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Post-Partum Renal Light Microscopy and Detection of Immune Deposits in Pre-Eclampsia

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Abstract

It is believed that immune complexes play a role in the development of renal pathology in pre-eclampsia. To ensure this 10 cases with residual proteinuria were biopsied 2-4 weeks post-partum. The biopsies were studied by light microscopy and tested for immunofluorescence (IF). Light microscopy revealed the occurrence of endotheliosis, together with axial mesangial cellular proliferatin with or without increase of matrix and one specimen showed focal segmental sclerosis. In addition tubular degeneration (7 cases) and interstitial lymphocytic infiltration (2 cases were noticed). IF showed positive granular subendothelial and mesangial deposits of IgM (9 cases), IgG (6 cases), C3 (5 cases) and fibrin (7 cases). Renal biopsies of 2 cases with post-partum haemorrhage leading to acute renal failrue, revealed endotheliosis but showed no deposits by IF. The placentae of 8 of the cases and 8 normal primigravida labours were tested for deposits by IF and revealed the occurrence of fibrin deposits and negligible immunoglobulins in most of the specimens and C3 and C4 deposits in 4 of the pre-eclampsia cases. These findings suggest an important pathogenic role of immune complexes in renal involvement in pre-eclampsia.

Introduction

THE aetiology of pre-eclampsia and its pathology has not yet been definitely outlined. Several factors have been accused in the pathogenesis and they may be primarily co-existing or develop in sequence.

An endothelial insult is considered by several authors to be the primary cause of pre-eclampsia. There may be an abnormality in the synthesis of the factors responsible for maintaining the endothelial integrity including prostaglandins [1].

The other important view is that there occurs an initial immunologic insult, initiated by the foreign foetal and placental antigens ensuing an immune reaction. The formation of immune complexes, which might be an exaggeration of a normal physiologic feature accompanying pregnancy would be

the initial pathogenic mechanism [2,3].

In this study we are trying to ensure the pathologic role of the disturbed immune respnse in pre-eclampsia concerning its reflection on the renal pathology and function.

Material and Methods

In this study 10 women who had pre-eclampsia and residual post-partum proteinuria with or without hypertension were studied. In addition 2 cases giving history of post-partum haemorrhage, oliguria and impairment of their renal functions were included.

The criteria for diagnosing pre-eclampsia were the development of proteinuria with or without dependant oedema and hypertension (blood pressure < 140/90 mmHg) late in pregnancy. Those who in addition developed one attack or more of convulsions, without previous history of epilepsy, were considered to have eclampsia. None of the patients gave history of previous hypertension or renal troubles.

Biopsies from the placentae of 8 of the pre-eclampsia cases and another 8 normal deliveries were analyzed by light microscopy and immunoflourescent staining.

The investigations done one week after labour included:

- Serum creatinine.
- 24 hours urinary proteins and its electrophoresis.
- Liver functions including: serum bilirubin, glutamic oxalacetic transaminase, glutamine pyruvic transaminase, albumen and total proteins.
- Fasting and 2 hours post prandial blood sugar.
- Serum A.N.F. and ds-D.N.A.
- Platelet count, bleeding time, clotting time, prothrombin time and A.P.T.T.
- Renal ultrasonography.

After taking their consents, renal biopsies were performed and included 2 specimens for light microscopy and immunofluorescent staining.

Immunofluorescent technique was done using Behring fluorescin labelled rabbit antihuman IgG, IgM, IgA, C_3, C_4 and fibrinogen.

The specimens were snap frozen in O.C.T. compound, cryostat out at 5 microns, stained by the direct technique, mounted in glycerine and examined on a Leitz incident-light immunofluorescent microscope [4].

Sections for light microscopy were fixed in 10% buffered formaline, embedded in paraffin, cut at 3 microns and stained with hematoxylin and eosin, PAS, Masson trichrome and Congo red when needed.

Results

The patients showed normal liver functions and coagulation fprofiles. None were diabetic and had negative results for the lupus markers performed (A.N.F. and anti ds DNA).

Their ultrasonography showed normal parameters and was used for localization for biopsies.

The results of the improtant relevant clinical and laboratory data are shown in Table (1).

