (12.3 percent) smoked less than a pack, 56 (49.5 percent) one pack, 28 (24.7 percent) more than one pack per day and 3 (2.6 percent) were ex-smokers.

Forty (35.4 percent) patients had a family history of coronary artery disease.

Fifteen (13.2 percent) patients had a history of hypertension for less than five years. The blood pressure was under control in all but one patient.

Ten (8.8 percent) patients had a body weight of 20 percent more than the ideal body weight. One (0.8 percent) was known to have polycytemia vera. One (0.8 percent) women was using oral contraceptive pills.

Ten patients (8.8 percent) were free of risk factors.

ECG findings: Table I summarizes the ECG findings. Anterior wall myocardial infarction was found to be the most frequent pathology in our series.

TABLE I

SUMMARY OF ECG CHANGES

ECG Changes	Patients (%)
ECG changes associated with anterior wall	51 (45.2)
Anteroseptal myocardial infarction	28 (24.8)
Anterior wall myocardial infarction	23 (20.4)
Inferior myocardial infarction	38 (33.6)
Lateral or high lateral myocardial infarction	4 (3.5)
Inferior ischemia	7 (6.2)
Infero lateral ischemia	4 (3.5)
Anteroseptal ischemia	2 (1.8)
Normal ECG findings but a positive treadmill test	7 (6.2)

Metabolic studies: Of the 113 patients 29 (25.6 percent) were hyperlipidemic with 18 (15.5 percent) patients having hypercholesterolemia and 11 (8.7 percent) having hypertriglyceridemia. Only one (0.8 percent) patient was diabetic and the plasma glucose levels had been regulated by an oral antidiabetic agent.

Immediate complications: The patients were hospitalized for approximately 3 days in the coronary care unit. During this period 13 (11.5 percent) had congestive heart failure and 6 (5.3 percent) patients had ventricular fibrillation. Only 3 (2.6 percent) died of pump failure during this period.

Angina pectoris after myocardial infarction: Seventy two (63.7 percent) patients continued to have angina pectoris after myocardial infarction.

Coronary angiography: A cardiac catheterization and coronary cineangiography was performed in 47 (41.6 percent) patients within 6

months following acute myocardial infarction. It can be seen from Table II that most patients had one vessel lesion and left anterior descending was the leading affected artery. Thirty six (31.8 percent) patients were shown to have a left ventricular aneurysm by angiography.

TABLE II

SUMMARY OF THE CORONARY CINEANGIORAPHY FINDINGS

Coronary cineangiography findings	Patients (%)
Three vessel disease	12 (25.5)
Two vessel disease	12 (25.5)
One vessel disease	21 (44.7)
Left anterior descending artery	16 (34.1)
Right coronary artery	4 (8.5)
Circumflex artery	1 (2.1)
Malformation of right coronary artery	2 (4.3)

Discussion

The risk factors for premature coronary artery disease are similar to the ones in older patients but the evidences from the previous reports have indicated that risk factors are more prevalent in patients below the age 40, while a larger number of patients with no known risk factors exist in the older population.[8-10] It is important to identify these risk factors since they are amenable to change and it seems that premature coronary artery disease may be prevented with strict control of these risk factors.

Because of genetic or enviromental reasons, the risk factors may be different in developed and devoloping countries. We tried to identify the risk factors for our own country and found that smoking was the predominant factor. These findings were similar to the results of a study conducted in 9 countries indicating the major risk factor to be hyperlipidemia in in developed and smoking in developing countries.[11]

It was also interesting to note that 79 percent of our patients had no prior symptoms of angina pectoris before hospitalization.

The early complications during the coronary care unit phase were found to occur at the same rate in both older and young patients.[12, 13] But the coronary angiography revealed different results; the changes in coronary arteries tended to be localized to one vessel only in young patients showing that myocardial infarction was not the end stage advanced coronary artery disease. Interestingly enough, the rate of aneurysm formation was found to be much higher in the young age group.[14]

This shows the need to consider invasive revascularization procedures earlier in this group to prevent further derangement of left ventricular function.

We conclude that the determination and elimination of risk factors early in the course and agressive therapeutical measures can prevent subsequent morbidity and mortality from ischemic heart disease in the younger patient population.

REFERENCES

1. The Pooling Project Research Group: Relationship of blood pressure, serum cholesterol, smoking habit, relative weight and ECG abnormalities to incidence of major coronary events: Final report of the Pooling Project. J Chronic Dis. 1978; 31: 201-306.
2. Slone D, Shapiro S, Rosenberg L, et al. Relation of cigarette smoking to myocardial infarction in young women. N Engl J Med. 1978; 258; 1273-6.
3. Rosenberg L, Shapiro S, Kaufman DW, et al. Cigarette smoking in relation to the risk of myocardial infarction in young women: Modifiying influence of age and predisposing factors. J Epidemiol. 1980; 9: 57-63.
4. Slone D, Kaufman DW, Shapiro S, et al. Risk of myocardial infarction in relation to current and discontinued oral contraceptive use. N Engl J Med. 1981; 305: 420-4.
5. Kaplan AS. Acute myocardial infarction in patients 35 years of age and under. Dis Chest. 1967; 51: 137.
6. Simonson E, Berman R. Myocardial infarction in young people. Am Heart J. 1972; 84: 814.
7. Epstein FH. The epidemiology of coronary heart disease, a review. J Chronic Dis. 1965; 18: 735.
8. Uhe GS, Farell PW. Myocardial infarction in young adults: Risk factors and natural history. Am Heart J. 1983; 105: 548-53.
9. Bergstrand R, Vedin A, Wilhehlsson C, et al. Myocardial infarction among men below age 40. Br Heart J. 1978; 40: 783.
10. Gohlke H, Gohnke-Barwolf C, Sturzenhofecker P, et al. Myocardial infarction at young age-Correlation of angiographic findings with risk factors and history in 619 patients. Circ ulation 1980; 62 (Suppl III): 35.
11. Dolder MA, Oliver MI. Myocardial infarction in young man: Study of risk factors in 5 counties. Br Heart J. 1975; 37: 493-503.
12. Lawrie DM, Higgins MR, Godman MJ, Julian DG, Donald KW. Ventricular fibrillation complicating acute myocardial infarction. Lancet. 1968; 2: 523.
13. Bertrand ME, Rousseau MF, Lablanche JM, Carré AG, Lekieffre JF. Cineangiographic assesment of left ventricular function in the acute phase of transmural myocardial infarction. Am J Cardiol. 1979; 43: 472.
14. Abrams DL, Edelist A, Luria MH, Miller AJ. Ventricular aneurysm: A reappraisal based on a study of 65 consecutive autopsied cases. Circulation. 1963; 27: 164.

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Radiological Anatomy of the Human Hand with Polydactyly

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Summary

In this work, the radiological anatomy of a total of 25 human hand cases with polydactyly was examined, from the hospital archives.

Of these cases, 16 had an extra finger on the radial side of the hand and 9 on the ulnar side. The radial side polydactyly was generally seen on the right hand. In addition, 18 out of 25 cases were observed to be unilateral and 7 were bilateral. All of the 16 radial side polydactyly cases were unilateral. Of the 9 ulnar cases, 7 were bilateral and 2 unilateral.

The frequency of duplication related with particular fingers was observed to be on the thumb, little finger and ring finger. Syndactyly was also observed on the ring finger. During our investigations, no duplication of the middle and index fingers were observed.

Key Words: Polydactyly, Human Hand, Radiological Anatomy.

Introduction

Polydactyly is a condition in which there is more than the usual number of fingers or toes.

Polydactyly, being a hereditary anomaly of the hand or foot, has been known for many years. This anomaly may be found not only in the human race and monkeys, but also in horses, cattle, dogs, cats, guinea pigs, mice, poultry and other animals.[1, 2]

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The extent of polydactyly is highly variable and it is often associated with syndactyly, brachydactyly and with the other congenital anomalies. Generally, the supernumerary digits can be seen as small nubbins of skin, with or without bones; these are usually attached to the ulnar side of the hand. Most commonly the supernumerary digit is rudimentary and has no tendon, but occasionally it is a complete extra digit with metacarpal, tendons and nerves.[1,3-6]

Polydactyly may be a dominant, recessive or intermediate trait, tending to be recessive at first and becoming increasingly dominant through succeeding generations.[4]

Some authors have suggested that blacks are affected with this anomaly ten times more than whites.[7-9] Polydactyly is still endemic in some regions. It was reported that hexadactyly was very usual in an Arabian tribe of Hyabites, even if children born with five fingers were regarded as a deviand and were sacrificed. A person with thirteen fingers on each hand and twelve toes on each foot was also reported as an unusual case. On the other hand, an infant with forty digits, ten on each limb was reported.[1]

Although polydactyly is a congenital anomaly of hand or foot, it can be seen also in various syndromes and even takes an important role in the description of those syndromes.

Published reports indicate that any agent causing a temporary growth discrepancy between the mesoderm and the ectoderm of the preaxial limb bud at the beginning of maximum cell proliferation will result in a high incidence of thumb polydactyly.[10]

Materials and Methods

In our study we examined some patients who had polydactyly on their hands or feet, as described in medical documents from various hospitals. We found a total of 25 cases of the human hand with polydactyly. We also examined their respective roentgenograms. The rates and percentages of bilateral, unilateral on both hands, radial-sided and ulnar-sided of the examined polydactyly cases and also the comparisons among them were carried out.

Results

We examined 25 cases of polydactyly; 18 (72 %) of these were unilateral and 7 (28 %) bilateral. Thus, polydactyly tends to be unilateral (Table I).

14 (77,8 %) out of 18 cases which were found to be unilateral cases were observed on the right hand and 4 (22,2 %) on the left hand. In conclusion, unilateral side polydactyly frequently tends to be on the right hand (Table I, II).

TABLE I
TOTAL POLYDACTYLY APPEARANCE FORMS AND PERCENTAGES

Total Polydactyly	Unilateral	%	Bilateral	%	Right Hand	%	Left Hand	%	Radial Side	%	Ulnar Side	%
25	18	72	7	28	14	77.8	4	22.2	16	64	9	36

TABLE II
COMPARISONS OF POLYDACTYLY APPEARANCE FORMS

	Unilateral	Bilateral	Right Hand	Left Hand
Radial Side	16	–	13	3
Ulnar Side	2	7	1	1

The polydactyly, most commonly is on the radial side of the human hand. 16 (64 %), out of a total of the 25 cases were situated on the radial side and 9 (36 %) were on the ulnar side of the hand (Table II).

All of the radial-sided polydactyly were observed to be unilateral, and also were found commonly on the right hand (13). 3 cases were on the left hand (Table II).

Of the 9 ulnar cases, 7 were observed bilateral and 2 unilateral. The ulnar-sided polydactyly was bilateral and was found one on each hand (Table II).

The findings also show that there are six different types of thumb polydactyly. In one of typical cases, on the left hand, the supernumerary digit has articulated with the metacarpophalengeal joint and it had three phalanges, but the middle phalanx is smaller than the others (Figure 1).

In another type of thumb polysyndactyly, the proximal phalanx of the thumb on the right hand was extremely broad and was divided into two branches, each branch had only one phalanx (Figure 2).

In a unusual type of thumb polydactyly on the right hand the extra finger had only one thin-phalanx which was over the metacarpophalangeal joint; perhaps the 2 phalanges can be fused (Figure 3).

Five different types of polydactyly of the little finger have been found. Among these cases only one is unusual. On the centre of 5th metacarpal of the left hand there is a notch where a small extra digit with only 2 phalanges was located (Figure 4).

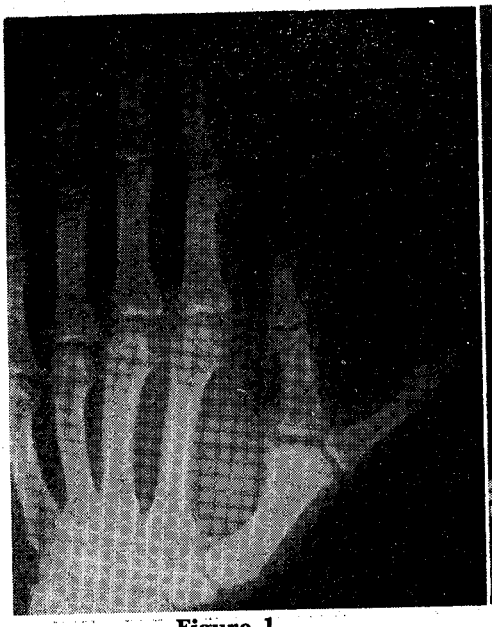

Figure 1
Polydactyly of the thumb on the left hand. Extra thumb has tree phalanges and each thumb articulating with the head of the first metacarpal.

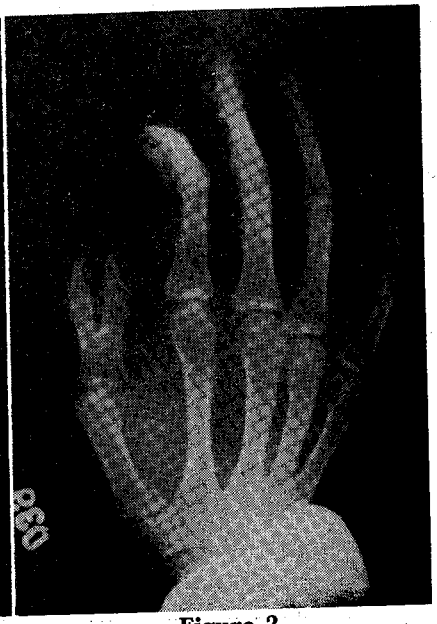

Figure 2
Another variety of polydactyly of the thumb on the left hand. Note that there is symphalangism between proximal phalanges of the normal and extrathumb.

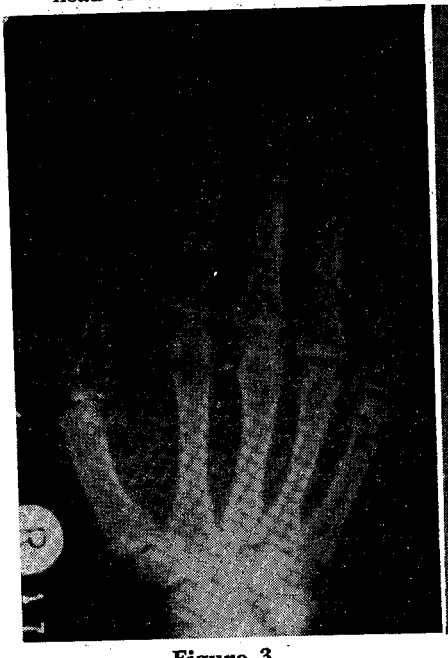

Figure 3
An unusual type of polydactyly of the thumb on the right hand. The extra digit has only one thin phalanx.

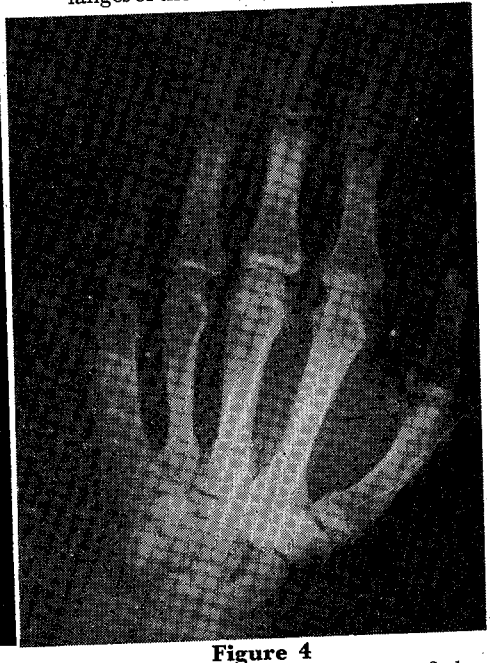

Figure 4
An unusual type of polydactyly of the little finger on the left hand. Note that there is a notch on the middle of the 5 th metacarpal where is located an extra finger, has only two phalanges.

The duplication of the ring finger had been observed only in two cases. In the first case, polydactyly had been complicated by syndactyly. On the right hand of the person the proximal phalanx of the 4th metacarpal was short and had two facets for articulation with the fourth and supernumerary digit. In addition the syndactyly that was seen between these two fingers and the normal ring finger was in the same length with little finger (Figure 5).

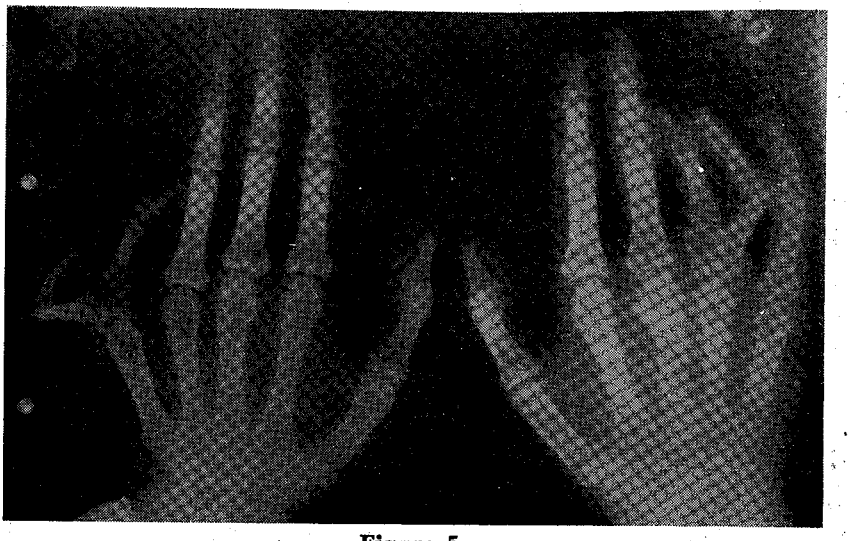

Figure 5

On the left side, an unusual type of bilateral polysyndactyly. On the left hand, proximal phalanx of the little finger is divided two branches and each branch has two phalanges, note that middle phalanx of the normal little finger is very small. And also there is a syndactyly between normal and extra little finger. On the right side, proximal phalanx of the ring finger is short and is gave a branch toward little finger, has two phalanges. In addition, there is syndactyly between two ring fingers, and these digits are nearly same length as little finger.

On the left hand of the same person we saw that duplication of the little finger had two phalanges. The proximal phalanx of the 5th metacarpal had been shaped "V" and had two phalanges; the middle phalanx of the normal little finger was very short and it was similar to a chickpea (Figure 5).

In the second case, we saw an unusual type of bilateral polysyndactyly. The ring finger had been duplicated on both hands and also the proximal phalanges of the normal and extra ring fingers were fused. There was a syndactyly between the middle fingers of both hands and duplicated ring fingers. In addition, between 3th and 4th metacarpals of each hand there was a small bone which had been articulated with the base of extra ring fingers (Figure 6).

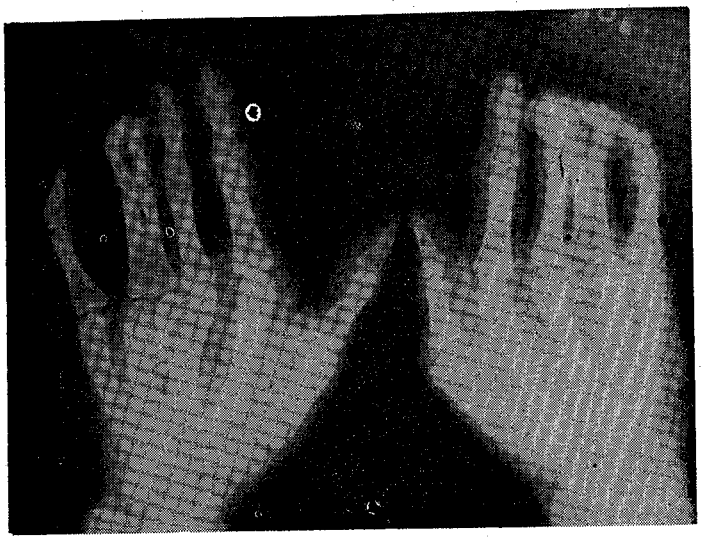

Figure 6

Bilateral polysyndactyly.The ring fingers are dupliceated and their proximal plalanges are fused. In addition, there is a bone between 3 th and 4 th metacarpal on each hand. The base of proximal phalanx on the middle finger is articulated with this bone.

