奈医誌. (J. Nara Med. Ass.) 48, 162～168, 1997

IMMUNOGLOBULIN A NEPHROPATHY ASSOCIATED WITH DIABETES MELLITUS : A SUMMARY OF 10 CASES AND REVIEW OF LITERATURE

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Received April 16, 1997

Abstract : Case reports of 10 patients with IgA nephropathy associated with diabetes mellitus are presented. The clinical characteristics of each of the patients are summarized. We determined the incidence of IgA nephropathy in a total of 313 patients with diabetes mellitus who underwent renal biopsy between 1982 and 1996 : it was 3.2% for the group of all diabetic patients, and 10.8% for diabetic patients with overt proteinuria. Clinicopathologic features of IgA nephropathy observed in diabetic patients are discussed in the context of a review of the literature.

Index Terms

diabetes mellitus, IgA nephropathy, renal biopsy

INTRODUCTION

Immunoglobulin A (IgA) nephropathy is in many countries the most common form of primary glomerulonephritis[1]. Correspondingly, the association of IgA nephropathy with diabetes has been mentioned in some reports[2-13]. However, the precise incidence of this association and detailed profiles of affected patients have not been given. We review the clinicopathologic features of IgA nephropathy observed in diabetic patients in our series, and discuss them with respect to the literature.

CASE REPORTS

Case 1

A 42-year-old woman suffering from glucosuria and massive proteinuria was admitted to our hospital in August 1985. She had been well until 2 years earlier, when glucosuria and proteinuria were first detected on an annual medical check-up. Her diabetes was controlled with insulin therapy, at 12 units daily. However, proteinuria and microscopic hematuria gradually developed during the two months preceding admission. There was no history of numbness or visual disturbance. On physical examination, blood pressure was 140/74 mmHg, and the pulse 72/min and regular. The head, neck, chest and abdomen were normal. There was no pretibial edema, and neurologic examination was normal. Funduscopic examination disclosed no evidence of hypertensive change or diabetic retinopathy. Urinalysis revealed numerous red cells, and urinary protein excretion was 2.9 g/day. Total protein concentration was 5.9 g/dl with an albumin fraction of 3.7 g/dl. A high serum IgA (409 mg/dl) was noted. Creatinine clearance

was 76 ml/min. Light microscopic examination of a renal biopsy specimen revealed advanced mesangial proliferative glomerulonephritis. Immunofluorescence examination revealed strong staining in mesangial regions for IgA and C 3.

Case 2

A 68-year-old man was admitted to our hospital in September 1992 for glucosuria and proteinuria. Two years earlier, he was found to have glucosuria on an annual medical check-up. Five months prior to admission, proteinuria was first detected at another hospital. On admission, blood pressure was 120/66 mmHg with a pulse of 60/min. Physical examination demonstrated no abnormalities in the neck, chest or abdomen. No peripheral edema was observed. Although neurologic examination was normal, funduscopic examination revealed simple diabetic retinopathy (grade A 2). Urinalysis disclosed the following: protein 2+ ; glucose 2+ ; occult blood 2+ ; and hyaline casts in the sediment. Laboratory investigation revealed a urinary protein of 0.8 g/day, creatinine clearance 63 ml/min, total protein 6.0 g/dl, serum albumin 3.8 g/dl, and HbA_1c 5.2%. Light microscopic examination of a renal biopsy specimen revealed moderate mesangial proliferative glomerulonephritis. Immunofluorescence examination revealed strong staining of mesangial regions for IgA, C 3, and fibrinogen.

Case 3

A 68-year-old diabetic woman suffering from proteinuria and microscopic hematuria was admitted to our hospital in June 1996. At age 55, she was found to have microscopic hematuria by her personal physician, who made the diagnosis of nephrolithiasis. The nephrolithiasis was treated by ESWL. At age 63, glucosuria and proteinuria were first detected on an annual medical check-up. Her diabetes was controlled with dietary therapy, but glycemic control had been poor (HbA_1c 8.0%). Proteinuria and microscopic hematuria then gradually developed, and she was referred to our hospital. There was no history of numbness or visual disturbance. On physical examination, blood pressure was 132/74 mmHg, and the pulse was 66/min and regular. The head, neck, chest and abdomen were normal. There was no pretibial edema, and

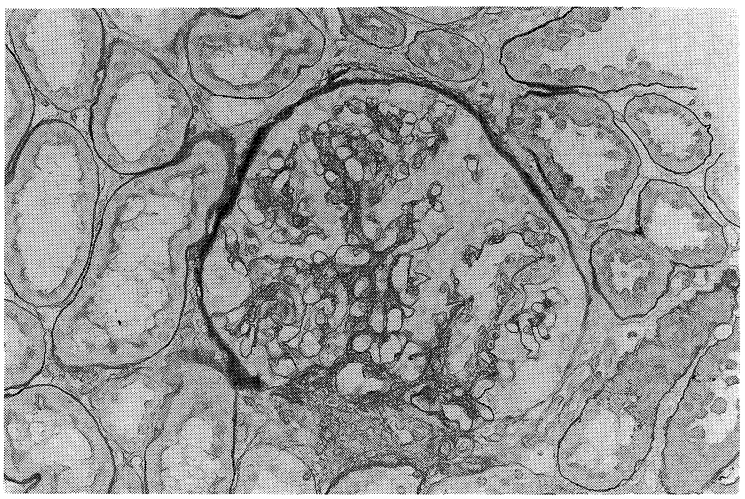

Fig. 1. Light microscopic findings of a renal biopsy specimen in case 3 (PAS stain, ×80).