Patients number (1) and (6) had mild impairment of their renal functions. Patients number (5) and (9) had residual hypertension.

The patients had a mean daily proteinuria of 1.29±1.63 g. It was not enough for electrophoresis in 5 cases. The rest showed a mean A/G ratio of 0.17±0.18, which was selective albuminuria in 2 cases and non-selective in the other 3 (number 6, 9 and 10).

Table (2) shows the pathology results of the kidney biopsies and their immunofluorescent staining together with the results of the immunofluorescent staining of the placenta specimens.

Discussion

The aetiology of pre-eclampsia is still debatable, but there seems to be an agreement that it is a placental disorder [5]. This disorder is believed to be predisposed to by several genetic [6,7], immunologic [8] and constitutional and/or foetal factors operating separately or collectively [5].

One view considers a primary disturbance of the prostanoid metabolism affecting the balance between the opposing actions of prostacyclin and thromboxane. This may affect the platelet aggregability and vascular tone [5]. The latter may be a reflection of deficient vaso-dilatory prostaglandins and the potent endothelial vaso-constrictor peptide endothelin. The resulting endotheliosis with narrowing of the capillary lumina predisposes to platelet aggregation and fibrin deposition initiating the syndrome [1]. The cause of these abnormalities being unknown, their inconsistency in the syndrome and failure to recur with repeated pregnancies, are points which need to be clarified [5]. They may be a seondary phenomenon to an immune insult [9]. Furthermore, the occurrence of this capillary wall expansion had been debated by others [10].

The other point of view considers that pregnancy is a physiologic immunologic chalenge with the frequent occurrence of circulating immune complexes (C.I.Cs) [2,3]. And when an abnormal immune response occurs, depending on the nature of the antigen, the nature of antibodies or the titres of these CICs, this phenomenon may be no more physiologic and would result in pathologic consequences [2,11].

In a previous study done by our group, we demonstrated a significantly higher titre of CICs in pre-eclampsia than in normal pregnancy and that the titre of CICs of pre-eclampsia cases in labour was close to normal control nuliparous non pregnant women. These data suggested an important pathologic role of CICs in pre-eclampsia [12].

Deposition of complexes and/or fibrin had been demonstrated by several workers who detected them mainly in endothelial and subendothelial sites [13,14]. The frequency and intensity of their occurrence in biopsies taken from pre-eclamptic women late in pregnancy was higher than when they were taken in the early post-partum period, for durations ranging from hours and up to 7 days in one study [15], 9 days in another [10], or 15 days in a third study [16]. They were absent from biopsies taken from similar cases 8 months after delivery [16].

In our study 2 cases were biopsied 3 weeks post-partum and one case 4 weeks post-partum. The other seven were biopsied 2 weeks after labour. Positive immuno-fluorescent deposits were detected in 9/10 cases. The negative case was one of the cases biopsied 2 weeks post-partum.

This represents a high prevalence rate concerning number and timing.

In other studies Packham et al. [17]

Table (1): The Clinical and Laboratory Data of the Pre-eclampsia Cases.

	Pre-Partum							Post-partum			
Case No.	Age	Gravida	Duration of pregnancy	Blood pressure mmHg	Protein-urea	Edema	Convulsions	Serum creatinine µmol/L	Blood pressure	Protein-uria g/day	Urine protien A/G ratio
1	35	Primi.	40 w	170/110	++	+	-	221.2	130/80	0.2	-
2	37	Primi.	38 w	190/110	++	++	-	106.2	140/80	0.5	-
3	30	Primi.	40 w	180/120	++	+	-	115	140/90	0.7	0.0
4	28	Primi.	38 w	200/150	++	++	-	88.5	140/90	0.2	-
5	27	Primi.	40 w	190/130	++	+	+	106.2	140/80	0.5	-
6	20	Primi.	30 w	200/120	+++	+++	-	159.3	170/100	5.6	0.3
7	27	4	40 w	180/110	++	++	-	79.6	140/85	1.0	0.0
8	35	8	40 w	170/100	++	+	+	70.8	120/80	0.5	-
9	23	Primi.	39 w	150/110	+++	++	-	70.8	150/100	1.0	0.39
10	30	3	40 w	180/110	++	+		97.3	140/90	2.0	0.16
Mean	29.2		39.5 w					111.5		1.29	0.17
S.D.	±5.41		±0.85					±46.5		±1.63	±0.18

Table (2): Pathology Results and I.F. of Kidney Specimens and I.F. of Placentae Specimens.