Among our cases we did not see the duplication of the index finger or middle finger.

Discussion

Among our cases, unilateral polydactyly was nearly twice as common as bilateral polydactyly; and the radial-thumb duplication was nearly twice that of the ulnar (Table I). Similar observations have been made by other researchers.[1, 4, 6, 9, 11] According to one study, bilateral polydactyly is more common than the unilateral polydactyly and bilateral polydactyly is usually on the ulnar side.[3]

In Barsky's series there was thirty-eight cases of polydactyly: twenty-five of these were unilateral and thirteen bilateral. Twelve of his thirteen bilateral cases, however, were involvement of the ulnar part of the hand. This position, of course, is similar to our cases in which all of the 7 bilateral polydactyly were on the ulnar side of the hand.[1]

Among our cases, thumb duplication was first in frequency. Duplication of the little finger was next in frequency. This was followed by the ring finger. Barsky found the same frequency of the fingers.[4]

In our study, supernumerary fingers with a soft tissue appendage have always been found on the ulnar side at the level of the metacarpophalangeal joint. Blauth also stated similar observations.[5]

The supernumerary digit may be the same size as the normal or may differ in size. If the extra finger locates on the centre of hand, it is often accompained by syndactyly.[1, 4, 6] Duplication of the ring finger, was also observed to be syndactyly between extra and normal fingers (Figure 6).

Several syndromes associated with polydactyly and ectrodactyly have been described, but always the same digit is involved (absence or duplication). And the presence of rudimentary nails at the tip of the ectrodactylous hand suggests that the primary injury was located in the mesoderm not in the ectoderm. In addition, some researcher say that postaxial polydactyly is a more frequent anomaly than preaxial polydactyly.[12]

Duplication of the thumb may have several different forms. There are some opinions concerning whether the extra phalanx is a proximal phalanx or really a metacarpal. Cohn believes that the first metacarpal disappeared in the process of evolution, and what is usually considered the first metacarpal is actually a proximal phalanx. In support of his view he points out that the epiphysis of the first metacarpal is at the proximal end of the bone, as in the phalanges, rather than at the distal end, as in the other four metacarpals.[13]

In addition to the dominant type of polydactyly, there is evidence to indicate the existence of a recessive type. Apart from these, in the report of Temtamy and Mc Kusick, isolated polydactyly and split hand or foot deformity were usually an autosomal dominant inheritance.[14]

Sometimes, there is an extra bone, usually lying in a transverse or oblique position between two metacarpals (Figure 6). Barsky also says that he has observed these bones.[4]

A five-fingered hand associated with partial or complete tibial absence and pre-axial polydactyly of probable autosomal dominant inheritance have been described by Lamb (1983).[15]

Postaxial polydactyly can also occur as part of syndrome (eg., Ellis-Van Creveld, Jeune thoracic dystrophy, Trisomy 13 syndrome, Laurence-Moon-Biel syndrome and Meckel dysencephalica splanchnocystica) has been reported by Buttiens.[16]

Barsky says that a careful study should be made before operating. Sometimes it is difficult even to determine which of two digits should be removed. Since the nerves, tendons and blood vessels are likely to be atypical, careful consideration must be given to the function that will be retained or secured. If there is the slightest doubt about the tendinous attachments, they should be explored at operation. In addition, especi-

ally, in the case of the thumb, one must ensure that the tendinous attachments and the intrinsic musculature are preserved. It may be necessary to transfer a tendon or muscle from the accessory digit or even from another part of the hand.[3]

Grabb says that the extra digit may be connected by soft tissue only and is easily removed when the digit is connected by bone. It is important that remotion should be completed to prevent regrowth from the base.[17]

REFERENCES

1. Barsky AJ. Congenital anomalies of the hand and their surgical treatment. Charles, C. Thomas, Springfield. III., 1958.
2. Senders CW, Eisele P, Freman LE, Sponenberg P. Observations about the normal and abnormal embriyogenesis of the canine lip and palate. Journal of Craniofacial Genetics and Developmental Biology Supplement 2. 1986; 241-8.
3. Barsky AJ. Congenital malformations of the hand. Princes and practice of plastic surgery. 1964; 708-14.
4. Barsky AJ, Kahn S, Simon BE. Congenital anomalies of the hand. Converse. Reconstructive Plastic Surgery. 1964; 1703-7.
5. Blauth W, Sickert FS. Congenital deformites of the hand. Springer-Verlag, Berlin Heidelberg, New York. 1981; 119-20.
6. Serafin D, Georgiade NG. Congenital anomalies of the hands. Classification and general considerations. Pediatric Plastic Surgery, 1984; 2: 1000.
7. Fraizer TM. A note on race specific congenital malformation rates. Am J Obstet Gynecol. 1960; 80: 184-5.
8. Mellin GW. The frequency of birth defects. In: Fishbein M (Ed), Birth defects. Lippincott, Philedelphia. 1963; 1-7.
9. Nardi LG, Zuidema GD. A concise guide to clinical practice. Surgery. Little, Brown and Company, Boston. 1972; 682.
10. Wassel HD. The results of surgery for polydactyly of the thumb: A review. Clin Orthop. 1969; 64: 175.
11. Dobyns JH, Lipscomb PR, Cooney WP. Clinical orthopaedics and related research. Clin Orthop. 1985; 195: 26-44.
12. Van Regemorter N, Milaire J, Ramet J, Haumont D, Rodesch F. -Familial ectrodactyly and polydactyly: variable expressivity of one single gene embriological considerations. Clinical Genetics. 1982; 22: 206-10.
13. Cohn I. Skeletal disturbances and anomalies. A clinical report and review of the literature. Radiology. 1932; 18: 592.
14. Temtamy S, Mc Kusick V. The genetics of hand malformations. Birth Defects. Original Article Series. Vol. XIV, No: 3, 1978.
15. Lamb DW, Davies RW, Whitmore JM. Five-fingered hand associated with partial or complete tibial absence and pre-axial polydactyly. J Bone Joint Surg. 1983; 65B: 1.
16. Buttiens M, Fryns JP, Jonckheere P, Buttiens KB, Van den Berghe H. Scalp defect associated with postaxial polydactyly: Confirmation of a distinct entity with autosomal dominant inheritance. Human Genetics. 1985; 71: 86-8.
17. Grabb WC. A concise guide to clinical practice. Plastic Surgery. 1968; 647-9.

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Postdate Pregnancy: Risk Factors and Management

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Summary

38 postterm pregnant women were followed according to a preset protocol. The incidence of postterm pregnancy in the study period was 2,3 percent. Diminished fetal movements, meconium stained amniotic fluid, intrauterine growth retardation, abnormal biophysical tests and falling estriol levels were accepted as indications for intervention. If none of the risk factors existed the patients were followed conservatively under close surveillance. The cesarean section rate was 23,6 percent. There was no perinatal mortality and 6 infants were regarded as dysmature.

Key Words: Postdate pregnancy, management.

Introduction

The average length of a human pregnancy is 280 days. Pregnancy is regarded as abnormal if it's prolonged beyond 294 days or 42 weeks. Prolonged, postterm or postdate pregnancies are encountered in approximately 10 percent of all pregnancies.[1] The data vary but it is estimated that about 12 percent of women are undelivered at the end of 42 weeks' gestation. In one series 7,3 percent of women delivered after 43 weeks.[2]

Because of the inherent risk of uteroplacental insufficiency in prolonged pregnancies, perinatal morbidity and mortality is increased if timely intervention is not undertaken.[3] It has been reported that the 10,5/1000 incidence of perinatal mortality at 38-41 weeks doubled to 20 by 42 weeks and doubled again to 43 by 44 weeks.[4] Close surveillance during the antepartum and intrapartum period coupled with precise timing and the termination of pregnancy should decrease the perinatal morbidity and mortality.[5]

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This was a prospective study in which 38 postdate women were enrolled and managed according to a preset protocol in our hospital.

Material and Methods

38 postdate pregnant women were followed during a 6 month period according to the preset protocol in University of Hacettepe, Obstetrics and Gynecology Department. The incidence of postdate pregnancy during the same period was 2,3 percent. Of the 38 patients 9 were under regular antenatal control, but 29 had applied for the first time after 40 weeks of gestation. These women were followed according to the protocol given below and the pregnancies terminated accordingly.

Step I: Under specific conditions we delivered the fetus between 40-42 weeks and did not let her go over 42 weeks. This first step was preventive.

- Women with bad obstetric history
- History of dystocia
- History of traumatic delivery
- Repeat section or previous uterine surgery
- Macrosomic fetus
- Intrauterine growth retardation
- Multiple pregnancy
- Placenta previa
- Diabetic pregnancy
- Hypertensive disorders

Step II: In this step we carefully analysed the factors contributing to prolonged gestation.

- Cephalopelvic disproportion
- Malpresentation
- Major fetal anomaly
- Placenta previa
- Miscalculated gestational dates

Step III: After the preventive measures were taken and the factors contributing to prolonged gestation were analysed, in this step we diligently searched for uteroplacental insufficiency. If uteroplacental insufficiency was detected frestalling delivery was contrindicated.

- Diminishing fundal hieght
- Nonreactive nonstress test
- Positive stress test
- Declining levels of E_3 and HPL

- Diminished fetal movements
- Oligohydramnios
- Intrauterine growth retardation
- Meconium stained amniotic fluid on amnioscopy.

Step IV: If steps I, II and III were negative a conservative attitude was taken and the patient was monitored, clinically, biophysically and biochemically. Delivery could be forestalled till the 44'th week if everything seemed to be in order.

Step V: Delivery: The method of delivery depended on the pelvic score. Cesarean section was performed for obstetric indications. The pediatrician should be informed of the patient before delivery and should be present at the delivery.

Monitarisation of the pregnant woman with a prolonged pregnancy:

1. Serial measurements of the fundal height: Diminishing fundal height is omnious.
2. Patients' self monitoring of fetal activity:Diminished or absent fetal movements point out to detoriorating fetus.
3. Biophysical tests: These consist of a NST in the first place. A nonreactive NST should be maneged either by a contraction stress test or biophysical scoring as described by Manning.[6] The presence of fetal breathing movements coupled with an adequate amniotic fluid can also ensure fetal well-being.[7]
4. Ultrasonographic parameters: Estimation of the amniotic fluid volume, placental grading, fetal measurements, fetal breathing movements, fetal movements are assessed by ultrasound scanning.
5. Daily estriol measurements can be a useful adjunct to biophysical parameters.

Results

The median age of the study group was 26,05 years with a range of 19-37 years. The mean parity was 0,6, where 23 patients were primiparas and 15 patients were multiparas. All of the patients had gestational ages of 42 weeks or over counted from the first day of the last menstrual period. 6 women delivered at 43 weeks and 2 at 44 weeks of gestation.

Intervention was undertaken because of diminished fetal movements in 14 patients.(36) The pregnancy was terminated because of abnormal biophysical parameters in 2 patients, falling estriol levels in 2 patients, intrauterine growth retardation in 2 patients diminshed amniotic fluid in 4 patients, meconium stained amniotic fluid in 7 patients and because of a repeat section in 1 patient (Table I).

TABLE I
INDICATIONS FOR INTERVENTION AFTER 42 WEEKS

Indication	No of Patients	%
Diminished fetal movements	14	36,8
Meconium stained amnion	7	18,4
Falling E_3 levels	2	5,2
Abnormal biophysical parameters	2	5,2
Oligohydramnios	4	10,5
IUGR*	2	5,2
Repeat section	1	2,6
No intervention	6	16,1
Total	38	100,0

* Intrauterine growth retardation.

The cesarean section rate for this patient population was 23,6 % with only 1 patient being a repeat section. The indications for cesarean section are given in Table II. There was no intrapartum fetal distress but 2 patients developed fetal distress at the second stage of labor and were delivered by forceps.

TABLE II
INDICATIONS FOR CESAREAN SECTION

Indication	No. of patients	%
CPD*	2	22,2
Malpresentation	1	11,1
Unfavorable pelvic score	3	33,3
Twin pregnancy	1	11,1
IUGR**	1	11,1
Repeat	1	11,1
Total	9	100,0

* Cephalopelvic disproportion
** Intrauterine growth retardation

Two of the newborns weighed over 4000 gm. and 1 baby weighed less than 2500 gm. Dysmaturity was evident in 6 of the newborns with wrinkled skin, diminished subcuteneous fat and diminished vernix. Neonatal morbidity is given in Table III.

TABLE III
NEONATAL MORBIDITY

	No	%
Dysmaturity	6	15,7
Hyperblirubinemia	3	7,8
Cephalhematoma	1	2,6
Total	10	26,1

Discussion

It is now universally accepted that some kind of monitorisation should be applied to postterm pregnant women. If fetal surveillance is not undertaken, perinatal mortalitiy and morbidity increases markedly.[8] From this point of view action should be taken after 40 weeks and preventive measures to decrease morbidity and mortality instituted.

Some kind of intervention should be applied, either expectantly under close surveillance or active in the form of induction of labor and delivery after 42 weeks.

Under the light of our own experience and the accumulated knowledge in the literature we tried to set a protocol and use it on 38 postterm patients. Clinically a decrease or the lack of fetal movements has been accepted as an omnious prognostic sign.[9] Fetal activity determination has also been regarded as more accurate than estriol and other biochemical parameters in reflecting fetal stress.

Decrease in the fundal hieght correlated with a decrease in fetal weight and corresponding ultrasonic measurements is another factor altering the safety of intrauterine enviroment. IUGR and prolonged gestation sharply increases perinatal mortality.[5] Decrease in the amniotic fluid volume almost always accompanies intrauterine growth retardation. Without intrauterine growth retardation dimished amniotic fluid volume has been regarded as a chronic sign of fetal distress.[7]

When the cervix enables direct visualisation of membranes through amnioscopy, this is an invaluable tool. Discoloration of the fluids by meconium prohibits any further expectant waiting. Meconium stained amniotic fluid occurs twice as often in postterm pregnancies than in term pregnancies (25 percent versus 12 percent).[8]

Nonreactive nonstress testing, although with a very high percentage of false positive results, is one of the most valuable means to survey postterm pregnancy.[6] A nonreactive nonstress test should be supported with either a nipple stimulation or oxytocin induced contraction stress test. Ultrasonic scoring of the fetus as proposed by Manning can also be used reliably in this situation.

If the cervix is favorable and the dates are known with accuracy we prefer induction of labor and delivery at 42 weeks. If the cervix is not favorable we elect expectant waiting and keep the mother and the baby under close surveillance. Cesarean section is performed for obstetric indications.

The problems associated with prolonged gestation is reflected as perinatal morbidity and mortality. We belive that if these patients were left unobserved, perinatal mortality with high rates would have been encountered. The absence of perinatal mortality in this select group of patients is the probable end result of close surveilance and rapid intervention when indicated.

REFERENCES

1. Grandos JL. Survey of the management of postterm pregnancy. Obstet Gynecol. 1984; 63: 651-7.
2. Danforth DN, Postterm pregnancy. Obstetrics and Gynecology. J.B. Lippincott Company, Philadelphia. 1986: 484-7.
3. Vorherr H. Placental insufficiency in relation to postterm pregnancy and fetal postmaturity. Am J Obstet Gynecol. 1975; 123: 67-72.
4. McClure-Brown JC. Postmaturity. Am J Obstet Gynecol. 1963; 85: 573-7.
5. Lagrew OC, Freeman RK. Manegement of postdate pregnancy. Am J Obstet Gynecol. 1986; 154: 8-13.
6. Johnson JM, Harman CR, Lange IR, Manning FA. Biophysical scoring in the manegement of postterm pregnancy: An analysis of 307 patients. Am J Obstet Gynecol. 1986; 154: 269-73.
7. Vintzileos AM, Winston AC, Nochimson DJ, Weinbaum PJ. The use and misuse of fetal biophysical score. Am J Obstet Gynecol. 1987; 156: 527-33.
8. Eden RD, Gergely RZ, Schifrin BS, et al. Comparison of antepartum testing for postdate pregnancy. Am J Obstet Gynecol. 1982; 144: 683-8.
9. Sadowsky E. Antepartum monitoring of fetal movements. Niels H. Lauersen, Modern Management of High-risk pregnancy. Plenum Medical Book Company. New York/London. 1983; 325-47.

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Nonsteroid Antiinflammatory Drug Treatment in Idiopathic Carpal Tunnel Syndrome

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Summary

The symptoms and signs resulting from the compression of the median nerve in the carpal tunnel at the wrist is known as the carpal tunnel syndrome. In this study, 20 patients who were diagnosed to have idiopathic carpal tunnel syndrome by means of electroneuromyographic examination were given benzydamine hydrochloride (Tantum) as an antiinflammatory drug treatment. On the second electroneuromyographic examination which was performed a month later, statistically significant decreases were observed in the median nerve distal motor latencies and motor nerve conduction velocities, from 12 idiopathic bilateral carpal tunnel syndrome patients. The lack of statistically significant changes in 8 of the idiopathic unilateral carpal tunnel syndrome patients leads us to consider other etiologies which might cause median nerve compression.

Key Words: Carpal tunnel syndrome, nerve compression syndromes, antiinflammatory drug treatment.

Introduction

The symptoms and signs caused by compression of the median nerve which is sufficient to cause impairment of nerve function as it passes from the forearm to the palm is known as the carpal tunnel syndrome.[1,2] While the arch of carpal bones makes up the floor of this tunnel, the roof is formed by the flexor retinaculum or transverse carpal ligament, which is a thick fibrous band.[4] The tunnel contains the median nerve and 9

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flexor tendons.[5] Many etiologies have been proposed to account for the increased pressure in the carpal tunnel with subsequent compression of the median nerve. This includes trauma, rheumatoid arthritis, congenital anomalies, tumors, diabetes mellitus, hypothyroidism, acromegali, scleroderma, systemic lupus erythmatosus, dermato-polymyositis, HLA-B27 associated spondylarthropaties, tuberculosis, hemophiliac arthritis, amyloidosis, some of the mucopolysaccharidoses, gout, pseudogout (or hydroxyapatite deposition in the flexor retinaculum) pregnancy and creation of arteriovenous fistulas for hemodialysis.[5-7]

However, a larger patient group with no apparent underlying disease is also considered to have idiopathic carpal tunnel syndrome. Females, especially 40-60 year of age, are most frequently affected.[5, 8] Carpal tunnel syndrome is reported to occur most often in the dominant hand.[9] In the clinical diagnosis, characteristic symptoms of nocturnal tingling and numbness in the thumb, index and middle fingers[10] are enough to awaken the patient during night sleep.[11] These may be relieved by shaking the hand or hanging it out of the bed. In addition, tunel sign, phalen test, and extension of the wrist, tourniquet test and thenar muscle atrophy are important in the diagnosis.[6, 12] Among them, the phalen test is the most reliable one, yielding 75 % positive results.[10] In the electroneuromyographic (ENMG) examination of the carpal tunnel syndrome, stimulation of the median nerve at the wrist shows delayed motor and sensory distal latencies.[13] For the treatment of carpal tunnel syndrome, night splinting, local corticosteroid injections and vitamin B_6 are suggested, in addition to surgical decompression.[1, 2, 5, 10, 14-19]

In this resarch, the effect of oral benzydamine hydrochloride as non-steroid antiinflammatory drug treatment on early idiopathic carpal tunnel syndrome was studied.

Patients and Method

In our clinic, median nerve distal motor latencies, evoked motor unit action potential (MUAP) amplitude and motor nerve conduction velocity were measured at constant skin temperature of 34°C among the patients who suffered from tingling and numbness of the hand. While taking these measurements the active recording needle electrode was in m.opponens pollicis of the thenar muscle group and stimulation was given 4 cm proximal to the recording needle electrode at the wrist by using a DISA type 14 H 05 electroneuromyograph and a DISA type 14 G 01 digital averager. Patients with distal motor latencies over 4 milisec and without muscle atrophy were included in the study. A group of laboratory tests consisting of hemoglobin, white blood cell count

(WBC), erythrocyte sedimentation rate (Westergreen method), antistreptolysin 0 (ASO), C-reactive protein (CRP), latex, urea, creatinine, uric acid and fasting blood glucose level were performed. The 20 patients included in the study were between the ages 22-76 years (mean 45.7 years) of which 12 suffered from bilateral and 8 from unilateral carpal tunnel syndrome. Except for one male patient in the unilateral carpal tunnel syndrome group, all the other patients were female. After the inquiry for gastrointestinal contraindications, patients were given benzydamine hydrochloride (Tantum), an antiinflammatory agent with proven properties[20-25] 150 mg/day and were invited for ENMG re-examination a month later.