neurologic examination was normal. Funduscopic examination disclosed no evidence of hypertensive change or diabetic retinopathy. Urinalysis revealed 10-19 red cells, and urinary protein excretion was 0.4 g/day. Total protein concentration was 7.1 g/dl with an albumin fraction of 3.8 g/dl. Creatinine clearance was 69 ml/min. Light microscopic examination of a renal biopsy specimen revealed moderate mesangial proliferative glomerulonephritis (Fig. 1). Immunofluorescence examination revealed strong staining in mesangial regions for IgA, IgM and C 3.

The other cases

The clinical and laboratory characteristics of the other cases (cases 4-10), as well as cases 1, 2 and 3, are summarized in Table 1. There were 3 males and 7 females, aged 36 to 68 (mean, 54) years. The mean duration of diabetes was 4.2 years. One of the patients had hypertension, seven had hematuria, and three had diabetic retinopathy. Mean protein excretion was 0.9 g/day, and mean creatitine clearance wan 70 ml/min. The light microscopic and immunofluorescent findings are summarized in Table 2. Light microscopy revealed mild to severe mesangial cell proliferation. In the immunofluorescent microscopy, the deposition of IgA was observed

Table 1. Summary of present cases

Items	Case									
	1	2	3	4	5	6	7	8	9	10
Age (yo)	42	68	68	45	60	36	57	62	50	48
Gender	F	M	F	F	M	F	F	F	M	F
Duration of diabetes (yr)	2	2	5	7	2	1	2	13	2	6
SBP (mmHg)	140	120	132	120	104	130	178	114	94	112
DBP (mmHg)	74	66	74	72	56	80	98	54	50	60
Retinopathy	(−)	A2	(−)	(−)	(−)	(−)	A2	A1	(−)	(−)
Neuropathy	(−)	(−)	(−)	(−)	(−)	(−)	(+)	(+)	(−)	(−)
Treatment	Ins	Diet	SU	Ins	Diet	Diet	SU	Diet	SU	Diet
UP (g/day)	2.9	0.8	0.4	1.7	0.3	1.2	0.5	0.8	0.3	0.2
Hematuria	(3+)	(+)	(2+)	(+)	(+)	(−)	(−)	(−)	(+)	(2+)
Ccr (ml/min)	76	63	69	41	60	115	56	77	66	80
HbA_1c (%)	7.9	5.2	10.3	10.0	7.1	7.7	10.8	9.1	6.5	6.1
Serum IgA (mg/dl)	409	242	909	535	ND	434	272	458	ND	382

Table 2. Summary of light microscopic and immunofluorescent findings

Items	Case									
	1	2	3	4	5	6	7	8	9	10
Light microscopy										
Mes. proliferation	+++	++	++	++	++	+	+	+	+	+
IF study										
IgA	++	++	++	++	++	+	+	+	+	+
IgG	−	−	−	+	−	−	+	−	−	−
IgM	−	+	+	+	−	−	−	−	−	+
C3	+	+	++	+	++	−	−	+	+	−
Fbg	−	++	−	−	−	++	+	+	−	−

Abbreviations are: Mes. proliferation, mesangial cell proliferation; IF, immunofluorescence; Fbg, fibrinogen. Mesangial cell proliferation were divided into three grades (+, mild; ++, moderate; and +++, severe). The intensity of IF staining: −, no detectable staining; +, weak; ++, strong.

diffusely in the glomerular mesangial area. In some cases, IgG, IgM, C3 and fibrinogen (Fbg) deposits were also observed.

Incidence of IgA nephropathy associated with diabetes mellitus

We attempted to determine the incidence of IgA nephropathy associated with diabetes mellitus in a total of 313 consecutive diabetic patients who had undergone renal biopsy in the First Department of Internal Medicine of Nara Medical University between 1982 and 1996 (Fig. 2). We found 33 patients with non-diabetic renal disease (10.5 %) and 10 with IgA nephropathy (3.2 %) in this entire group of patients. When subjects were classified into subgroups with