Cases									Controls			
Pre-eclampsia	Time of biopsy P.P.	Kidney light microscopy	Kidney I.F.			Placentae I.F.			No.	Placentae I.F.		
			Deposit	Intensity	Site	Deposit	Intensity	Site		Deposit	Intensity	Site
1	3w	Mesang. Prolif.	IgA	+ve	tub.	IgA	-ve	inter. v.	1	IgA	+ve	inter.v.
			IgG	+ve	interst.	IgG	+ve			IgG	+ve	inter.v.
			IgM	+ve	gr.s.end.	IgM	-ve			IgM	-ve	
			C3	-ve		C3	-ve			C3	-ve	
			C4	-ve		C4	-ve			C4	-ve	
			Fib.	-ve	interst.	Fib.	+ve	inter. v.		Fib.	+ve	inter.v.
2	2w	Endoth. prolif.	IgA	+ve	tub.	IgA	-ve		2	IgA	-ve	
			IgG	-ve		IgG	+ve	inter. v.		IgG	+ve	inter.v.
			IgM	-ve		IgM	-ve			IgM	-ve	
			C3	-ve		C3	-ve			C3	-ve	
			C4	-ve		C4	-ve			C4	-ve	
			Fib.	+ve		Fib.	+ve	vill.		Fib.	+ve	inter.v.
3	2w	- Endoth. prolif. - B.M. thickening	IgA	+ve	mesang. &tub.	IgA	-ve		3	IgA	+ve	vill.
		-Mesang. prolif. and increased matrix	IgG	+ve	mesang.	IgG	+ve	inter. v.		IgG	-ve	
			IgM	+ve	interst.	IgM	-ve			IgM	-ve	
		- Artl. mild thickening	C3	-ve		C3	-ve			C3	-ve	
			C4	-ve		C4	-ve			C4	-ve	
		- Tub. epith. necrosis	Fib.	-ve		Fib.	+ve	vill		Fib.	+ve	vill.
		- Mild interstitial lymph. infilt. and patchy fibrosis										

Table (2) cont.

Cases									Controls			
Pre-eclampsia	Time of biopsy P.P.	Kidney light microscopy	Kidney I.F.			Placentae I.F.			No.	Placentae I.F.		
			Deposit	Intensity	Site	Deposit	Intensity	Site		Deposit	Intensity	Site
4	2w	- Endoth prolif. - Tub epith. necorsis - Patchy interstitial fibrosis	IgA IgG IgM C3 C4 Fib.	+ve +ve +ve +ve -ve -ve	tub. gr.mesang gr. s. end. gr. s.end interst.				4	IgA IgG IgM C3 C4 Fib.	+ve -ve -ve -ve -ve -ve	inter.v.
5	3w	- Endoth. prolif. - Mesang. prolif. - Moderate tub. epith. atrophy	IgA IgG IgM C3 C4 Fib.	+ve +ve +ve +ve -ve +ve	tub. gr.s. end. gr.s. end. mesang. artl intest.	IgA IgG IgM C3 C4 Fib.	-ve +ve -ve +ve +ve -ve	vill. nter.v. inter.v.	5	IgA IgG IgM C3 C4 Fib.	+ve +ve -ve -ve -ve +ve	inter. v. vill. vill.
6	2w	- Endoth. prolif. - B.M. thickening - Axial mesang. prolif. and increase matrix - arterl. hyalinosis - tub. epith. atrophy - patchy interstitial fibrosis	IgA IgG IgM C3 C4 Fib.	+ve -ve +ve +ve -ve +ve	tub gr.s.end. artl. intest.				6	IgA IgG IgM C3 C4 Fib.	-ve +ve -ve -ve -ve +ve	 vill. vill.

Table (2) cont.