Results

The mean laboratory values of 20 idiopathic carpal tunnel syndrome patients were as follows: hemoglobin: 12.9, WBC: 5990/mm^3, erythrocyte sedimentation rate: 11.45 mm/hour, ASO: 1/106 Todd unit, CRP: negative, latex: negative, urea: 14.2 mg, creatinine: 0.7 mg, uric acid: 5.3 mg, fasting blood glucose level: 93.5 mg. During the therapy which lasted a month no serious side effects were observed. The median nerve distal motor latencies, motor nerve conduction velocity and evoked MUAP amplitude obtained in the first and second visits were statistically compared by applying the T-test. Results are shown in Table I.

The mean value of distal motor latency in 20 idiopathic carpal tunnel patients decreased from 4.938 milisec on the first visit to 4.522 milisec on the second visit indicating statistical significance ($P < 0.05$). On the other hand, the mean motor nerve conduction velocity dropped from 63.313 m/sec on the first visit to 58.313 m/sec on the second visit, and the mean evoked MUAP amplitude increased from 6.081 milivolt on the first visit to 6.481 milivolt on the second visit. However, both values had no statistical significance ($P > 0.05$).

In bilateral cases, the first and the second visit mean differences of the distal motor latencies and motor nerve conduction velocities were compared. The means of distal motor latencies and motor nerve conduction velocities on the first visit dropped from 5.054 milisec to 4.550 milisec and from 65.667 m/sec to 58.792 m/sec respectively. Both values indicated statistical significance ($P < 0.05$).

Moreover, the mean of evoked the MUAP amplitude increased from 5.588 milivolt to 6.275 milivolt. However, this increase had no statistical significance ($P > 0.05$).

TABLE I

ENMG FINDINGS AND STATISTICAL ANALYSIS OF CARPAL TUNNEL PATIENTS

	Visit:	Mean:	Mean Diff:	STD Error:	T-Value	P
CTS Distal Latencies	1	4.938				
	2	4.522	-0.416	0.128	3.25	< 0.05
CTS Nerve Cond. Velocity (NCV)	1	63.313				
	2	58.313	-5.00	2.644	1.89	> 0.05
CTS Muap Amplitude	1	6.081				
	2	6.481	0.400	0.716	0.56	> 0.05
Bilateral CTS Distal Latencies	1	5.054				
	2	4.550	-0.504	0.148	3.40	< 0.05
Bilateral CTS NCV	1	65.667				
	2	58.792	-6.875	3.281	2.10	< 0.05
Bilateral CTS Muap Amplitude	1	5.588				
	2	6.275	0.688	0.734	0.94	> 0.05
Unilateral CTS Distal Latencies	1	4.588				
	2	4.438	-0.150	0.242	0.62	> 0.05
Unilateral CTS NCV	1	56.250				
	2	57.875	1.625	3.316	0.49	> 0.05
Unilateral CTS Muap Amplitude	1	7.563				
	2	7.100	-0.463	1.902	0.24	> 0.05
Normal Side Distal Latencies	1	3.625				
	2	3.663	0.037	0.026	1.43	> 0.05
Normal Side NCV	1	58.875				
	2	59.125	0.250	2.583	0.10	> 0.05
Normal Side Muap Amplitude	1	7.875				
	2	7.375	-0.500	1.658	0.30	> 0.05

CTS: Carpal tunnel syndrome NCV: Nerve conduction velocity.

Despite the fall in the mean of the distal motor latencies in unilateral carpal tunnel patients from 4.588 milisec on the first visit to 4.438 milisec on the second visit, the difference of the mean values had no statistical significance.

The means of motor nerve conduction velocities and evoked MUAP amplitudes on the first and the second visits of unilateral carpal tunnel patients also showed no statistically significant difference. Finally, in unilateral carpal tunnel syndome patients, the means of distal motor latencies, motor nerve conduction velocities and the evoked MUAP amplitudes of the normal side revealed no significant differences between the first and the second ENMG examinations.

Discussion

Although a previous study reported that the carpal tunnel syndrome was found in 2 % of patients consulting a neurologist and psychiatrist, no serious study has been performed to determine the real prevalance.[8] The carpal tunnel syndrome is clained to be reliably diagnosed by nerve conduction studies or, retrospectively, by the benefical effect of release surgery.[11] Carpal tunnel syndrome frequently occurs as an occupational disease among persons who perform repetitive work with their hands.[26] Thenosynovitis of the flexor compartment of the wrist is also reported to cause carpal tunnel syndrome.[5, 27] Proliferation and oedema have been observed at the surrounding tissues of the median nerve in the carpal tunnel.[28] In the most of the patients with carpal tunnel syndrome, nonsteroid antiinflammatory drug treatment is reported to help solve the problem.[29] In our study, we carried out nonsteroid antiinflammatory drug treatment for reducing oedema and curing thenosynovitis in order to decrease the pressure in the carpal tunnel. After benzydamine hydrochloride treatment in the carpal tunnel patients we observed statistically significant decreases in median nerve distal motor latencies.

When the bilateral and unilateral carpal tunnel syndromes are examined seperately, we observed statistically significant decreases in the median nerve distal motor latencies and motor nerve conduction velocities in the bilateral carpal tunnel syndrome patients. The motor nerve conduction velocity decreases on the second ENMG examination, because on the first visit, the delayed distal motor latency causes the motor nerve conduction velocity to be calculated relatively higher. After the treatment, the decrease in the distal motor latency causes a difference between proximal latency and the distal latency to be higher, resulting in a lower motor nerve conduction velocity.

We have found no statistically significant changes in the amplitude of evoked MUAP among bilateral carpal tunnel syndrome patients. It has been reported that, 4-6 months after the surgical decompression of the carpal tunnel, a pronounced increase was observed in the median nerve action potential amplitudes.[18] In our study, patients were examined on a monthly basis. Todate, we have not observed any statistically significant increase in the evoked MUAP amplitude. This result is consistent with the previous study.

In 5 out of 8 patients the unilateral carpal tunnel syndrome was observed on the dominant side. This is also consistent with the previous studies.[9]

The lack of statistically significant changes in the median nerve distal motor latencies, motor nerve conduction velocities and evoked MUAP amplitudes in unilateral carpal tunnel syndome patients leads us to consider other etiologies causing median nerve compression.

When the possible complications of the surgical decompression of carpal tunnel syndrome are taken into account,[19] benzydamine hydrochloride as nonsteroid antiinflammatory drug treatment is initially suggested for those patients with tingling and numbness in their hands, having median nerve distal motor latencies over 4 milisec in ENMG examination and without thenar muscle atrophy.

Although we worked on a restricted number of idiopathic carpal tunnel patients this is the first reported study, based on objective criteria that investigated the effect of antiinflammatory drug treatment in carpal tunnel syndrome. We hope that this study leads to further studies in this field.

REFERENCES

1. Daniel J. Mc Carthy, Arthritis and Allied Conditions, Foreward by Joseph Hollander. Lea and Febiger. 1979; 995.
2. Kasdan NL, Janes C. Carpal tunnel syndrome and vitamin B_6. Plast Reconst Surg. 1987; 79: 460-2.
3. Stevens JC. The electrodiagnosis of carpal tunnel syndrome. Muscle and Nerve. 1987; 10: 99-113.
4. Dorwart BB. Carpal tunnel syndrome: A Review. Semin Arthritis Rheum. 1984; 14: 134-40.
5. Voitk AJ, Mueller JC, Farlinger DE , et al. Carpal tunnel syndrome in pregnancy. Can Med Assoc J . 1983; 128: 277-81.
6. Laban MM, Friedman NA, Zemenick GA. Tethered median nerve stress test in chronic carpal tunnel syndrome. Arch Phys Med Rehabil. 1986; 67: 803-4.
7. Johnson EW, Gatens T, Poindexter D, et al. Wrist dimensions: Correlation with median sensory latencies. Arch Phys Med Rehabil. 1983; 64: 556-7.
8. Comi G, Lozza L, Galardi, et al. Presence of carpal tunnel syndrome in diabetics. Acta Diabetol Lat. 1985; 22: 259-62.
9. Marin EL, Wernick S, Friedman LW. Carpal tunnel syndrome: Median nerve stress test. Arch Phys Med Rehabil. 1983; 64: 206-8.
10. Heywood PL. Through the carpal tunnel. Br Med J. 1987; 294: 660-1.
11. Maryniak O. Carpal tunnel syndrome. Can Med Assoc J. 1983; 128: 1052-7.
12. Bowles AP, Asher SW, Pickett JB. Use the tinel's sign in carpal tunnel syndrome. Ann Neurol. 1983; 13: 689-90.
13. Andrews JC, Johnson RJ. Electrodiagnosis. An anatomical and clinical approach. JB Lippincott Company. 1986; 290-300.
14. Richards AJ. Carpal tunnel syndrome and subsequent rheumatoid arthritis in the fibrositis syndrome. Ann Rheum Dis. 1984; 43: 232-4.

15. Godfrey CM. Carpal tunnel syndrome in pregnancy. Can Med Assoc J. 1983; 129: 928.
16. Pilar S. Carpal tunnel syndrome in pregnancy. Can Med Assoc J. 1983; 129: 536.
17. Scheyer RD, Haas DC. Pyridoxine in carpal tunnel syndrome. Lancet. 1985; 6: 42.
18. Smith GP, Rudge NJ, Peters TJ. Biochemical studies of pyridoxal and pyridoxal phosphate status and therapeutic trial of pyridoxine in patients with carpal tunnel syndrome. Ann Neurol. 1984; 15: 104-7.
19. Louis DS, Greene TL, Noellert RC. Complications of carpal tunnel surgery. J Neurosurg. 1985; 62: 352-6.
20. Turchetti A. Clinical and functional data on the activity of non-steroid anti-inflammatory preparations. Observations on Benzydamine Excerpta Medica International congress series no: 82 396-410.
21. Silvestrini B, Garau A, Pozzatti C, et al. Pharmacological research on Benzydamine. A new analgesic, anti-inflammatory drug. Arzneim Forsch. 1966; 16: 59-65.
22. Schlag G, Kopera H, Stulemeijer SM, et al. The anti-inflammatory effect of Benzydamine Hidrochloride demonstrated with a new clinical pharmacological method. Arzneim Forsch. 1970; 20: 1725-8.
23. Harrison RG, O'Donnel PJ. The anti-inflammatory effect of Benzydamine. Toxicol Appl Pharmacol. 1970; 17: 355-60.
24. Kopera H. Comparative trials with Benzydamine hydrochloride and a reference preparation in conditions with pain and swelling.Excerpta Medica International Congress series no: 163: 100-106.
25. Segre G, Hammarström S. Aspects of the mechanisms of action of Benzydamine. Int J Tiss Reac. 1985; 7: 187-93.
26. Armstrong TJ, Castelli WA, Evans FG, et al. Some histological changes in carpal tunnel contents and their biomechanical implications. J Occup Med. 1984; 26: 197-201.
27. Pinalis RS. Traumatic Arthritis and allied conditions in Arthritis and Allied Conditions. Lea and Febiger. 1985; 1213-4.
28. Wilhelm K, Feldmeier CH, Brigel J, et al. Genese des Carpal tunnel syndroms. Munch Med Wochenschr. 1982; 124: 661-2.
29. Alexander SJ. Cost containment in carpal tunnel syndrome. Arthritis Rheum. 1979; 1415-6.

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Pseudoepileptic and Epileptic Seizures in Childhood

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Summary

During a two year period twenty four children were referred to the outpatient department of psychiatry with the inital diagnosis of pseudoepileptic seizure. This retrospective study revealed that seven of these twenty four patients were misdiagnosed as pseudoseizures instead of epileptic seizures. In the pseudoseizure group the age range was 11-16 years, and for the epileptic group it was 5-16 years. The mean duration of symptoms and seizure duration differed significantly between the two groups. There was psychiatric disorder in the personal and family histories of the pseudoepileptics in contrast to the epileptic patients. Initial EEG's in both groups were either normal or had minor abnormalities. Serial EEG's, while continuing to be normal in the pseudoepileptic group, displayed seizure activity in the epileptic patients. This paper emphasizes the need for repeated EEG's to avoid misdiagnosis.

Key Words: Hysteria, Epilepsy, Seizures.

Introduction

Pseudoepileptic seizures are attacks of sudden unconsciousness usually associated with dramatic motor manifestations which simulate epileptic attacks.[1] They are said to be a clinical rarity in modern psychiatric practise.[2] However their occurance in childhood, in underdeveloped and developing countries, is not uncommon.

The diagnosis of pseudoepileptic seizures can usually be made correctly on clinical grounds alone.[3] Often though, they closely resemble epileptic seizures and differentiation may be quite difficult. The reverse is

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also valid and epilepsy can be misdiagnosed as hysterical or pseudoepileptic seizure. In the first condition where pseudoepileptic seizure is mistaken for epilepsy, the patient is subjected to unnecessary treatment with anticonvulsants; potentially toxic medications. In the latter case, the result of the erroneous diagnosis can be much more devastating for the patient.

Much of the recent literature has drawn attention to coexistance of genuine epileptic and pseudoepileptic seizures in the same patient and to the mistake of diagnosing true epilepsy when attacks are actually those of pseudoepilepsy.[1, 3, 4, 5, 6] However just as important, though less frequent, is the risk of wrongly attributing the diagnosis of pseudoepilepsy to epileptic seizures. This study is an attempt to emphasize the latter condition and point out differenciating characteristics to assist early and accurate diagnosis.

Material and Method

The medical records of twenty four children, ages between 5-16 years, which were referred to psychiatry out-patient department with the initial diagnosis of pseudoepileptic seizure during Jan. 1986-Dec. 1987, have been reviewed. Data were tabulated from the medical history, physical and psychiatric examination, laboratory studies (skull x-ray, EEG and CT) and clinical course of each patient. The final diagnosis of pseudoepileptic seizure was based on the combination of clinical features, physical and psychiatric findings, EEG results and subsequent clinical course.

Results

The review of medical records of 24 children with the referral diagnosis of pseudoepileptic seizure disclosed that seven patients were eventually diagnosed as epilepsy (These patients will be referred to as the epileptic group throughout the manuscript).

In the pseudoepileptic seizure group the age range was 11-16 years (mean age: 14 ± 0.41 years), for the epileptic group this range was 5-16 years (mean age: 11.57 ± 1.52 years).

In the pseudoepileptic seizure group there were 13 females and 4 males. In the epileptic group six of the seven patients were females. The incidence of pseudoepileptic seizures between the sexes was approximately equal at age 12 and below. This was not so in the epileptic group.

All the attacks in the pseudoepileptic seizure group resembled generalized seizures. In the epileptic group there were three patients with partial, three psychomotor and one with generalized seizures. Other data regarding the seizures are given in Table I.

TABLE I
CHARACTERISTICS OF THE SEIZURES

	Pseudoepileptic group	Epileptic group	Significance of difference (p)
Mean duration of symptoms (months)	7.28 ± 3.34	17.37 ± 5.29	< 0.05
Mean seizure frequency (days)	1.07 ± 0.31	2.61 ± 1.15	> 0.05
Mean seizure duration (minutes)	49.64 ± 17.98	14.23 ± 7.97	< 0.05

Four patients (23.5 %) of the pseudoepileptic seizure group had some psychiatric disorder in their past personal histories: namely anxiety reaction, suicide attempt, depression and behavior disorder. Members of the epileptic group had no such histories. Family histories of the pseudoepileptic seizure group revealed that two patients (11.7 %) had psychiatric disorder (enuresis and schizophrenia) in the first degree relatives, but no epilepsy. The reverse was true for the epileptic group with two patients (28.5 %) having family history of epilepsy but no psychiatric illness.

Ten patients (59 %) of the pseudoepileptic seizure group were the second child in the reverse birth order with an age difference of 4-5 years between their younger siblings.

There were two patients in each group that had no additional psychiatric problems. In the pseudoepileptic seizure group, there were anxiety (70.58 %) and depression (41.17 %) as psychiatric findings. As for the epileptic group, 5 patients (71.42 %) had anxiety but none had depression. In both groups neurological examination showed no pathology.

Review of the laboratory results displayed that all the patients had skull X-ray, EEG and that some also had CT. The initial EEGs in both groups were either normal or had minor abnormality. Serial EEGs while continuing to be normal in the pseudoepileptic seizures, showed seizure activity in the epileptic group.

Discussion

Differentiation between pseudoepileptic and epileptic seizures can be difficult. Unexplained seizures or altered levels of consciousness in the absence of pathology in the EEG may be mistaken for pseudoepileptic seizures.[5] Especially partial and psychomotor seizures, more so than the generalized ones, resemble pseudoepileptic seizures. In this study only one of the epileptic patients that were misdiagnosed had generalized seizures.

Despite difficulties encountered in the differential diagnosis there are some marked differences between epileptic and pseudoepileptic seizures which may be an aid in diagnosis. In this study a significant difference was noted between the age ranges of the two groups. Epilepsy tended to begin at younger ages whereas pseudoepileptic seizures were more frequently seen in the teen years. This finding is similar to that of Schneider and Rice.[4] The mean duration of symptoms was significantly lower in the pseudoepileptic seizure group compared with that of the epileptic patients ($p < 0.05$). This is in contrast with the literature.[5, 7] Frequent seizures are unusual in epilepsy with the exceptions of status epilepticus, petit mal and partial seizures.[1] In our study there was no significant difference in the mean seizure frequency of the two groups, possibly due to the majority of the patients having psychomotor and partial seizures in the epileptic group. The duration of pseudoepileptic seizures are generally longer than epileptic attacks.[8] Accordingly, in our study the mean duration of pseudoepileptic seizures was significantly longer than that of the epileptic group ($p < 0.05$).

It is reported that patients with pseudoepileptic seizures display other features indicative of psychopathology: past personal history of psychiatric disorder, family history of psychiatric illness and concurrent affective symptoms.[1] Our findings are in accordance with this notion. The presence of psychiatric disorder is common in the past personal and family histories of only pseudoepileptics, while no such finding exist in the epileptic group. However, anxiety, as a psychiatric finding, should not be used for differentiation between epileptic and pseudoepileptic seizures, as in this study, anxiety can co-exist in epileptics too.

Schneider and Rice[4] emphasized birth order in their series of 32 pseudoseizures. 90 % of their patients were first or second in the birth order. In our study, the majority of the pseudoepileptic patients were second child in the reverse birth order. The epileptic group did not show such a feature. This finding is interesting and may be explained with with possible sibling rivalry, accentuated by 4-5 years age difference between the patient and the last child of the family.

As previously noted, differential diagnosis of pseudoepileptic seizures and epilepsy can sometimes be difficult and misdiagnosis may result, especially if the EEG is normal and the manifestations of the attack are atypical.[9] For accurate diagnosis, repeated EEGs might be necessary. Additional studies like provocative EEG tests, EEG telemetry and video tape analysis can aid the diagnosis.[7, 10-13]

REFERENCES

1. Fenton GW. Epilepsy and hysteria. Br J Psychiatry. 1986; 149: 28-37.
2. Nemiah JC. Somatoform disorders. In: Kaplan HI, Sadock BJ, eds. Comprehensive Textbook of Psychiatry. Baltimore: Williams & Wilkins, 1985; 928.
3. Ramani SV, Quesney LF, Olson D, Gumnit R. Diagnosis of hysterical seizures in epileptic patients. Am J Psychiatry. 1980; 137: 705-9.
4. Schneider S, Rice DR. Neurologic manifestations of childhood hysteria. J Pediatr. 1979; 94: 153-6.
5. Finlayson RE, Lucas AR. Pseudoepileptic seizures in children and adolescents. Mayo Clin Proc. 1979; 54: 83-7.
6. Liske E, Forster F. Pseudoseizures: a problem in the diagnosis and management of epileptic patients. Neurology (Minneap). 1964; 14: 41-9.
7. Holmes GL, Sackellares JC, Mc Kierman J, Ragland M, Dreifuss FE. Evaluation of childhood pseudoseizures using EEG telemetry and video tape monitoring. J Pediatr. 1980; 97: 554-8.
8. Lesser RP. Psychogenic seizures. Psychosom. 1986; 27: 823-9.
9. Williams DT, Spiegel H, Mostofsky DI. Neurogenic and hysterical seizures in children and adolescents: differential, diagnostic and therapeutic considerations. Am J Psychiatry. 1978; 135: 82-6.
10. Cohen RJ, Suter C. Hysterical seizures: suggestion as a provocative EEG test. Ann Neurol. 1982; 11: 391-5.
11. King DW, Gallagher BB Murvin AJ, Smith DB, Marcus DJ, Hartlage LC, Ward LC. Pseudoseizures: diagnostic evaluation. Neurology (Ny). 1982; 32: 18-23.
12. Gulick TA, Spinks IP, King DW. Pseudoseizures: ictal phenomena. Neurology (Ny). 1982; 32: 24-30.
13. Luther JS, Mc Namara JO, Carwile S, Miller P, Hope V. Pseudoepileptic seizures: methods and video analysis to aid diagnosis. Ann Neurol. 1982; 12: 458-62.

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Tuberculosis of the Tonsils

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Summary

Two patients are presented with tonsillar tuberculosis (TB). The first was a 29-year-old male whose TB was diagnosed histologically and had no evidence of active TB. The second was a 26 year old male who had symptoms mainly of tonsillitis but in addition had active pulmonary TB with involvement of the larynx and the tonsils.

Key Words: Tonsils, tuberculosis.

Introduction

Tuberculosis (TB) of the tonsils is rare: In a series of 215 cases of extra-pulmonary TB reviewed by Monie and co-workers there was not a single patient with tonsillar TB.[1] This findings were conformed by Alvarez and McCabe,[2] who also reviewed 136 cases of extra-pulmonary tuberculosis occuring over a ten year period at Boston City Hospital and other affiliated hospitals and found no case of tonsillar involvement.

We report here two cases of tonsillar TB. The first was diagnosed histologically and he had no evidence of active pulmonary TB. However, the second, who had symptoms of mainly of tonsillitis, had TB involving the lungs larynx and tonsils.

Case Reports

Case 1: A 29-year-old male was admitted to the ENT department because of repeated attacks of tonsillitis. He also complained of discharge from the left ear since childhood. Physical examination revealed a perforated ear drum on the left side and enlarged and chronically inflammed tonsils. There were in addition enlarged lymph nodes in the left anterior cervical area. Apart from slight lymphocytosis, all the initial laboratory investigations were within normal limits.

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Tonsillectomy was performed, histological examination of the right tonsil showed focal chronic inflammatory changes. However, that of the left revealed numerous granulomata with early caseating necrosis in the germinal centre. No tubercle bacilli were seen.

He was referred to the pulmonary clinic for management. He denied any respiratory symptoms but stated that his older brother had a lung operation for an inflammatory disease a few years back. Physical examination confirmed the cervical lymphadenopathy, and apart from a late systolic click in the mitral area, there was no other abnormality.

Investigations: PPD with 3 1μ resulted in 30 mm induration. Three consecutive sputum cultures did not show any growth of tubercle bacilli ECG was normal apart from sinus bradycardia and echocardiogramphic study demonstrated a late systolic mitral valve prolapse. Chest x-ray and tomography showed some fibrotic changes on the right apex and localized cystic changes behind the left hilum. Bronchography revealed cystic bronchiectasis in the superior segment of the left lower lobe.

He was treated with a combination of isoniazid, rifampicin and ethambutol for two months, followed by a further 7 months administration of isoniazid and rifampicin. He made an uneventful recovery.

Case 2: The patient was a 26-year-old male who presented at the ENT department because of a severe sore throat associated with bleeding, hoarseness, and a high fever. The initial ENT examination revealed extensively infected and bleeding tonsils. There were also enlarged and matted anterior, posterior cervical lymph nodes. A smear from the tonsils stained with Ziehl-Neelsen showed several tubercle bacilli. Histopathological examiation of a biopsy of the tonsil also revealed granulomata with casseating necrosis. In the chest x-rays there were bilateral, diffuse micronodular opacities especially in the right upper lobe. Smears and culture for acid-fast bacilli in the sputum were also positive.

He was treated with a combination of isoniazid, rifampicin, streptomycin and pyrazinamide. His fever subsided after four days and he felt better. He was later transferred to the Tuberculosis Hospital for further management.

Discussion

Sanford and Becker,[3] in a review of Tonsillar TB referred to Aronneim's and Mullen's studies of tuberculosis of tonsils; latent tonsillar TB constituted 5 to 9 per cent of all routine tonsillectomy at term of this century. Following the discovery of anti-tuberculous drugs, some fifty years later, the incidence decreased significantly to less than 1 per cent.

40-70 % of patients with active pulmonary TB have latent tonsillar TB, Secondary infections of the tonsils from pulmonary disease is mostly due to endogenous spread either through infected sputum or via the blood stream.

The first patient had chronic tonsillitis with cervical lymphadenopathy. The strongly positive PPD, fibrous reactions in the lung associated with localised bronchiectasis in the superior segment of left lower lobe and histological demonstration of granulomata with caseating necrosis in the germinal center strongly suggest latent tonsillar TB. The absence of demonstrable acid-fast bacilli in such cases has been previously observed and is believed to be due to the bacteriolytic action of the tonsillar tissue.[3]

This patient also had mitral valve prolapse. Although the prevalance of mitral valve prolapse in the population is high[4, 5], so far there has been no report of an increased incidence of pulmonary or tonsillar tuberculosis in patients with this abnormality.[6]

Sanford and Becker,[3] referred to Capo, who in a comprehensive study of 2500 TB cases, found 55 with active pharyngeal and tonsillar TB. Furthermore 92 per cent of these patients had associated laryngeal TB. Infection in the tonsillar crypts from infected sputum is usually associated with laryngeal involvement.

In our second patient, the presence of tubercle bacilli in the tonsillar secretions and clear evidence of active pulmonar TB would suggest tonsillar TB and the possible of laryngeal involvement as well.

We agree with the statements of Sanford and Becker,[3] that in patients with chronic tonsilitis who do not respond to conventional treatment, and especially those who also have cervical lymph node enlargement, a diagnosis of TB should be considered. The tonsils, when removed, should be subjected to histopathology to exclude the possibility of latent tonsillar TB.

REFERENCES

1. Monie RDH, Hunter AM, Rocchicioli KMS, White JP, Campbell IA. Management of extrapulmonary tuberculosis in South and West Wales, Br Med J. 1982; 285: 415-8.
2. Alvarez S, McCabe W. Extrapulmonary tuberculosis revisited . A review of experience at Boston City and other hospitals, Medicine. 1984; 63: 25-55.
3. Sanford DM, Becker GD. Tuberculosis of the tonsils. Arch Otolaryngol. 1986; 84: 343-5.

4. Procacci PM, Savran SV, Schhreiter SL, Bryson AL. Prevalence of clinical MVP in 1169 young women. New Eng J Med. 1976; 294: 1086-8.
5. Davies MJ, Moore BP, Braimbridge MV. The floppy mitral valve. Study of incidence, pathology and complications in surgical, necropsy and forensic material. Br Heart J. 1978; 40: 468-81.
6. Beton DC, Brear SG, Edwards JD, Leonard JC. Mitral valve prolapse: An assessment of clinical features, associated conditions and prognosis. Q J Med. 1983; 52: 150-64.

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Bromocriptine Therapy for Pituitary Tumor Enlargement Presenting with Neurological Symptoms in Pregnancy

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Summary

One of the means of treating neurological complications due to pituitary tumor enlargement during pregnancy is medical. A pregnant woman presented with an enlarged prolactinoma and bitemporal hemianopsia. She was treated with bromocriptine.

Key Words: Prolactinoma, pregnancy, bromoergocriptine.

Introduction

Current practice enables many hyperprolactinemic women to become pregnant. Pregnancy carries with itself the inherent risk of pituitary tumor enlargement if such a tumor is present. It is reassuring that such complications showed a low incidence in several reported series.[1] However neurological complications in the range of 30 % with about 6 % being emergency neurological situations have also been reported.[2]

Case Report

Mrs. S.K., 29 years old, was referred to the Department of Neurosurgery because of unremitting headaches and galactorrhea. She had been married for 7 years and haven't concieved. She was taking bromoergocriptine in varying doses for the last two years because of menstruel disordders and infertility. Her Prolactin (PRL) levels were elavated mildly in the range of 40-60 ng/ml.

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Upon administration, her PRL level was 35 ng/ml and a computerized Brain Scan revealed a microadenoma of the pituitary gland. The visual field examinations performed at this time showed no abnormality. Bromocriptine was instituted and she was scheduled for transsphenoidal surgery but, from a sonographic examination performed for a missed period, it was found out that she was 8 weeks pregnant.

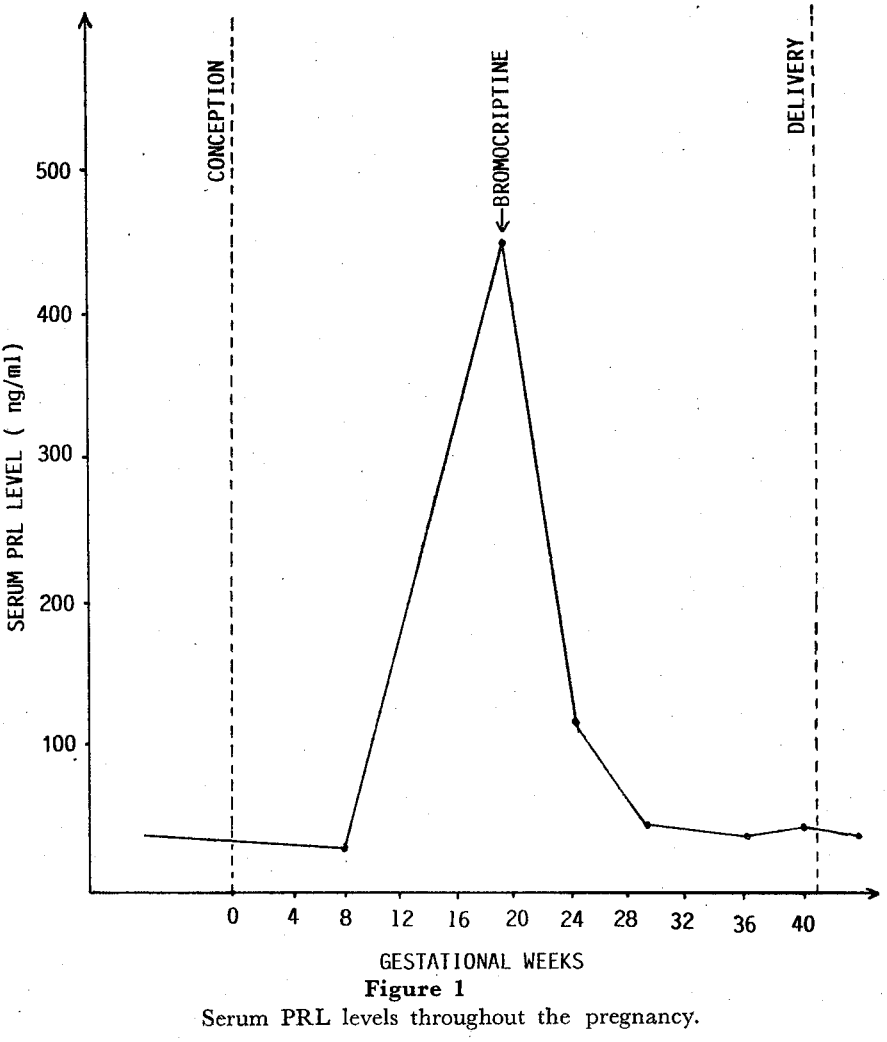

Figure 1
Serum PRL levels throughout the pregnancy.

She was referred to the obstetrics outpatient clinic. Bromocriptine was discontinued. At this time her PRL level was 30 ng/ml, and she was symptom free. At the 19th week of her pregnancy she again complained of severe headaches and visual disturbances. Her visual field examination

revealed bitemporal hemionopsia. She was hospitalized in the highrisk prenatal care unit. Bitemporal hemionopsia was regarded as a neurological emergency and bromocriptine was started immediately; and her visual activity was now monitored. The PRL level at this time was 475 ng/ml. Her complaints resolved daramatically and a repeat visual field examination 10 days later revealed normal findings. The PRL level dropped to 109 ng/ml and the bromocriptine dose was titrated to keep the PRL level below 40 ng/ml throughout the remainder of pregnancy (Figure 1).

The rest of pregnancy course was uneventful and she was followed with visual field examinations and PRL levels at two weeks intervals. She delivered a healthy baby weighing 3900 gm by primary cesarean section. This was because of failure to progress at 40 4/7 weeks of gestation.

Discussion

Pregnancy complicated by a pituitary tumor is considered high-risk. PRL secreting adenomas or prolactinomas are relatively common, found in 22 % of asymptomatic individuals at autopsy.[3] Estrogen induced growth of these tumors during pregnancy can occur rapidly, although the exact incidence of this complication is unknown. Jewelewics and Van de Wiele found that none of the 25 patients they followed with microadenomas suffered neurologic or visual sympotms.[4] Randall *et al* followed 37 patients, 25 with microadenomas and 12 with microadenomas throughout 70 pregnancies and found no evidence of tumor growth.[5] In contrast to this Gamzell and Wang and other investigators reported a 30 % incidence of neurological complications with 6 % being emergency neurological situations.[2, 6, 7]

In regard to normal PRL physiology, the hormone level at the onset of pregnancy increases 10-20 times by the third trimester, reacting concentrations of 200-300 ng/ml and occasionally 600 ng/ml.[8] Measurements of serum PRL levels in patients with proloctinomas showed that the increase in serum concentrations is quite similar to that observed in normal pregnancy.[9] Therefore serial PRL measurements is an unreliable method to monitor tumor growth. Pregnant women with pituitary tumors should be monitored with serially performed visual field examinations for detection of tumor enlargement.[10] Although tumor enlargement in small prolactinomas (microadenomas) is quite rare, when neurologic or visual symptoms are discovered, bromocriptine should be instituted immediateley as initially suggested by Bergh *et al* in 1978[11] and surgical decompression must be considered in the progressive cases. The drug

is started at doses 5-7.5 mg/day and increased gradually until the symptoms disappear. It has been reported that keeping the PRL level below 20 ng/ml prevents any further complications.[12] This therapy can be complemented with Dexamethasone 0.5-1 mg/day should the symptoms fail to disappear. Symptoms disappear very rapidly once bromocriptine therapy is instituted. Bromocriptine affects the growth of prolactinomas by reducing mitotic activity and by inhibiting estrogen induced cellular proliferation.[13] It also decreases both intra and extracellular water concentration and diminishes the tumor size. The patient should be followed very closely with visual field examinations, preferably every few days or even daily sometimes.

Among the patients surveyed by Turkali *et al*, who continued taking their medication during early pregnancy, congenital malformation rate was not different from that seen in general population.[14] The bromocriptine induced decrease in the serum PRL levels appears to cause no interference with the normal secretory functions of the placenta or the maternal endocrine system.[15]

Delivery does not constitute any special problems. Cesarean section is performed for obstetric indications.[10] There is no reason to avoid breast feeding when a patient wishes to nurse her child.[10]

Bromocriptine can be discontinued after delivery and the tumor can regresses to its prepregnancy size; the PRL levels may remain depressed. One month after delivery all patients with adenomas must have a check-up including neurologic, opthalmologic and radiologic evaluations as well as serum PRL determinations.[10]

REFERENCES

1. Child DF, Gordon H, Mashiter K, Joplin GF. Pregnancy, prolactin and pituitary tumors. Br Med J . 1975; 4: 87-92.
2. Gamzell C, Wang CF. Outcome of pregnancy in women with pituitary adenoma. Fertil Steril. 1979; 31: 363-79.
3. Castello RT. Subclinical adenoma of the pituitary gland. Am J Pathol. 1936; 12: 191-6.
4. Jewelewics R, Van de Wiele RL. Clinical course and outcome of pregnancy in 25 patients with pituitary microadenomas. Am J Obstet Gynecol. 1980; 136: 339-45.
5. Randall S, Laing I, Chapman AJ, Shalet SM, Beadwell CG, Kelly WF, David D. Pregnancies in women with hyperproloctinemia: obstetric and endocrinological management of 50 pregnancies in 37 women. Br J Obstet Gyneacol. 1982; 89: 20-7.
6. Thorner MC et al. Pregnancy in patients presenting with hyperprolactinemia. Br Med J. 1979; 2: 771-9.

7. Canales S, Garcia C, Ruiz E, Zarate A. Bromocriptine as prophylactic therapy in proloctinoma during pregnancy. Fertil Steril. 1981; 36: 524-9.
8. Tyson JE, Hwang P, Guyda H. Studies of prolactin secretion in human pregnancy. Am J Obstet Gynecol. 1972; 113: 14-20.
9. Zarate A, Canales S, Alger M, Forbach G. The effect of pregnancy and lactation on pituitary prolactin producing tumors. Acta Endocrinol (Copenh) 1979; 92: 407-9.
10. Velasco VR, Tolis G. Pregnancy in hyperprolactinemic women. Fertil Steril. 1984; 41: 793-9.
11. Bergh T, Nillius SJ, Wide L. Clinical course and outcome of pregnancies in amenorrheic women with hyperprolactinemia and pituitary tumors. Br Med J. 1978; 2: 875-81.
12. Knopka P, Raymond JP, Merceron RE, Sneze J. Continous administration of bromocriptine in the prevention of neurological complications in pregnant women with prolactinomas. Am J Obstet Gynecol. 1983; 146: 935-40.
13. Parkes D. Drug therapy: Bromoergocriptine. N Engl J Med. 1979; 301: 873-6.
14. Turkalj I, Braun P, Krupp P. Surveillance of bromocriptine in pregnancy. JAMA. 1982; 247: 1589-91.
15. Heinonen OP, Slone D, Shapiro S. Birth defects and drugs in pregnancy. Littleton Publishing Sciences Group, London, New York 1977.

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Thyrotoxicosis and Polymyalgia Rheumatica

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Summary

Polymyalgia rheumatica (PMR) is a clinical syndrome of elderly patients and its cause is still unknown. There have been few previous reports of associated thyrotoxicosis and PMR, and these reports have suggested that this relationship is not rare. A male patient with PMR developed two years after the remission of thyrotoxicosis is reported. An interesting point was the devolopment of PMR just following the thyroid scintigraphy.

Key Words: Polymyalgia rheumatica, Thyrotoxicosis, Thyroid scintigraphy.

Introduction

The association between thyrotoxicosis and giant-cell arteritis (GCA) was first recognized in 1974.[1] Two subsequent prospective studies[2,3] suggested a relationship between autoimmune thyroid disease and polymyalgia rheumatica (PMR) - GCA. The existence of a common etiology for these two disease in susceptible individuals is possible.[4]

The cause (s) of PMR is still unknown.[5] A significant increased prevalance of HLA-DR3 and -DR4 antigens has been shown in recent reports suggesting an immunogenetic mechanism.[5-7] Infective or other environmental pathogenetic mechanisms have also been considered.[5]

We report a case of PMR developed following the thyroid scintigraphy in a patient with thyrotoxicosis in remission.

Case Report

A 62 year old Caucassian male was admitted to hospital in March, 1987, with a two month history of bitemporal headache and tenderness,

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neck and shoulder pain, malaise and anorexia. During this period he had a weight loss of 20 kg. In history he had a thyphoid fever 40 years ago and thyrotoxicosis diagnosed three years ago. He had been treated with propylthiouracil (PTU) (300 mg/day and then 150 mg/day) for ten months. Administration of PTU had been terminated after reaching the euthyroid state and the patient had been followed-up in outpatient department. He had a thyroid scintigraphy two months ago, and the next day he developed malaise, anorexia, chilling followed by bitemporal headache and tenderness and neck and shoulder pain within a week.