Cases									Controls			
Pre-eclampsia	Time of biopsy P.P.	Kidney light microscopy	Kidney I.F.			Placentae I.F.			No.	Placentae I.F.		
			Deposit	Intensity	Site	Deposit	Intensity	Site		Deposit	Intensity	Site
7	2w	- Endoth prolif.	IgA	+ve	tub.	IgA	-ve		7	IgA	-ve	
		-Mesang. prolif. and	IgG	+ve	tub.	IgG	-ve			IgG	+ve	inter. v.
		increase matrix	IgM	+ve	gr.s.end.	IgM	-ve			IgM	+ve	inter. v
		- Mild tub. epith.	C3	+ve	gr.s.end.	C3	-ve			C3	-ve	
		atrophy	C4	-ve		C4	-ve			C4	-ve	
			Fib.	+ve	artl.	Fib.	+ve	vill.		Fibrin.	+ve	vill.
8	2w	- Endoth. prolif.	IgA	+ve	tub.	IgA	-ve		8	IgA	-ve	
		- Mesang. prolif	IgG	-ve		IgG	-ve			IgG	+ve	vill.
		- Mild tub. epith.	IgM	+ve	gr.s.end.	IgM	-ve			IgM	-ve	
		atrophy	C3	-ve		C3	+ve	vill.		C3	-ve	
			C4	-ve		C4	+ve	inter.v.		C4	-ve	
			Fib.	-ve		Fib.	-ve			Fib.	+ve	vill.
9	4w	- Axial mesang.										
		prolif.	IgA	+ve	tub.	IgA	+ve	vill.				
		- Focal segmental	IgG	+ve	gr.s.end.	IgG	-ve					
		sclerosis	IgM	+ve	gr.s.end.	IgM	+ve	vill.				
		- Mild tub. deg.	C3	-ve		C3	-ve					
			C4	-ve		C4	+ve	vill.				
			Fib.	-ve		Fib.	+ve	vill.				

Table (2) cont.

Cases								
Pre-eclampsia	Time of biopsy P.P.	Kidney light microscopy	Kidney I.F. Deposit	Intensity	Site	Placentae I.F. Deposit	Intensity	Site
10	2w	- Endoth prolif. - Axial mesang. prolif. - Thickened artl. - Tub. epith. atrophy	IgA IgG IgM C3 C4 Fib.	+ve +ve +ve +ve -ve -ve	tub. gr.s.end. gr.s.end. gr.s.end artl.	IgA IgG IgM C3 C4 Fib.	-ve -ve -ve -ve +ve +ve	 vill. vill.
P.P. Hge.								
1	2w	- Endoth. prolif. - Tub. epith. deg.	IgA IgG IgM C3 C4 Fib.	+ve -ve -ve -ve -ve -ve	tub.			
2	2w	- Endoth. prolif. - Tub. epith. atrophy	IgA IgG IgM C3 C4 Fib.	-ve -ve -ve -ve -ve -ve				

endoth. = endotheliak; prolif. = proliferation; Lymph. = lymphocytic; vill. = villous
mesang. = mesangial; epith. = epithelial; B.M. = basement membrane; inter v. = intervillous
deg. = degeneration; artl. = arterioles; infilt. = infiltration; gr. = granular
tub. = tubular; Fib. = fibrin; P.P. = post partum; s.end. subendothelial

demonstrated positive I.F. in 7/10 cases biopsied 3-9 days post-partum, Fiaschi & Naccarto [16] in 9/9 cases biopsied during the 15 days following delivery and Vassali et al. [15] in 7/7 cases biopsied before 7 days post-partum.

The deposits in our 9/10 positive cases were mainly granular subendothelial and this is in agreement with the finding of other investigators. In addition there were occasional mesangial 3/9, arteriolar 3/9, interstitial 3/9 and tubular deposits 1/9. Packham et al. [17] reported, in addition to the subendothelial depsotis, 3/7 mesangial and 3/7 arteriolar deposits.

While Packham et al. [17] tested for I.F., by firbin, immunoglobulins and complement anti-sera, the data of Fiaschi/ Naccarato [16] and Vassali et al. [15] were for anti-fibrin sera only.