On admission the patient was in a deppressive mood. He was found to have a pulse rate of 112 per minute (which dropped to 96 and 84 on consequtive two days without treatment), temperature of 37°C, an arterial blood pressure of 130/70 mmHg and bilateral moderate exophthalmos. His symptoms included severe bitemporal headache, morning pain and stiffness in the neck, shoulder girdle and proximal arms, and transient visual blurring for several minutes. Passive mobility was normal and proximal muscle weakness of the upper limbs was mild. There was a small, diffuse goitre with no bruit, and tremor, nervousness, sweating and thyroid dermopathy were not present. On ophthalmologic examination, there were 22 Hertel exophthalmos bilaterally and an old haemorrhagic focus on left macula. He had bitemporal tenderness on palpation without redness or thickening.

A full blood count revealed a mild normocytic normochromic anemia with hemoglobin concentration of 11 g/dL and hematocrit 34%. WBC count was 5.2 x 10^9 /L and erythrocyte sedimentation rate (ESR) was 72-110-115 mm/h. Serum creatinine, BUN, electrolytes, SGOT, SGPT, glucose, lipids and biluribins were normal. Alkaline phosphatase level was 6.0 Bodansky unit (normal range 1.5-4.5) and serum albumine and globuline levels were 3.2 and 4.0 g/dL, respectively. Serum protein electrophoresis showed a decrease in albumin (40 %), and increases in alpha$_2$-globulin (14 %) and gamma-globulin (25 %) fractions. There was no monoclonal peak. Serum IgG-HC was 219 IU/mL (n.r. 92-207), IgA 350 IU/mL (n.r. 54-268) and IgM 378 IU/mL n.r. 69-287). CRP was (++), latex (–) and LE cell (–). Screening for hepatitis B antigen and antibody, salmonella and brucella antibodies and cold agglutinin were negative. Repeated blood, urine and sputum cultures grew no organisms. Radiological examination of the chest, bones, gastrointestinal tract and kidneys (IVP) , as well as abdominal CT revealed no pathologic findings. Bone marrow smears showed no abnormality.

Serum triiodothyronin (T_3) RIA level was 1.75 nmol/L(n.r. 0.8-2.7) and thyroxin(T_4) RIA level 158 nmol/L(n.r. 62-160). We couldn't per-

form the free T_3 and T_4 levels, and TRH-stimulation and RAIU tests for practical reasons. Autoantibody screening results, including anti-thyroglobulin, antinuclear, anti-smooth muscle, anti-mitochondrial and anti-parietal cell, were negative. Thyroid-stimulating immunoglobulins and anti-thyroid microsomal antibodies were not estimated.

The patient refused the temporal artery biopsy. A presumptive diagnosis of polymyalgia rheumatica was made and the patient was put on prednisolone therapy with a daily dose of 15 mg, which is proposed as usual initial dose for PMR therapy.[5, 8] There was an excellent response to treatment, with cessation of symptoms within three days. Nine days later, ESR was 55 mm/h and CRP (+), and by three weeks ESR decreased to 7 mm/h and CRP became negative. At present, on the same dose of prednisolone the patient is still symptom-free with normal laboratory findings.

Discussion

The association between thyrotoxicosis and PMR-GCA was first recognized in five female patients among 101 cases with temporal arteritis in 1974.[1] Previously Hauser *et al*[9] had mentioned about 19 patients with temporal arteritis, four had undergone a previous thyroidectomy for thyrotoxicosis prior to their temporal arteritis. Dent and Edwards[2] found three patients with temporal arteritis and a history of thyrotoxicosis in a prospective study of 250 patients with autoimmune thyroid disease. A fourth patient had PMR following thyrotoxicosis. Simultaneous occurence of thyrotoxicosis and PMR-GCA has also been reported.[1, 4, 10]

Both PMR-GCA[11, 12] and thyrotoxicosis[13] are generally accepted as having an immunological pathogenesis. An increased incidence of HLA-B8 in patients with thyrotoxicosis is a well-known feature, and increased frequency of HLA-B8[14, 15] and recently HLA-DR3 and DR4[6, 7] antigens in PMR patients has been shown. It is possible that HLA-B8, or an allele in linkage disequilibrium with it, may predispose to immunopathological process common to both disease, thus explaining their association.[10]

Our patient fulfilled the diagnostic criteria of Jones and Hazleman[16] for PMR, and had the criteria for clinical diagnosis of temporal arteritis proposed by Ellis and Ralston.[17] Rapid response to a low dose steroid therapy also supported the diagnosis. Although PMR patients with clinical signs of temporal arteritis need higher doses of prednisolone, there is, however, no evidence that 60 mg of prednisolone daily as an initial dose is superior to 20 mg in preventing GCA-related complica-

tions.[5] Since 15 mg daily dose was sufficent to control symptoms and signs of the patient, we didn't consider to increase the dose of prednisolone.

Of the cases with associated autoimmune thyroid disease and PMR-GCA, none of the Thomas' and Croft's patients[1] and only one of the 29 cases of How's and Brewster's series[3] have been male. The second male patient was the case reported by Nicholson *et al.*[10] In view of the marked female predominance in autoimmune thyroid disease and the slight female predominance in PMR-GCA, it is not surprising to find a female predominance in cases with associated thyrotoxicosis and PMR-GCA.[10] To the best of our knowledge, our case is a third male in literature.

We didn't consider our case as an "antithyroid arthritis syndrome" because he had discontinued the antithyroid drug at least two years ago and had no arthritis; besides his ESR was very high, which would be normal in this syndrome.[18] Euthyroid state of the patient and increased ESR excluded the possibility of thyrotoxic myopathy.[5] The dose of radioactive iodine for thyroid scintigraphy is very low to develop a thyroiditis, while such an occurence is also extremely rare even with large doses administered to treat thyrotoxicosis.[19] Furthermore, our patient lacked other signs and symptoms of thyroiditis, such as pain, tenderness and nodularity over the thyroid, or pain referred to the lower jaw and ear, or thyrotoxic or hypothyroid state.

A mild increase in alkaline phosphatase was present in our case. Elevated serum alkaline phosphatase levels have been reported in 20 to 55 percent of PMR-GCA patients.[5]

Autoimmune disorders are known to be able to occur together in the same patient. Autoimmune thyroid disorders have been shown to occur in association with connective tissue disorders such as rheumatoid arthritis, Sjögren syndrome and systemic lupus erythematosus.[20] In most of the autoimmune connective tissue disorders where an association with thyrotoxicosis is present, thyrotoxicosis precedes the connective tissue disorder[1] as in our case. The association of thyrotoxicosis with PMR-GCA has been known since 1974.[1] Antithyroid antibodies were negative in our patient. Antithyroid antibodies frequently become normal several years after patients have been treated.[20]

An interesting point of our case was the development of PMR just following the thyroid scintigraphy, which was probably coincidental, but may also reflect the interaction of an environmentally derived stimulus with the host immune system, probably by altering the antigenicity of an unidentified antigen.[21] Both PMR-GCA and thyrotoxicosis are generally

accepted as having an immunological pathogenesis. Reports of Hickstein *et al*[22], Garfinkel *et al*[23] and Kyle *et al*[24] supported an infective or other environmental pathogenetic causes.

We want to emphasize that a physician should remain alert to the possibility of the development of PMR-GCA in elderly patients with autoimmune thyroid disease.

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REFERENCES

1. Thomas RD, Croft DN. Thyrotoxicosis and giant cell arteritis. Br Med J. 1974; 2: 408-9.
2. Dent RF, Edwards OM. Autoimmune thyroid disease and the polymyalgia rheumatica-giant cell arteritis syndrome. Clin Endocrinol (Oxford) 1978; 9: 215-9.
3. How J, Brewster PD. (letter) Clin Endocrinol (Oxford). 1980; 12: 209-10.
4. Whitby M, Hobson D. Simultaneous onset of thyrotoxicosis and temporal arteritis. Med J Aust. 1982; 2: 483-4.
5. Olhagen B. Polymyalgia rheumatica. Clin Rheum Dis. 1986; 12: 33-47.
6. Armstrong RD, Behn A, Myles A, Panayi GS, Welsh KI. Histocompatibility antigens in polymyalgia rheumatica and giant cell arteritis. J Rheumatol. 1983; 10: 659-61.
7. Lowenstein MB, Bridgeford PH, Vasey TB, Germain BF, Espinoza LR. Increased frequency of HLA-DR3 and DR4 in polymyalgia rheumatica-giant cell arteritis. Arthritis Rheum. 1983; 26: 925-7.
8. Healey LA. Polymyalgia rheumatica. In: Mc Carty DJ, ed. Arthritis and Allied Conditions. Philadelphia, Lea & Febiger, 1979, 681-4.
9. Hauser WA, Atkins HC, Richards P. Temporal arteritis in Rochester, Minnesota, 1951 to 1967. Mayo Clin Proc. 1971; 46: 597-602.
10. Nicholson GC, Carroll WM, Gutteridge DH, Armstrong BK. Autoimmune thyroid disease and giant cell arteritis: A review, case report and epidemiological study. Aust NZ J Med. 1984; 14: 487-90.
11. Gallagher P, Jones K. Immunohistochemical findings in cranial arteritis. Arthritis Rheum. 1982; 25: 75-9.
12. Ilfeld D, Barzilay J, Vana D, Ben-Bassat M, Joshua H, Pick I. IgG monoclonal gammopathy in four patients with polymyalgia rheumatica. Ann Rheum Dis. 1985; 44: 501-2.
13. Volpe R. The pathogenesis of Graves' disease. Clin Endocrinol Metabol. 1978; 7: 3-29.
14. Rosenthal M, Muller W, Albert ED, Schattenkirchner M. HLA antigens in polymyalgia rheumatica. N Engl J Med. 1975; 292: 595.
15. Hazleman B, Goldstone A, Vocak D. Association of polymyalgia rheumatica and giant cell arteritis with HLA-B8. Br Med J. 1977; 2: 989-91.
16. Jones JG, Hazleman BL. Prognosis and management of polymyalgia rheumatica. Ann Rheum Dis. 1981; 40: 1-5.

17. Ellis ME, Ralston WS. The ESR in the diagnosis and the management of the polymyalgia rheumatica/giant cell arteritis syndrome. Ann Rheum Dis. 1983; 42: 168-70.

18. Shabtai R, Shapiro MS, Orenstein D, Taragan R, Shenkman L. The antithyroid arthritis syndrome reviewed. Arthritis Rheum. 1984; 27: 227-9.

19. Greenspan FS, Rapoport B. Thyroiditis. In: Greenspan FS, Forsham PH, eds. Basic and Clinical Endocrinology. Los Altos, Lange Medical Publications, 1983, 174-6.

20. Goh KL, Wang F. Thyroid disorders in systemic lupus erythematosus. Ann Rheum Dis. 1986; 45: 579-83.

21. Dasgupta B, Duke O, Kyle V, Macfarlane DG, Hazleman BL, Panayi GS. Antibodies to intermediate filaments in polymyalgia rheumatica and giant cell arteritis: a sequential study. Ann Rheum Dis. 1987; 46: 746-9.

22. Hickstein DD, Gravelyn TR, Wharton M. Giant cell arteritis and polymyalgia rheumatica in a conjugal pair. Arthritis Rheum. 1981; 24: 1448-50.

23. Garfinkel D, Bograd H, Salamon F et al. Polymyalgia rheumatica and temporal arteritis in a married couple. Am J Med Sci. 1984; 287: 48-9.

24. Kyle MV, Hazleman BL, King RH. Polymyalgia rheumatica/giant cell arteritis in husband and wife. Clin Rheumatol. 1984; 3: 395-6.

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Spondyloepiphyseal Dysplasia Tarda

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Summary

A case of spondyloepiphyseal dysplasia tarda in adolescence is presented with a discussion of clinical and radiological findings. This is an established familial bone dysplasia, presenting in childhood or adolescence in a person with short stature and poor posture. There is generalized platyspondyly, frequently associated with back pain. It occurs only in males.

Key Words: Osteochondrodysplasias, Back pain, Dwarfism, Spine.

Introduction

The syndrome of short stature inherited as an x-linked recessive trait was first reported by Jacobsen who described one family under the title "hereditary osteochondrodystrophia deformans".[1] Three more pedigrees were studied by Maroteaux. Lamy and Bernard, who proposed the name dysplasia spondyloepiphysaire tardive or spondyloepiphyseal dysplasia tarda(SEDT).[2] Because of the specific mode of genetic transmission and the consistent roentgen findings in the spine with relative sparing of the extremities, the authors believed that this condition could be differentiated from Morquio-Brailsford disease.

The criteria for this rare syndrome may be listed as follows: 1- x-linked recessive inheritence, 2- Short stature first evident in childhood between 5-14 years, 3- Shortness due to impared growth of spine,4- Radiologically characteristic flattening of vertebrae with central humping, 5- Dysplastic changes of femoral heads and neck, 6- Minor changes in other bones.[3]

The case reported here is an example of this rare syndrome.

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Case Report

A boy of fourteen years of age was admitted with chief complaints of inadequate stature, poor posture and back pain. Apart from these complaints he has remained symptom free.

The specific measurements were: Weight: 43 kg. Height: 145 cm; he was 15 cm shorter than average for his age.[4] Span: 158 cm, Lower segment: 74 cm.

Family history: The mother was 160 cm in height and father was 170 cm. The mother stated that her aunt had 4 male children with severe short stature and poor posture and her brother was also short; below 150 cm. The pedigree of this family is seen in Figure 1.

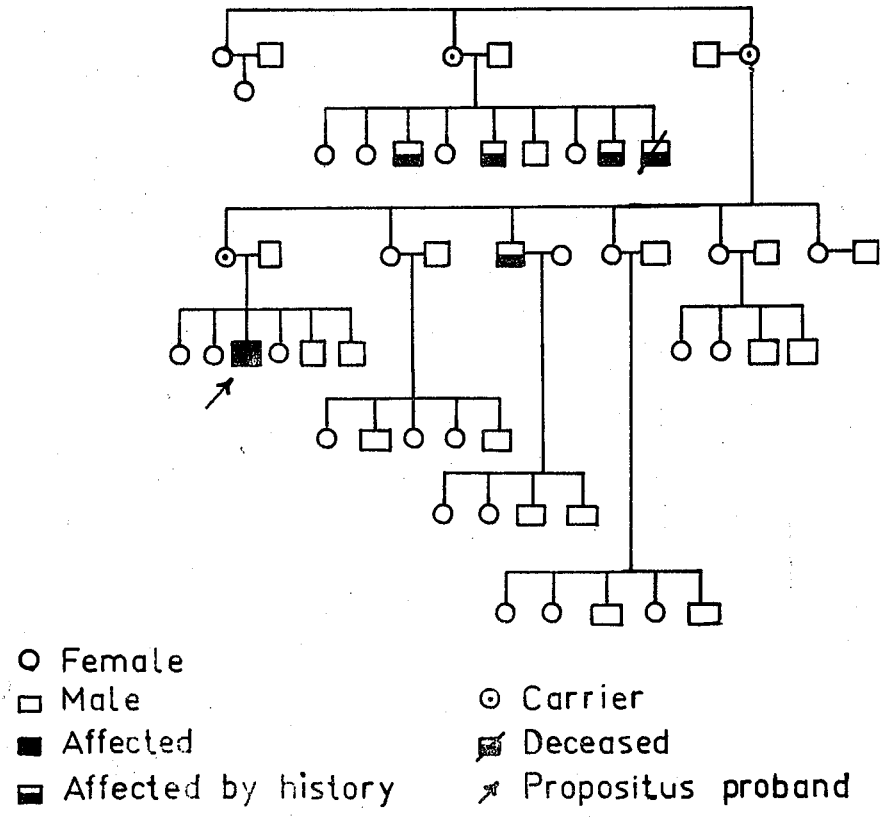

Figure 1
Pedigree of the family.

Developmental history : The boy weighted 3 Kg at birth and no abnormality was noted at birth or during infancy. He walked and talked at the usual time.

Physical examination: The patient appeared appreciably younger than his given age of 14 years. The trunk showed mild dorsal kyphosis and scoliosis convex to the right. Because of the shortening of the spine, his fingertips reached almost to his knees when in the standing position (Figure 2). Genitalia were normal and there were no abnormalities outside the skeletal system, in particular no corneal clouding, cardiac abnormality, hepatosplenomegaly or neurological defect. Dentition was normal.

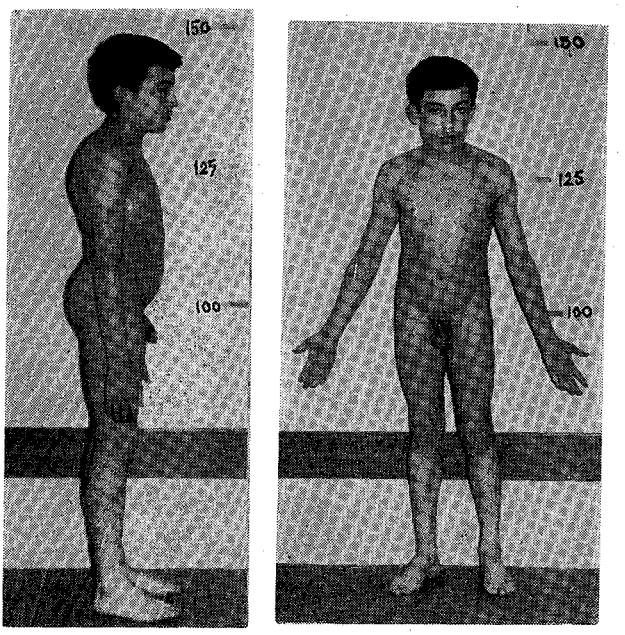

Figure 2
Photograph of the patient. Note shortness of trunk as compared to length of extremities and mild dorsal kyphosis.

Roentgen findings: Examination of the thoracolomber spine showed generalized flattening of the vertebral bodies with increase in the anteroposterior and lateral diameters and a relative decrease in the vertical height of the vertebral bodies. There was also anterior pointing of the vertebral bodies (Figure 3). Films of the knees revealed mild flattening of the bony margins of the joints and the tibial plateaus and the proximal tibial epiphyses were widened (Figure 4). The pelvis and hip joints demonstrated only minimal changes. The pelvis showed small ilia with a long deep configuration due to elongated pubic and ischial bones. The acetabula were deep (Figure 5). The hands and pelvis disclosed a skeletal age of twelve years (Figure 6) and epiphyseal flattening was seen.

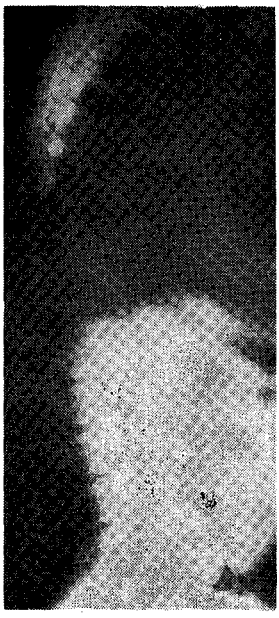

Figure 3
Lateral view of dorsolumbar spine showing platyspondyly involving all segments.

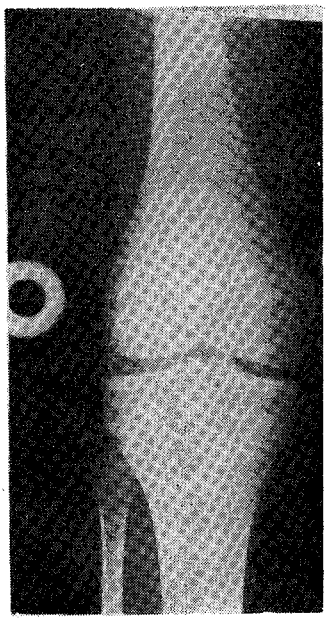

Figure 4
Frontal view of one of his knee showing mild flattening of the bony margins.

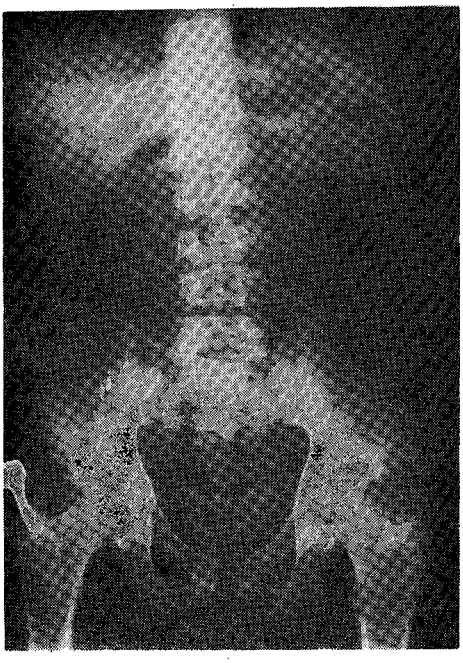

Figure 5
X-ray of pelvis and hips showing narrow pelvis and mild dysplastic changes in the acetabulae.

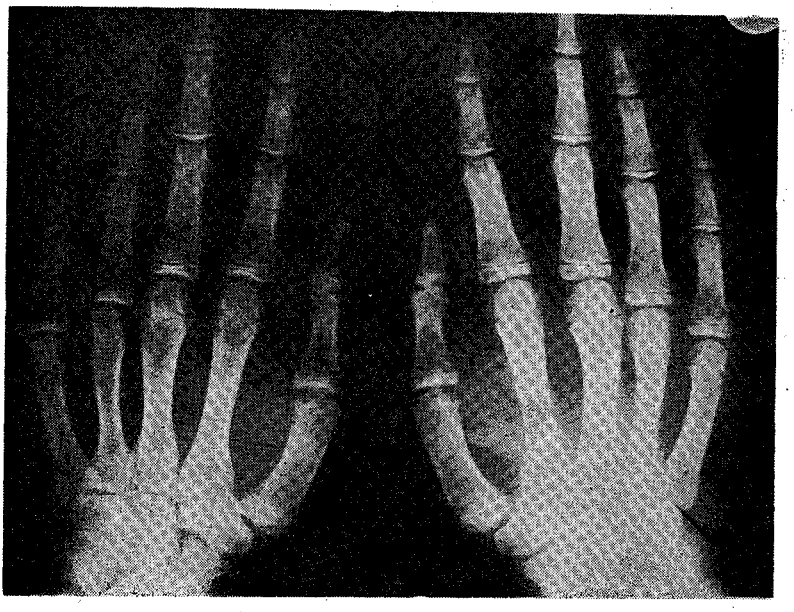

Figure 6
X-ray of hands with mild epiphyseal flattening.

Laboratory work-up: Routine blood counts and urinalysis studies were normal. Urinary mucopolysaccharide (chondroitin sulfate) excretion was also normal; 6.5 mgr/twenty-four hours. Homogentisic acid was absent.

Discussion

The term "platyspondylosis" was first used by Putti in 1910 in describing the appearance of the vertebral body.[5] Lane in 1960 described platyspondyly as an unusual finding in multiple epiphysial dysplasia.[6]

The clinical features of SEDT have been described by previous authors mentioned in the introduction, particularly Maroteaux *et al.*[2] The radiological findings have been set out by Langer, but his patients were seen at ages of fourty-seven, fourty-two, thirty-nine and twenty-five years. In addition to the references already cited, two brothers reported by Halberstaedter probably had SEDT,[8] and a single case was reported in detail by Specht.[9] In 1965 Poker et al reported four cases in childhood and adolescence and some considerations regarding platyspondyly, because they beleived that these patients illustrated typical findings of SEDT in a younger age group.[10] They proposed that characteristic and diagnostic changes were seen at 11.2 and 14.7 years like our case. Less specific changes were seen at 6.7 and 8.0 years.

Platyspondyly characteristically occurs in certain chondrodysplasias. It is the essential finding in Morquio-Brailsford osteochondrodystrophy in SEDT. It is common in Hunter-Hurler disease (gargoylism, dysostosis multiplex)and may be seen in achondroplasia, certain rare cases of multiple epiphyseal dysplasia and also occasionally in adolescent kyphosis (Scheuermann's disease), although this last named entity is not usually grouped with the chondroplasias.[11, 12]

The radiological changes can be as follows: The vertebral bodies show a generalized flattening with a humpshaped mound of dense bone occupying the central and the posterior portions of the bodies throughout the spine to the level of the second cervical vertebra. The region of the ring apophyses shows an apparent complete lack of bone. A mild scoliosis becomes apparent in adolescence and the disc spaces become narrowed (Figure 3,5). As the result of the shortening of the spine the diameters of the chest become slightly increased. The pelvis has a deep narrow configuration with small iliac wings and long pubic and ischial bones. Mild dysplastic changes have been described in other joints as seen in our case (Figure 4). The course of the condition is usually benign with normal intelligence; complete absence of systemic complications and only reduction in height, frequently associated with back pain just like our case.[13]

The differential diagnosis of SEDT is principally from the mucopolysaccharidoses and from other bone dysplasias affecting the spine.[14, 15] The distinguishing features are the absence of extreme joint laxity, and of the consequent neurological complications. Also the absence of corneal clouding, of cardiac and visceral involvement and mucopolysaccharidurie excludes other members of this group. The distinctive radiological findings in the spine are quite unlike other types of spondiloepiphyseal dysplasia. In the adult ocronosis (alcaptonuria) may be confused on accound of the widespread disc calcification, homogentisic acid is present in the urine in this condition. No metabolic abnormality has so far been described in SEDT. The characteristic and perhaps pathognomonic vertebral bony configuration consists of hyperostotic new bone formation on the posterior two-thirds of the articular surfaces of the vertebral bodies. This appearence is accentuated by depression of the anterior thirds, often associated with anterior displacement of the nucleus pulposus, this resembling Schmorl's nodes. Narrowing of the disc spaces, calcification of the discs and spondylotic bridging characterise later stages of the disorder.[16,17] There was not such a finding in our case because of his being 14 years old. It seems that this case is similar to SEDT with inadequate stature, poor posture and back pain and also typical roentgenological findings without any abnormality in the laboratory investigation.

In the absence of serial radiographic studies of this condition in childhood, one can only speculate. However, on the basis of the case of Maroteaux and his associates,[2] and the typical clinical course with no symptomes or shortening in early life, it would appear that the structure of the vertebrae originally is grossly normal; and that over time, there develop demonstrable changes eventuating in the characteristic picture in mid or late adolescence. If this is true, early diagnosis would be impossible.[16]

REFERENCES

1. Jacobsen AW. Hereditary osteochondrodystrophia deformans. A family with twenty members affected in five generations. J Am Med Ass. 1939; 113: 121-4.
2. Maroteaux P, Lamy M and Bernard J. La dysplasie spondylo-epiphysaire tardive, description clinique et radiologique. Press Med. 1957; 65: 1205-8.
3. Bennerman RM, Ingall GB, Mohn JF. X-linked Spondyloepiphyseal Dysplasia Tarda Clinical and Linkage Data. J Med Genetics. 1971; 8: 291-301.
4. Tanner JM. Physical Development. Br Med Bul. 1986; 42: 131-8.
5. Putti V. Die angeborenen Deformitaten der Wirbelsaule. Rontgenstrahlen. 1910; 14: 285-313.
6. Lane JW. Roentgenographic Manifestations of the Cartilaginous Dysplasias. Am J Soc. 1960; 240: 636-70.
7. Langer LO. Spondyloepiphyseal Dysplasia Tarda. Hereditary Chondrodysplasia with Characteristic Vertebral Configuration in the Adult. Radiology. 1964; 82: 833-8.
8. Halberstaedter M. Familial Vertebral Dystrophy. Case reports. Br J Radiol. 1948; 16: 121-4.
9. Specht EE. Spondyloepiphyseal Dysplasia Tarda - A Case Report. Clin Ortop. 1968; 60: 159-62.
10. Poker N, Finby N, Reginald M, Archibald M. Spondyloepiphyseal Dysplasia Tarda. Four cases in Childhood and Adolescence and some considerations regarding platyspondyly. Radiology. 1965; 85: 474-80.
11. Rimoin DL, Lachman RS. The chondrodysplasias. In: Emery AEH, Rimoin DL (Eds). Principles and Practice of Medical Genetics. Great Britain: Churchill Livingstone, 1983; 703-35.
12. Horan FT. Genetic aspects of Orthopaedics: Bone dysplasias. In: Harris NH (Ed). Postgraduate Textbook of Clinical Orthopaedics. Great Britain: John Wright and Sons Ltd. 1987; 5-21.
13. Harper PS, Jenkins MB, Laurence KM, Path FR. Spondyloepiphyseal Dysplasia Tarda: a report of four cases in two families. Br J Radiol. 1973; 46: 676-84.
14. Horan F. Beighton P. Disorders of the Epiphyses and Metaphyses with Major Vertebral Involvement. In: Orthopaedic Problems in Inherited Skeletal Disorders. Great Britain: Springer-Verlag, 1982; 34-7.
15. Benson DR. The Back: Thoracic and Lumbar Spine. In: D'Ambrosia R, Musculoskeletal Disorders. USA: Lippincott. 1977; 245-319.
16. Langer LD. Spondyloepiphyseal Dysplasia Tarda. Hereditary Chondrodysplasia with Characteristic Vertebral Configuration in the Adult. Radiology. 1964; 82: 833-9.
17. Murray RO, Jacobson HG. Spondyloepiphyseal Dysplasia. In: The Radiology of Skeletal Disorders. New York: Churchill Livingstone, 1977; 172-9.

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Uterine Tumor Resembling Ovarian Sex Cord Tumors

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Summary

Uterine tumors resembling ovarian sex cord tumors are very rare. In this report we present a case with histopathologic features of Sertoli cell differentiation.

Key Words : Uterine tumors, ovarian Sex-Cord tumors, Sertoli Cell tumors.

Introduction

First described by Clement and Scully[1] in 1976, uterine tumors resembling ovarian sex cord tumors aroused interest mainly because of their uncertain histogenesis. Kantelip, Cloup and Dechelotte[2] found ten such cases in the literature, and added their own study which included ultrastructural features. Characteristically, the tumor is found as a mass attached to or in the uterine corpus with no connection to the ovaries. The lesion generally measures less than 15 cm and contains cysts filled with brownish hemorrhagic fluid.

Histologically, the tumor are predominantly epithelial with mixtures of cords, nests and anastomosing trabeculae. Well-formed tubules lined by cells resembling granulosa or Sertoli cells were also described, hence the name "uterine tumor resembling ovarian sex cord tumors".

The tumor behaved indolently in all instances except case number 14 of the Clement and Scully series which showed vascular invasion.[1] The age range was 32 to 86 with a preference for perimenopausal patients who came to attention mainly because of abnormal uterine bleeding.[1, 2]

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Case Report

A 45 years old woman was admitted to the hospital with a complaint of irregular bleeding from vagina. A bimanual examination disclosed a mass in the uterine corpus. All routine investigations were within normal limits. The patient was operated on with the preoperative diagnosis of the subserous uterine leiomyoma.

The operation specimen consisted of a 9x7x5 cm uterus and both adnexa. The gross appearance of the uterus and the adnexa was unremarkable except for a 9 cm subserosal mass which was partially cystic (Figure 1). The cut surface of the lesion showed numerous cysts ranging in size from 0.5 to 2 cm and filled with clear to cloudy fluid.

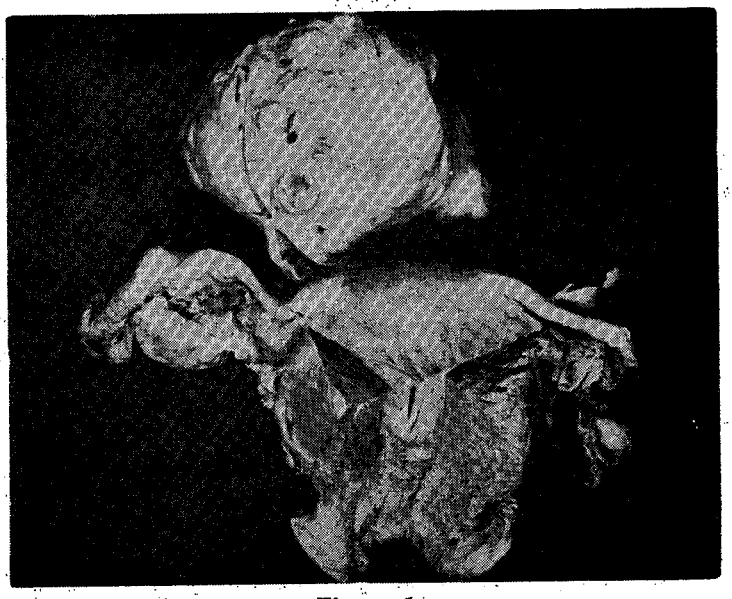

Figure 1

Gross appearance of the operation specimen. Note the location and multicystic nature of the tumor.

On histologic examination, an epithelial-like tumor was seen (Figure 2). Many blocks were processed in order to reach a conclusive diagnosis. The appearances of each section was almost uniform. The border between the tumor and normal myometrium was rather abrupt, but no significant sign of pseudoencapsulation could be seen. In all the fields, tubule-like structures encircled by a thin fibrous band predominated (Figure 3). The cysts, observed grossly, were lined by one or more rows of cuboidal cells of uncertain nature. The cytoplasm of the cells lining

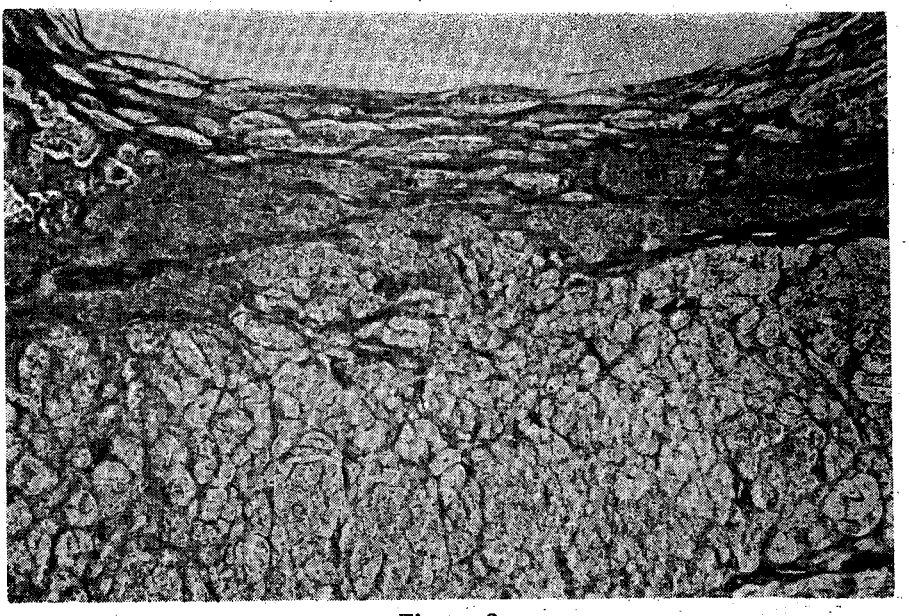

Figure 2

Low-power view of the tumor with a cyst at the upper part of the field. Note the epithelial appearance.

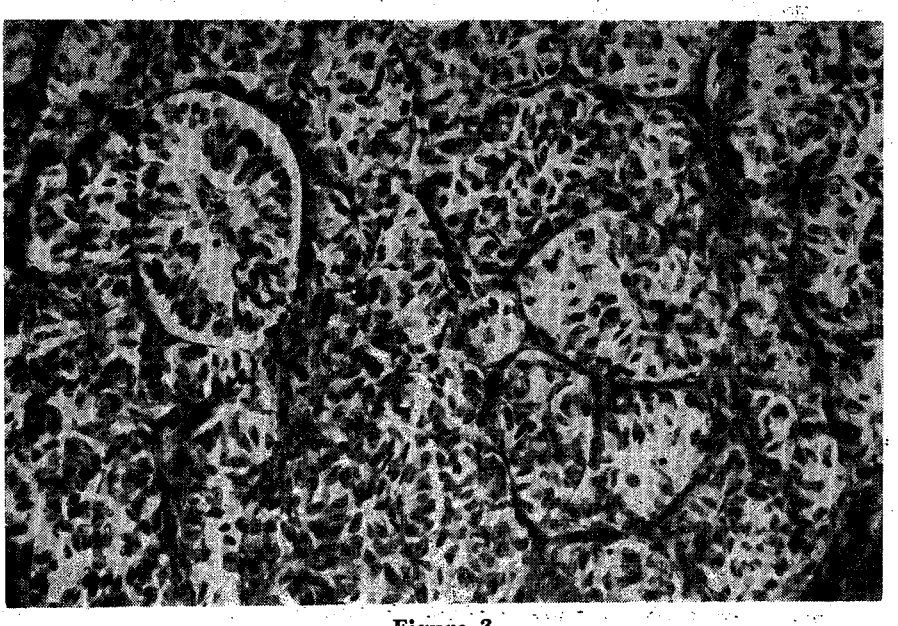

Figure 3

Tubules of different width. There is a strong resemblance to the sertoli cell tumors of the ovarii.

the tubule-like compartments were amphophilic to clear, and contained microvesicles which were regarded as tiny fat droplets. The nuclei were oval or spindle shaped and euchromatic. Lumen-like spaces were present in the centers of some nests. The stroma consisted of inactive looking spindle cells. Mitoses were rare and no vascular invasion was seen. There was no significant pathology in the other parts of the specimen.

A diagnosis of a uterine tumor resembling ovarian sex cord tumor was thus made. Dr. Scully of Massachusetts agreed on the diagnosis (pers. comm.). He also expressed his belief that the cells comprising the bulk of the tumor were probably not true Sertoli cells.

Electron microscopy, carried out on tissues recovered from formalin after a prolonged period of fixation, showed many artefacts and degenerative changes which made the interpretation almost impossible.

The postoperative period was uneventful and, 45 months after the operation, the patient was still free of any disease.

Discussion

The presence of cells resembling epithelia in mesenchymal tumors has long been a matter of interest and speculation. Myometrial tumors of this kind are very rare. They were grouped under various designation such as granulosa cell tumor[3] before the article of Clement and Scully[1] which presented 14 uterine tumors resembling ovarian sex cord tumors. In six of this cases the epithelial component was focal whereas in the remaining eight it was predominating. The number of these predominantly epithelial tumors is still too small to enable us to reach a conclusion about their nature and significance. For this reason, Kantelip *et al*[2] compared the ultrastructural features of their case with that of similar ovarian neoplasms and found some similarities between the two. The neoplastic cells observed in the case of Kantelip *et al*[2] were characterized by basement membrane, cell junctions, microflaments and a structure resembling Charcot-Böttcher crystals. From these observations the authors concluded that the cells showed Sertoli cell differentiation and that the exact origin of these cells is uncertain. On the other had, Mazur and Kraus,[4] in a review of seven uterine tumors with morphologic variations, postulated the probability of different histogenetic pathways. In case number 5 of their series, diagnosed as a plexiform tumor, they observed features such as a continuous basal lamina, desmosomes, and tonofilaments. They did not observe microvilli. In case number 6, diagnosed as leiomyoma with tubules, there were features such as discontinuous basal lamina, numerous microvilli, desmosomes, and tonofila-

ments which were regarded as evidence of mesothelial differentiation. In both of these ceses, Mazur and Kraus[4] shared the views of Clement and Scully[1] and favored the concept of endometrial stromal cell derivation.

Although the histology of our case was typical and easy to comprehend, the electron microscopy proved unrewarding due to poor preservation of the specimen. Electron microscopy is probably not necessary in the diagnosis of uterine tumors resembling ovarian sex cord tumors, but is certainly a part of histogenetic investigations.

Regarding histogenesis, one is left with the theory of multipotentiality of Mullerian mesenchyme as stated by Mazur and Kraus[4] and Clement and Scully.[1] The equally acceptable view would be one which regards the epithelial inclusions as the origin of these unusual tumors. At the present time we have no definitive proof to allow us to accept or reject either of these theories, nor do we have any other explanation.

REFERENCES

1. Clement PB, Scully RE. Uterine tumors resembling ovarian sex cord tumors. Am J Clin Pathol. 1976; 66: 512-25.
2. Kantelip B, Cloup N, Dechelotte P. Uterine tumor resembling ovarian sex cord tumors-report of a case with ultrastructural study. Hum Pathol. 1986; 17: 91-4.
3. Morehead RP, Bowmann MC. Heterologous mesodermal tumors of the uterus-report of a neoplasm resembling a granulosa tumor. Am J Pathol. 1945; 24: 53-61.
4. Mazur MT, Kraus FT, Histogenesis of morphologic variations in tumors of the uterine wall. Am J Surg Pathol. 1980; 4: 59-74.