In our study we found the commonest deposits to be of IgM nature 9/9, followed by fibrin 7/9, then IgG 6/9 and C_3 5/9 and an equivocal mesangial IgA in 1/9. Tubular IgA depsoits, which are believed to be formed locally by the medullary tubular cells have a negligible pathologic relevance [18]. This was partially matching with the study of Packham et al. [17] who also found IgM 7/7 and fibrin 5/7 to be the commnest deposits, but found more frequent mesangial IgA 4/7 and lesser IgG deposits in 2/7.

This might direct the attention to the importance of the nature of CICs encountered during pregnancy as several authors found the CICs encountered in normal pregnancy to be of IgG nature and that they were not injurious, while the CICs encountered in pre-eclampsia were of the IgM type [2,3,11]. And it is worth mentioning that the biopsies of our 2 cases with normal pregnancy and post-partum haemorrhage showed no immunofluoroescent deposits of any of the types tested.

The results of I.F. of the placenta specimens showed no significant difference concerning the fibrin and immuno-globulins deposits between the cases and the controls. Yet there was complement deposits in 4/8 placentae from pre-eclamptic cases which might direct the attention to a higher tendency of immune deposition in pre-eclampsia.

These findings strengthen the posibility that CICs is a main primary pathogenic factor in pre-eclampsia, at least concerning the renal involvement.

There has been a lot of debate about the light microscopic renal pathology of pre-eclampsia. While endotheliosis was considered by many authors to be not only the typical predominant finding, but also to be a pathognomonic lesion [19], yet other workers even denied the occurrence of this endotheliosis in biopsies taken 10-14 days post-partum [10] and other non specific lesions including mesangial proliferation [8,10,20] and basement membrane thickening [14] were described as the renal pathologic findings in pre-eclampsia cases biopsied after the first week post-partum.

Other investigators emphasized that the various components of the glomerulus in pre-eclampsia might be affected in sequence and that the temporal relation of the biopsy would alter the pathologic picture [21]. It was suggested that the endotheliosis would be present in late pre-eclamptic pregnancy and would persist for at least a week post-partum to be gradually replaced by other pathologic lesions representing a healing phase in the resolution of pre-eclampsia [8,17,20].

In our cases, endotheliosis was among the findings present in all the patients biopsied at 2 weeks post-partum 7/10 and in one of the 2 cases biopsied at 3 weeks post-partum. This endotheliosis was also encountered as a sole finding in our 2 normal cases with post partum haemorrhage who were also biopsied 2 weeks after labour. This would cast a lot of doubt on the nature of this endotheliosis and whether it is a characteristic lesion of pre-eclampsia or a finding accompanying even normal pregnancy. The answer to this requires more expanded studies.

In our cases endotheliosis was not encountered alone except in one case and was associated in the other cases by one or more findings including axial mesangial cellular proliferation with or without increase of the matrix 8/10, tubular degeneration 7/10 and interstitial lymphocytic infiltration in 2 cases.

In one case (number 9), which was biopsied 4 weeks post-partum there was a focal segmental glomerular sclerotic lesion. This finding was more encountered as a de novo lesion following pre-eclampsia by other investigators. Kida et al. reported it in 4/16 patients biopsied 4 weeks post partum [22] and Nochy et al. found it in 11/150 cases of pre-eclampsia biopsied between 1-12 weeks post partum and it was mentioned that these 11 cases had severe pre-eclampsia [23]. This latter information was noticed in our case with F.G.S., who had eclampsia.

The daily proteinuria of our cases performed 1week post-partum was 1.29±1.63 grams. Electrophoresis could be done to the 5 cases with more than 0.5 g/day. It was selective in 2 cases and non selective in the other 3 of whom 2 had residual hypertension. This reflects the severity of the renal pathology and with healing lesions proteinuria may be expected to decline both in quantity and non-selectivity. Quaas et al. [24] reporting on proteinuria during pregnancy found that the proteinuria of pre-eclamptic ladies studied before labour showed variable selectivity and that none had pure albuminuria.

We can conclude that there are sufficient data to considcr a primary pathogenic role of CICs in pre-eclampsia and that their deposition in the glomeruli is an essential factor in the renal involvement in this syndrome. This involvement is variable in severity and it is difficult to describe a characteristic or pathognomonic pathologic renal glomerular lesion in pre-eclampsia.

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