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Unusual Foreign Body in the Bladder and Urethra

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Summary

Foreign bodies in the lower genitourinary tract are quite common and they are inserted as a result of different motives.

We report such a case admitted to our department.

Key Words: Foreign body, bladder.

Introduction

Foreign bodies in male and especially female lower urinary tract are quite common. Unusual cases have been reported in the literature such as the self insertion of objects: ball point pen,[1] fishing line,[2] knotted string,[3] needles and animal feathers,[3] plastic rod,[4] glass cutter,[5] methamphetamine tablets,[6] etc., and some iatrogenic cases.[7]

In this paper we report a similar case, admitted to Marmara University Hospital, Department of Urology.

Case Report

A 42-year-old female patient, who had a past history of sectio operation eleven years ago, presented with the complaints of dysuria, followed by urinary retention, and a sponge that came out through the urethra a couple of hours before admission.

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On physical examination, the sponge was observed protruding through the urethra partially. There was dribbling of the urine via this gauze; yet a suprapubic mass, suggesting globe, was palpable. She was otherwise normal. An excretory urography revealed a left sided ureteral calculus, not obstructive, but no detailed information about the bladder. Ultrasound and CT scans (Figure 1) of the bladder revealed a large mass in the lumen, mostly free floating.

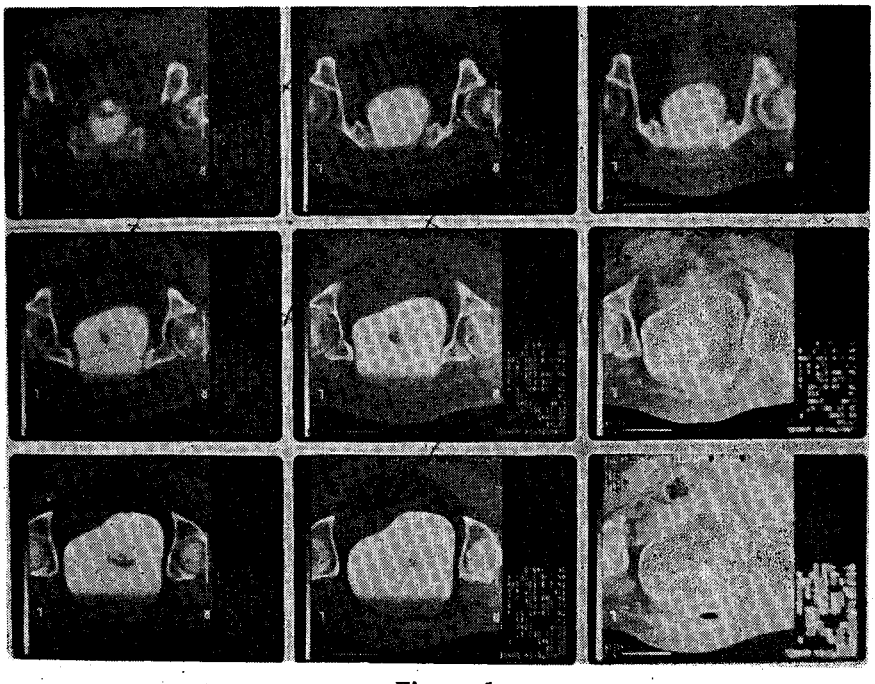

Figure 1

The sponge was pulled out under general anesthesia, and subsequent cystoscopy did not give evidence of any defect inside the bladder, nor were there signs of chronic inflammation or infection due to a foreign body.

On a later occasion, the information of recent self insertion of the sponge with unknown reasons, was given by the patient.

Her recovery was uneventful and she was discharged the day after.

Discussion

Foreign bodies in the bladder have been reported widely with the usual underlying causes either iatrogenic or self introduction. The latter has almost always a sexual motivation.[2] Migration of foreign bodies in to the urinary tract from adjacent body structures, like a toothpick from

gastrointestinal tractus,[8] or erosion of an inflatable penile prosthesis reservoir in to the bladder,[9] have been well documented. Displacement of the hip prosthesis in to the bladder has also been reported.[10]

The most important aspect is the differential diagnosis with the other space occupying lesions (i.e. neoplasms of the bladder or calculi).

We performed cystoscopy in our patient in order to rule out the possibility of migration of an unintentionally left sponge from the previous sectio operation site in to the bladder. There were no signs of such a possibility. We concluded that this case is an example of self insertion of a foreign body in to the bladder.

REFERENCES

1. Kaczmarek A. Unusual complication of foreign body in the bladder. Br J Urol. 1985; 57: 106.
2. Williams RJL, Freeman A, Brendler CB. Acute renal failure secondary to fishing line, Br J Urol. 1985; 57: 590.
3. Leoni S. Unusual foreign body in the urethra, J Urol. 1983; 55: 129.
4. Roemer KR, Das S. Transurethral endoscopic removal of cylindirical intravesical body, Urology. 1984; 6: 592-3.
5. Peters PC, Sagolowsky AI. Genitourinary trauma, In: Walsh P, Gittes RF, Perlmutter AD, Stamey TA, Campbell's Urology, Philadelphia, W.B. Saunders Co., 1986; 1219-20.
6. Ellison JM, Dobies DF. Methamphetamine abuse presenting as dysuria following urethral insertion of tablets, Ann Emerg Med. 1984; 13: 198-200.
7. Drach GW. Urinary lithiasis, In: Walsh P, Gittes RF, Perlmutter AD, Stamey TA. Campbell's Urology, Philadelphia, W.B. Saunders Co. 1985; 1165.
8. Plavcan WG, Mc Williams WA. Toothpick obstruction of the ureter. J Urol.1988; 139: 114-5.
9. Dupont MC, Hochman HI. Erosion of an inflatable penile prosthesis reservoir in to the bladder, presenting as bladder calculus, J Urol. 1988; 139: 367-8.
10. Sharma VP, Nobebux Y, Patni J. Unusual foreign body in the bladder Br J Urol. 1987; 59: 92.

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Physiopathology of Cerebral Ischemia

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Summary

Although a lot of progress has occurred, the physiopathology of cerebral ischemia is not yet understood. In this article we review the literature about this subject, however we do not discuss the therapy of cerebral ischemia and cerebral protection against ischemia.

Introduction

The normal brain receives around 750 to 800 ml blood and 52 ml. oxygen every minute, making it the third most perfused and oxygenated organ after kidneys and heart.[1] Brain energy requirements are normally about 8 cal/100 gr/min. Energy producing reactions of the brain consume 20 % of total body oxygen and 65 % of blood glucose, equivalent to the cerebral metabolic rates (CMR) for oxygen of 3 to 3.5 ml/100 gr/ min and for glucose of 4.5 to 5.5 mg/100 gr/min.[2] In the healty brain almost 100 % of glucose is metabolised, but if starved, it can satisfy up to 30 % of the glucose it needs from ketone bodies.[3]

Brain glucose metabolism occurs via 3 pathways; 1. the citric acid cycle and election tranport chain in mitochondria; most brain energy is derived from the aerobic citric acid cycle which metabolizes approximately 85 % of the glucose and produces 38 moles adenosine triphosphate (ATP) per mole of glucose, 2. the glycolytic pathway in the cellular cytoplasm; the anaerobic glycolytic pathway metabolizes about 15 % of the brain glucose, yielding only 2 moles ATP per mole of glucose, 3. the hexose monophosphate shunt; the hexose monophosphate shunt does not supply ATP but contributes pentose phosphates for synthesis of nucleotides and lipids.[4]

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Little glucose is synthesized into glycogen. The brain's limited reserves of glycogen and glucose are barely able to fuel normal brain activity up to 5 minutes. Energy stores are equivalent to about 20 cal/100 gr.[5]

ATP is used for neurotransmission, maintanence of membrane pumps and potentials, neurotransmitter sythesis and transporting proteins and other substances from the cell body to peripheral axonal sites.[6,7]

Ischemic Thresholds

In the normal healthy person, the cerebral blood flow (CBF) is autoregulated at 45 to 50 ml/100 gr/min (Figure 1) between the mean arterial blood pressures (MABP) of 60 and 130 mm/Hg.[8] Below this threshold the pressure of the CBF becomes increasingly dependent on the cerebral perfusion pressure and on the resistance of the intervening blood vessels.

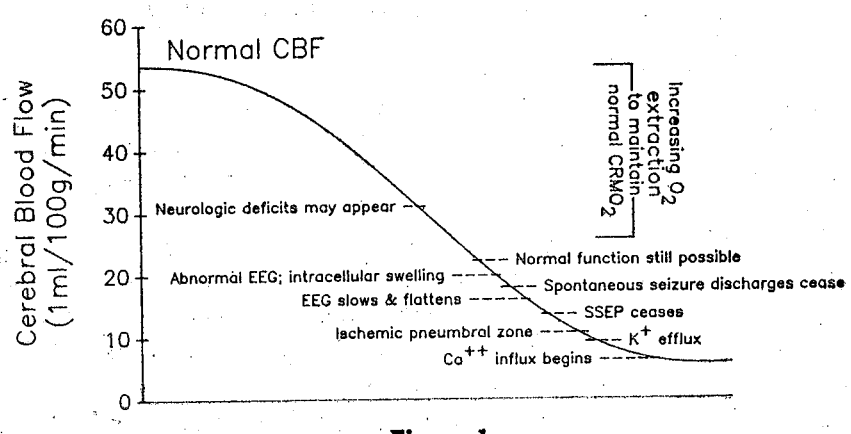

Figure 1

Ischemic thresholds of CBF (Modified from Lord RSA, ed. Surgery of occlusive cerebrovascular disease. St.Louis, Toranto, Princeton: The CV Mosby Company, 1986,p 73).

When the CBF falls below normal, neuronal function is initially preserved by increasing oxygen extraction from the arterial blood. By this means, the CBF levels as low as to 20 ml/100 gr/min can be tolerated, but further reductions in flow diminish regional tissue oxygen tensions so that no further extraction is possible and signs of ischemia appear. However, depending upon the duration of occlusion of the main cerebral arteries, 30 ml/100 gr/ min CBF may cause neurological deficits.[9]

When the flow falls to 20 ml/100 gr/min, irregular electrical discarges are generated as single neuron action potentials and the intracellular

migration of water from the extracellular fluid leads to a swelling of astrocytes because of ionic pump failure.[10]

At around 18 ml/100 gr/min of the CBF, these spontaneous seizure discharges referred to above cease.[11] Between 15 to 18 ml/100 gr/ min of the CBF the EEG progressively slows, gives lower voltages and finally flattens.

When the CBF is below 15 ml/100 gr/ min, corresponding to an oxygen utilization that is about 70 % of normal, somatosensory electrical responses fail to be evoked.[12] Failure of electrical activity is probably associated with cessation of orderly synthesis and release of neurotransmitters; electrical silence, however, does not mean the loss of viability.[13]

When the CBF decreases about 10 ml/100 gr/min, there is a sudden membrane depolarization of the neurons with rapid efflux of K+ into the extracellular fluid.[7, 11] At 6 to 10 ml/100 gr/min of the CBF, which is equivalent to an oxygen consumption of a brain that is 25 % of normal, calcium influx begins.[14]

Brief flows of 5 ml/100 gr/min cause nerve cells to lose their metabolic capacity to transport ions.[15] Flows close to 12 ml/100 gr/min persisting more than 2 hours and flows of 6 to 8 ml/100 gr/min lasting for 30 to 60 minutes produce permanent damage.[6] In acute cerebral ischemia, a rCMRO2 of less than 1.5 ml/100 gr/min consistently correlates with infarction.[6]

Since the density of ischemia produced by occlusion of the major cerebral artery depends on the residual flow, the zone of the infarction that is encircled by cells might be expected which are inactivated but potentially viable; this is defined as the ischemic penumbra.[16] This penumbral region contains cells which are exposed to various levels of blood flow above 10 ml/100 gr/min and have increased water content attributable predominantly to cytotoxic brain edema.[17]

Brain Metabolism During Focal Cerebral Ischemia

One of the primary acute reactions of the brain parenchyma to ischemia is swelling. Ischemic edema has been divided into an early cytotoxic (intracellular) and a late vasogenic (extracellular) phase.[6]

Cytotoxic edema initially involves perivascular glial cells, and findings suggest that it is a secondary reaction to alterations in permeability, rather than in a failure of energy substrate.[18, 19] Lactic acidosis seems to have critical role in glial edema.[20] The major detrimental effect of this edema is impingement on potential collateral flow.

Vasogenic edema occurs hours to days after vessel occlusion, which is secondary to irreversible ischemic endothelial damage.[6]

When the CBF falls to 10 ml/100 gr/min, it causes rapid depletion of ATP and the accumulation of lactic acid due to the lack of oxidative phosphorylation (Figure 2). Failure of ATP-dependent Na^+-K^+ transport causes the concentration of extracellular K^+ to rise.[15] Increased extracellular K^+ will depolarize the neuronal membrane. This situation results in opening of the voltage-sensitive calcium channels and increases calcium influx.[21]

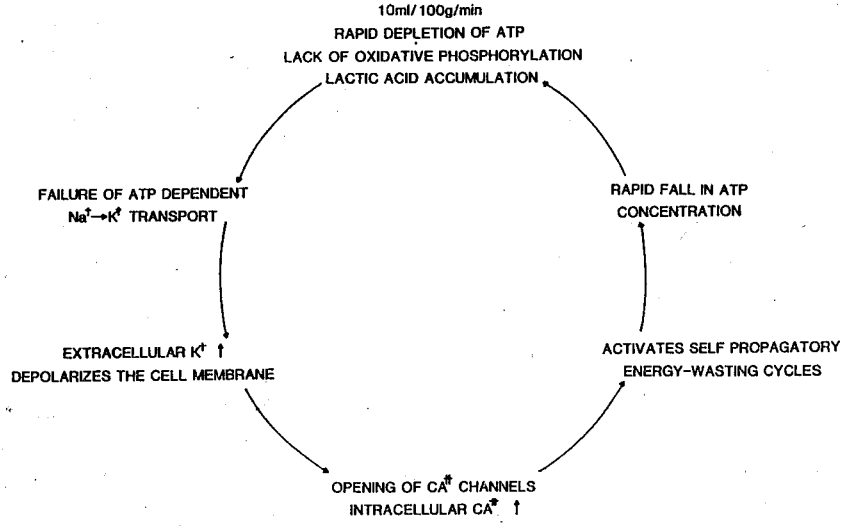

Figure 2
Results of ATP depletion during focal cerebral ischemia (Original-developed by the senior author).

Ionic calcium influx during ischemia is rapid and it activates self propogating energy-wasting cycles, causing a rapid fall in ATP concentration. Intracellular free calcium concentration is also enhanced by failure of the ATP-dependent sequestration of calcium by the endoplasmic reticulum and the mitochondria.[22-24]

This increase in intracellular calcium activates phospholipase A and C which will attack membrane phospholipids with the production of free fatty acids.[15, 25] This loss of membrane phospholipids will increase the permeability of neural and mitochondrial membranes, which will further increase calcium influx with additional detrimental effects on oxidative phosphorylation; in addition, other destructive reactions are activated by the calcium influx.[7]

The accumulated free fatty acids, especially arachidonic acid, may be oxidized along the cycloxygenase and lipoxygenase pathways in incomplete ischemia. The end result would be the accumulation of prostoglandins, lokotrienes and oxygen free radicals (Figure 3).[15, 25-27]

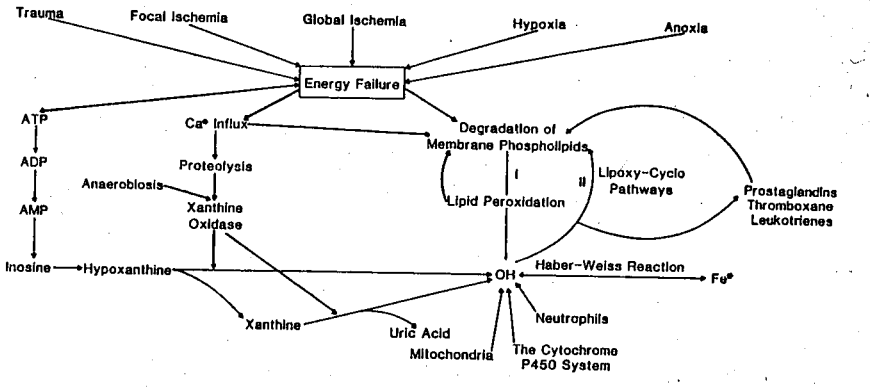

Figure 3
Possible hydroxyradical sources in the central nervous system ischemia-reperfusion injury (Original-developed by the senior author).

Oxygen free radicals (hydroxy radicals) in particular are extremely reactive and will attack and damage many cellular constituents including sugars, amino acids, nucleic acids and phospholipids.[28] Exposure of cell membranes to hydroxy radicals stimulates the process of lipid peroxidation, which proceeds through a free radical mediated chain reactions.[29, 30] Lipid peroxidation disturbs membrane functions and the hydrocarbons and aldehydes produced from their further degradation may cause more cell damage.[29, 31, 32]

Selective vulnerability to cerebral hypoxia exists between different cellular elements in the brain; the neuron is the most sensitive and the microglia and endothelial cells of the blood vessels are the least sensitive.[7] The selective vulnerability of some neurons may be accounted for by differences in the types of Ca^{++} channels present in their cell membranes, hence differences in their Ca^{++} flow thresholds.[7]

However, what makes some areas more suspectible to ischemic injury has been debated. In fact, selective vulnerability areas are often those that normally maintain the highest rates of blood flow.[33]

Selective vulnerability most likely results primarily from differences at the cellular level. Excitatory neurotransmitters such as glutamate (glu) and asparate (Asp) are neurotoxic. Since dentrites of the neurons are

localized in the most vulnerable areas of the brain that receive strong excitatory connections, and harbour glu or Asp, ischemic damage preferentially occurs in these areas.[33]

Lactate levels above 16 micromol/kg correlate with necrosis of the astrocytes and endothelial cells, as well as the neurons.[34] The lactic acidosis also has the following detrimental effects; denaturating of proteins with loss of enzymatic function, increasing glial edema that compromises potential collateral blood flow, suppressing regeneration of the reduced form of nicotinamide-adenine-dinucleotide and possibly increasing production of free radicals.[20, 35, 36]

An area of hyperemia sometimes seen in focal ischemia results from lactic acidosis in an area of low oxygen metabolism. This phenomenon was dubbed "luxury perfusion".[6] Marked hyperemia also occurs in hypoglycemia at an alkaline pH.[37] Since the ischemic brain tissue produces more lactic acid, preischemic hyperglycemia has more detrimental effects on the ischemic brain tissue.[34]

Cerebral ischemia also causes the degradation of protein synthesis and neurotransmitter synthesis.[6] Also the metabolic needs of the whole body increase during acute cerebral ischemia and are correlated with sympathetic neuronal activity.[38]

Brain Metabolism During Global (Complete) Cerebral Ischemia

Complete arrest of the CBF results in loss of consciousness in 10 seconds and the EEG becomes isoelectric between 10 to 20 seconds.[7] Within 4 minutes, morphological changes are visible in the synaptic vesicles as activity ceases in afferent fiber terminals. After 6 to 8 minutes irreversible lesions appear.[6] Swelling of cellular elements does not constitute edema since net brain water has not increased.[7] However, primitive brain functions may continue for up to an hour judging by metabolic and electrical indices.[39]

Complete (global) cerebral ischemia is less devastating to the brain than incomplete ischemia.[39]

Blood Brain Barrier (BBB)

The capillary endothelial cells in the brain differ from systemic capillary endothelial cells and impede the passage of substances into the brain. These cells are also involved in the formation of brain interstitial fluid and cerebrospinal fluid (this has been recently hypothesized).[40, 41]

Since the properties of these cells that contribute to formation of a barrier are the continuous tight junctions that tightly seal the endothelial cells together, the absence of fenestrations and transendothelial channels and transcellular vesicular transport make brain capillaries appear seamless (Figure 4).[40, 41]

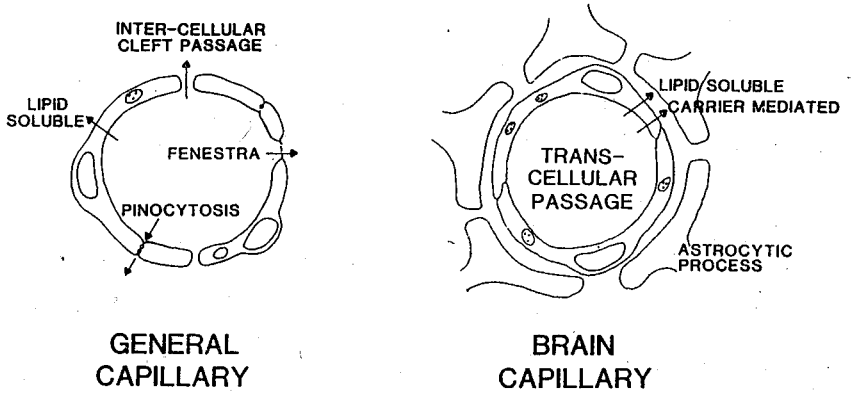

Figure 4
Properties of cerebral capillaries (Modified from Oldendorf, WH. The quest for an image of brain: A brief historical and technical review of brain imaging techniques. Neurology 1978; 28: 520).

The astrocyte foot processes invest the capillary incompletely and are probably only a minor structural barrier.[41, 42]

Brain capillaries are particulary resistant to ischemia.[43] Proteins are unable to breach the normal BBB, but after induction of ischemia, a tubulovesicular network appears and allows proteins to pass across the endothelial cell.[44]

Several observation suggest that disruption of the BBB is a two stage phenomenon.[6, 41] The first stage is functional, reversible and related to acute vasodilatation and the second is structural, irreversible, and caused by actual damage to endothelial cells.

Autoregulation of CBF During Cerebral Ischemia

In normotensive person the CBF is autoregulated by active variation of the caliber of precapillary resistance vessels, provided the MABP lies within the limits of 50 to 150 mm/Hg, but out of this range the CBF follows perfusion pressure passively.[6]

When the MABP falls to 50 mm/Hg, arterioles are maximally dilated so the intracellular function at this level of MABP strictly depends

on increased extraction of oxygen from arterial blood. Decreased MABP below the autoregulatory limit decreases tissue oxygen tensions and increases lactic acid levels simultaneously.[45]

If an acute increase of the MABP occurs, the BBB is dirupted and cerebral edema commences.[6]

The cerebral circulation is highly sensitive to alterations in extracellular pH changes in the arterial pCO_2 levels.[6] In a healthy brain, within the range 20 to 60 mm/Hg of pCO_2, induced hypercarbia is a potent vasodilator that increases the CBF by about 2 % or 1 ml/100 gr/min for every 1 mm/Hg rise in pCO_2. Within 1 hour of the onset of total ischemia, the CBF becomes independent of pCO_2 levels.[46]

Nerve fibers can be identified easily around the leptomenigeal vessels which are both adrenergic and cholinergic.[47, 48] In the normal brain, sympathetic stimulation mildly constricts the large cerebral arteries but has little effect on smaller vessels, apart from the maintaining the tone in the leptomeningeal arteries.

Parasympathetic stimulation has a weak vasodilator effect.[6] The function of the perivascular nerves is less certain in cerebral ischemia.[47]

Ischemic Flow Patterns

The initial circulatory changes following vessel occlusion are a darkening of the venous blood and then a decrease in the velocity of flow through the veins and venules.[49, 50] Consequently, blood viscosity and resistance to flow increase. Arteries and arterioles reveal an immediate vasodilation. The earliest indication of severe ischemia is the development cortical pallor.[51] When this cortical pallor invades an area with an underlying artery or arteriol, a spasm occurs in this vessel.[51] The mechanism of the ischemia-induced secondary vasospasm is unknown, but the causes that have been proposed include either an increase in extracellular K^+ which would trigger the vascular smooth muscle contraction, or Ca^{++} influx into smooth muscle cells. Dysautoregulation occurs in the whole hemisphere and it is most evident in areas where ischemia is most profound.[52]

After reperfusion of the ischemic region, these events are reversed. The venous blood turns bright red, the cortex recolorizes and the major vessels return to their normal caliber.

Post-Ischemic Flow Patterns

If the ischemic zone is reperfused, variable flow patterns are seen depending on the severity of the initial ischemia and method of study.

The no-reflow phenomenon is a reduction in flow to below pre-ischemic levels immediately following reperfusion.[53] Swelling of endothelial cells contributes to a no-reflow phenomenon besides arteriolar constriction, secondary to postischemic hypoperfusion, arteriovenous shunting and blood aggregation.[54-56] Since the BBB has been disrupted, tissue tension increases and progressive accumulation of edema fluid also contributes to no-reflow phenomenon.[57] Ischemia has to be complete and to last longer than 5 minutes to produce this no-reflow phenomenon.[6, 58] Some investigators have failed to detect this phenomenon even in severe ischemia.[50, 59] Little *et al.*[50] concluded that postischemic microcirculatory obstruction was related mainly to capillary swelling that followed rather than preceded neuronal damage. If flow is reestablished quickly the immediate recovery flow pattern may be nearly normal,[60] or may enter a brief hyperemic phase called "luxury perfusion",[61] when the tissue oxygen levels become normal or even increase.[62]

In some cases, hyperemia is more prolonged and in others it is biphasic; an initial phase of reactive hyperemia occurs within minutes after the brain is reperfused, followed by succesive phases of oligemia, and secondary hyperemia 20 hours or so later Figure 5.

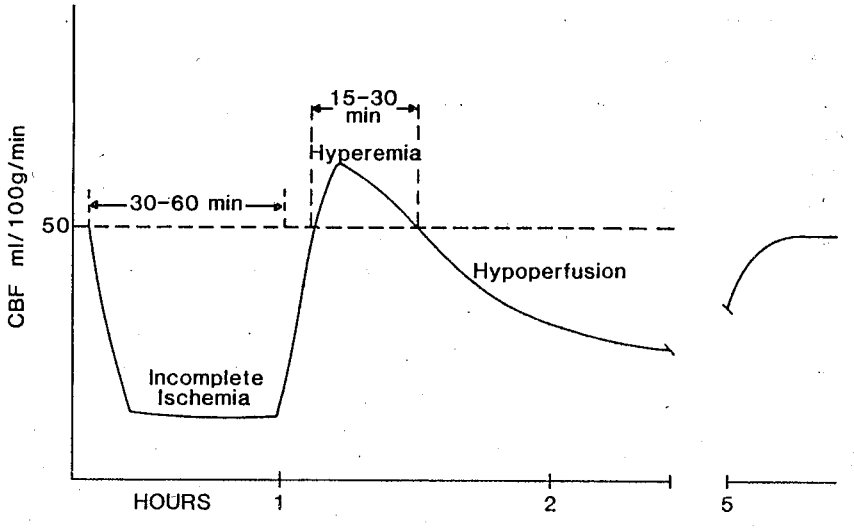

Figure 5

Postischemic flow patterns following incomplete cerebral ischemia (Modified from Lord RSA, ed. Surgery of occlusive cerebrovascular disease. St. Louis, Toranto, Princeton: The CV Mosby Company, 1985, p. 77).

In humans, hyperemia around an infarction may persist for up to 14 days.[6] The cause of the second hyperemic phase is uncertain, however

it usually develops in severely damaged brains and may result from total loss of autoregulatory function during the phase of cellular shrinkage; the latter supervenes after preliminary edema.[63] Studies with Evans blue indicate that the BBB is defective when a secondary hyperemic phase is manifest.

Postischemic hyperemia is not a uniform phenomenon with defined pathophysiological casue and clear prognostic implication.[54]

One week after infarction, regeneration of capillaries proceeds, and in some cases by endothelialization of necrotic vessels.[65, 66]

Blood flow within the substance of long-standing stable infarctions varies from very low to very high (8 to 89 ml/100 gr/min), but around the infarct's periphery, flow is consistently reduced.[67] Within the infarct, autoregulation is hardly evident, and the surrounding hemisphere CO_2 reactivity is reduced.[67]

REFERENCES

1. Zijlstra WG. Physiology of the cerebral circulation. In: Minderhoud JM, ed. Cerebral blood flow-basic konwledge and clinical implications. Amsterdam: Excerpta Medica. 1981: 34-66.
2. Kennedy C, Sokoloff L. An adaptation of the nitrous oxide method to the study of cerebral circulation in children: normal values for cerebral blood flow and cerebral metabolic rate in childhood. J Clin Invest. 1957; 36: 1130-42.
3. Owen OE. Brain metabolism during fasting. J Clin Invest. 1967; 46: 1589-95.
4. Cooper JR, Bloom FE, Roth RH, eds. The biochemical basis of neuropharmacoloyg. London: Oxford University Press, 1982; 60-99.
5. Maker HS. The quantitave histochemistry of a chemically induced ependymoblastoma. II. The effect of ischemia on substrates on carbonhydrate metabolism. J Neurochem. 1966; 13: 1207-11.
6. Lord RSA, ed. Surgery of occlusive cerebrovascular disease. St. Louis, Toranto, Princeton: The C V Mosby Company, 1986; 67-84.
7. Dearden NM. Ischemic brain. Lancet. 1985; 2: 255-9.
8. Lassen NA, Christensen MS. Physiology of cerebral blood flow. Br J Anaesth. 1975; 48: 719-34.
9. Boysen G, Engell HC, Pistolese GR, Fiorani P, Agnoli A, Lassen NA. On the critical lower level of cerebral blood flow in man with particular reference to carotid surgery. Circulation. 1974; 49: 1023-5.
10. Symon L, Branston NM, Chikovani O. Ischemic brain edema following middle cerebral artery occlusion in baboons: relationship between regional cerebral water content and blood flow at 1 and 2 hours. Stroke. 1979; 10: 184-91.
11. Astrup J, Symon L, Branston NM, Lassen NA. Cortical evoked potential and extracellular K^+ and H^+ at critical levels of brain ischemia. Stroke. 1977; 8: 51-7.
12. Morawetz RB, Crowell RH, De Girolami U. Regional cerebral blood flow thresholds during cerebral ischemia. Fed Proc. 1979; 38: 2493-4.

13. Ljunggren B, Norberg K, Siesjo BK. Influence of tissue acidosis upon restitution of brain energy metabolism following total ischemia. Brain Res. 1974; 77: 173-86.
14. Harris RJ, Symon L, Branston NM, Mayhen M. Changes in extracellular calcium activity in cerebral ischemia. J Cereb Blood Flow Metabol. 1981; 1: 203-9.
15. Siesjo BK. Cerebral circulation and metabolism. J Neurosurg. 1984; 60: 883-908.
16. Symon L, Pasztor E, Branston NM. The distrubution and density of reduced cerebral blood flow following acute middle cerebral artery occlusion: an experimental study by the technique of hydrogen clearence in baboons. Stroke. 1974; 5: 355-64.
17. Astrup J, Siesjo BK. Symon L. Thresholds in cerebral ischemia the ischemic penumbra. Stroke. 1981; 12: 723-5.
18. Sundt TM Jr., Grant WC, Garcia JH. Restoration of middle cerebral artery flow in experimental infarction. J Neurosurg. 1969; 31: 311-22.
19. Little JR, Sundt TM Jr., Kerr FWL. Neuronal alterations in developing cotical infarction; an experimental study in monkeys. J Neurosurg. 1974; 40: 186-98.
20. Rehncrona S, Rosen I, Siesjo BK. Excessive cellular acidosis; an important mechanism of neural damage in the brain. Acta Physiol Scand. 1980; 110: 435-7.
21. Wieloch T, Siesjo BK. Ischemic brain injury: the importance of calcium, lipolytic activities and free fatty acids. Pathol Biol (Paris). 1982; 30: 269-77.
22. Ginsberg MD, Mela L, Wrobel-Kuhl K, Reivich M. Mitochondrial metabolism following bilateral cerebral ischemia in the gerbil. Ann Neurol. 1977; 1: 519-27.
23. Nowicki JP, Mac Kenzie ET, Young AR. Brain ischemia, calcium antagonists. Pathol Biol (Paris). 1982; 30: 282-8.
24. Rehncrona S, Mela L, Siesjo BK. Recovery of brain mitochondrial function in the rat after complete and incomplete cerebral ischemia. Stroke. 1979; 10: 437-46.
25. Siesjo BK. Cell damage in the brain; a speculative synthesis. J Cereb Blood Flow Metabol. 1981; 1: 155-85.
26. Yoshida S, Inoh S, Asaon T, Sano K, Kubota M, Shimazaki H, et al. Effect of transient ischemia on free fatty acids and phospholipids in the gerbil brain: lipid peroxidation as a possible cause of postischemic injury. J Neurosurg. 1980; 53: 323-31.
27. Demopulos HB, Flamm ES, Pietronigo DD, Seligman ML. The free radical pathology and the microcirculation in the major central nervous system disorders. Acta Physiol Scand (Suppl). 1980; 492: 91-119.
28. Halliwell B, Gutteridge JMC. Oxygen toxicity, oxygen radicals, transition metals and disease. Biochem J. 1984; 219: 1-14.
29. Halliwell B, Gutteridge JMC. Lipid peroxidation, oxygen radicals cell damage and antioxidant therapy. Lancet. 1984; 1: 1396-7.
30. Slater TF. Overview of methods used for detecting lipid peroxidation. Methods in Enzymology. 1984; 105: 283-93.
31. Kaplan E, Ansari K. Reduction of polyunsaturated fatty acid hydroperoxides by human brain glutathione peroxidase. Lipids. 1984; 19: 784-9.
32. Demopulos H, Seligman M, Schwartz M, Tomasulu J, Flamm ES. Molecular pathology of regional cerebral ischemia. In: Bes A, Paoletti R, Siesjo BK, eds. Cerebral ischemia. Elsevier Science Publishers BV, 1984; 259-64.
33. Kaplan J, Dimlich RVW, Biros MH, Hedges J. Mechanisms of ischemic cerebral injury. Resuscitation. 1987; 15: 149-69.

34. Siesjo BK. Lactic acidosis in the brain; occurence, triggering mechanisms and pathophysiological importance. Ciba Found Symp. 1982; 87: 77-100.

35. Siesjo BK, Bendek G, Koide T, Westerberg E, Wieloch T. Influence of acidosis on lipid peroxidation in brain tissue in vitro. J Cereb Blood Flow Metabol. 1985; 5: 253-8.

36. Welsh FA, O'Connor MJ, Marcy VR, Spatacco AJ, Johns RL. Factors limiting regeneration of ATP following temporary ischemia in cat brain. Stroke. 1982; 13: 234-42.

37. Abdul-Rahman A, Agardh CD, Siesjo BK. Local cerebral blood flow in the rat during severe hypoglycemia and in the recovery period following glucose injection. Acta Physiol Scand. 1980; 109: 307-15.

38. Touho H, Karasawa J, Sawada T. Metabolism in acute cerebrovascular disease. Crit Care Med. 1986; 14: 1023-5.

39. Hossmann KA, Kleihnes P. Reversibility of ischemic brain damage. Arch Neurol. 1973; 29: 375-84.

40. Betz AL. Epithelial properties of brain capillary endothelium. Fed Proc. 1985; 44: 2614-5.

41. Pollay M, Roberts PA. Blood-brain barrier: A definition normal and altered function. Neurosurgery. 1980; 6: 675-85.

42. Cuevas P, Gutierrez Diaz JA, Reimers D, Dujovny M, Diaz FG, et al. Aspects of interastrocytic gap junctions in blood-brain barrier, in the experimental penumbra area, revealed by transmission electron microscopy and freeze-fracture. Experienta. 1984; 40: 471-2.

43. Nemoto EM. Pathogenesis of cerebral ischemia-anoxia. Crit Care Med. 1978; 6: 203-14.

44. Lossinsky AS, Garcia JH, Iwanowski L, Lightfoote WE Jr. New ultrastructural evidence of a protein transport system in endothelial cells of gerbil brains. Acta Neuropathol. 1979; 47: 105-10.

45. Wise RJS, Bernardi S, Frankowiak RSJ, Legg NJ, Jones T.Serial observations on the pathophysiology of acute stroke the transition from ischemia to infarction as reflected in regional oxygen extraction. Brain. 1983; 106: 197-222.

46. Koch KA, Jackson DL, Schmield M, Rossenblatt JI. Total cerebral ischemia effect of alterations in arterial pCO_2 on cerebral microcirculation. J Cereb Blood Flow Metabol. 1984; 4: 343-9.

47. Duckles SP. Innervation of cerebral vasculature. Ann Biomed Eng. 1983; 11: 599-605.

48. Taniguchi T, Fujiwara M, Tsukahara T, Handa H. Evidence for alpha-2 adrenergic receptors in bovine cerebral arteries. Adv Exp Med Biol. 1984; 175: 127-32.

49. Knisley MH, Bloch EH, Eliot TS, Warner L. Sludged blood. Science. 1947; 106: 431-40.

50. Little JR, Kerr FWL, Sundt TM Jr. Microcirculatory obstruction in focal cerebral ischemia; relationship to neural alterations. Mayo Clin Proc. 1975; 50: 264-70.

51. Sundt TM Jr. Waltz AG. Cerebral ischemia and reactive hyperemia studies of cortical blood flow and microcirculation before, during and after temporary occlusion of middle cerebral artery of squirrel monkeys. Circ Res. 1971; 28: 426-33.

52. Symon L, Branston NM, Strong AJ. Autoregulation in acute focal ischemia; an experimental study. Stroke. 1976; 7: 547-54.

53. Ames A III, Wright RL, Kowada M, Thurston JM, Majno G. Cerebral ischemia II: The no-reflow phenomenon. Am J Pathol. 1968; 52: 437-53.

54. Siemkowicz E. Cerebrovascular resistance in ischemia. Pflugers Arch. 1980; 388: 243-7.

55. Jackson DL, Dole WP, Mc Gloin J, Rossenblatt JI. Total cerebral ischemia; application of a new model system to studies of cerebral microcirculation. Stroke. 1981; 12: 66-72.

56. Miller CL, Lampard DG, Alexander K, Brown WA. Local cerebral blood flow following transient cerebral ischemia I. onset of impaired reperfusion within the first hour following global ischemia. Stroke. 1980; 11: 534-41.

57. Iannotti F, Hoff JH, Schielke GP. Brain tissue pressure in focal cerebral ischemia. J Neurosurg. 1985; 62: 83-9.

58. Kagstrom E, Smith MJ, Siesjo BK. Recirculation in the rat brain following incomplete ischemia. J Cereb Blood Flow Metabol. 1983; 3: 170-82.

59. Levy DE, Brierley JB, Siverman DG, Plum F. Brief hypoxia-ischemia initiall damages cerebral neurons. Arch Neurol. 1975; 32: 450-6.

60. Taşdemiroğlu E, Ardell JL, Taylor AE. CNS blood flow during ischemia-reperfusion injury in the rabbit brain. Physiologist. 1987; 30: 180.

61. Lassen NA. The luxury perfusion syndrome and its possible relation to acute metabolic acidosis localized within the brain. Lancet. 1966; 2: 1113-7.

62. Crockard HA. Changes in regional cortical tissue tension and cerebral blood flow during temporary middle cerebral artery occlusion in baboons. J Neurol Sci. 1979; 27: 29-43.

63. Garcia JH. The neuropathology of stroke. Hum Pathol. 1975; 6: 583-98.

64. Heiss WD. Postischemic hyperemia. RACD (Suppl. 3-17). 1987; 8: 51-2.

65. Chan PH, Fishman RA. Brain edema induction in cortical slices by polyunsaturated fatty acids. Science. 1978; 201: 358-60.

66. Cancilla PA, Frommes SP, Kahn LE, De Bault LE. Regeneration of cerebral microvessels; a morphologic and histochemical study after local freeze-injury. Lab Invest. 1979; 40: 74-82.

67. Symon L, Crockard HA, Dorsh NWC, Branston NM, Juhasz J. Cerebral blood flow and vascular reactivity in a chronic stable stroke in baboons. Stroke. 1975; 6: 482-92.

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