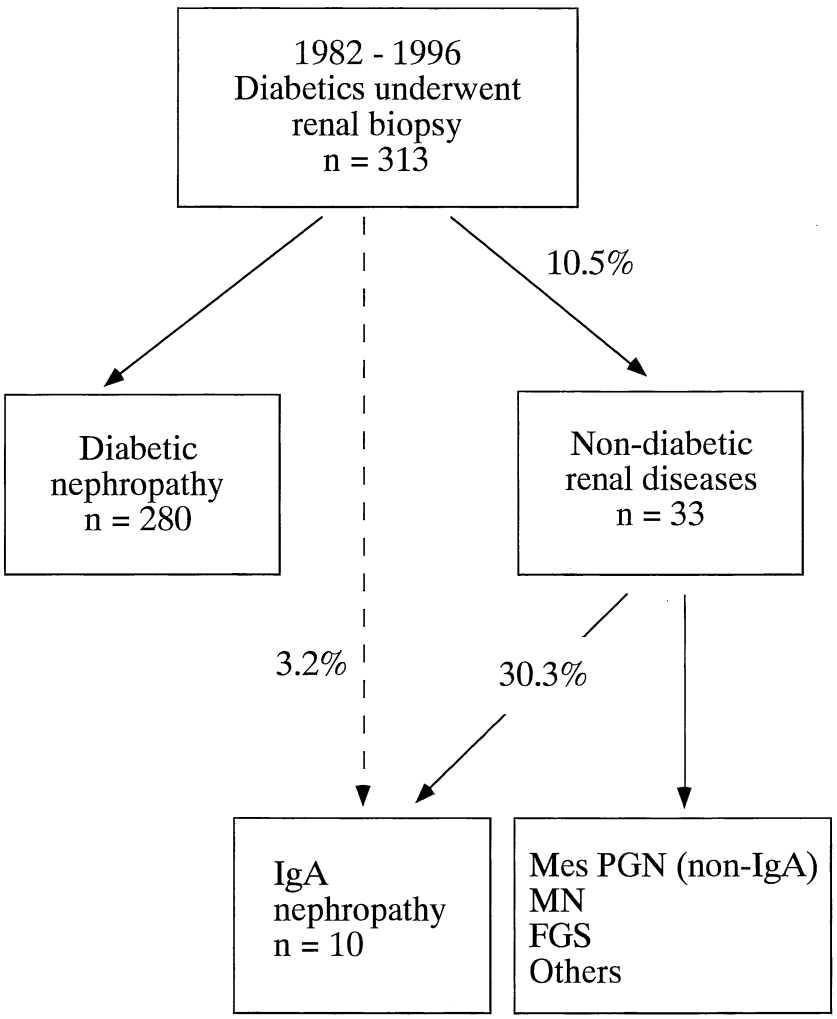

Fig. 2. Incidences of non-diabetic renal diseases and IgA nephropathy in diabetics in our series.
Mes PGN : mesangial proliferative glomerulonephritis (non -IgA nephropathy)
MN : membranous nephropathy
FGS : focal glomerulosclerosis

and without overt proteinuria, the incidence of IgA nephropathy in the overt proteinuric group was found to be 10.8 %.

DISCUSSION

In some diabetic patients, overt proteinuria may reflect a non-diabetic renal lesion superimposed on diabetic nephropathy. A variety of renal lesions other than diabetic nephropathy, such as membranous nephropathy[2-7,9,11,12,14-17], endocapillary glomerulonephritis[2,3,4,11,12], crescentic glomerulonephritis[3,4,11,12,18], and IgA nephropathy[2-13,18] can occur in diabetic patients. The discovery of non-diabetic renal disease in diabetic patients may require change in therapy for the renal impairment. For instance, membranous nephropathy was described more frequently in diabetics, and requires treatment with corticosteroid or immunosuppressive agent[19].

The precise incidence of renal lesions other than diabetic nephropathy in patients with diabetes mellitus is unknown. We found 12 reports[2-13] of renal biopsy studies specifically dealing with superimposed glomerulonephritis on diabetes (Table 3). These reports feature wide variation in the incidence of non-diabetic renal disease. The rate of IgA nephropathy varied between 0 and 10 %. These diverse findings might have been due to racial difference or selection bias for renal biopsy. First, the frequency of IgA nephropathy varies between countries[20]. Higher incidences are found in southern Europe, Australia, and Asia, which account for 20 to 40 % of patients with primary glomerulonephritis[21]. On the other hand, studies from the United States and Canada have reported the lowest incidence, about 5 %[21]. Second, with regard to selection bias, renal biopsies are usually made in diabetics due to the presence of symptoms and signs thought to be caused by a complicating glomerulonephritis, such as hematuria, overt proteinuria or nephrotic syndrome with short duration of diabetes, or unexpected renal failure. The incidence of non-diabetic renal lesions has been reported to be approximately 30 % in selected series of overt proteinuric diabetic patients[6,10,11]. Selection bias in renal biopsy will result in overestimation of the real incidence of non-diabetic renal diseases in diabetic patients. Findings on urinalysis were not helpful in differentiating diabetic nephropathy from other renal diseases. O'Neil et al.[22], studying 30 patients with clinical and

Table 3. Incidence of IgA nephropathy in diabetics

Author	Duration of study (yr)	Diabetic subjects	Non-diabetic renal disease	IgA nephropathy
Kasinath, et al. (1983)	23	122	10 (8 %)	0 (0 %)
Yum, et al. (1984)	9	18	8 (44)	0 (0)
Amoah, et al. (1988)	11	109	23 (21)	2*(1.9)
Nakamoto, et al. (1990)	10	133	16 (12)	7 (5.3)
Taft, et al. (1990)	7	136	38 (28)	4 (2.9)
Suzuki, et al. (1991)	33	128	20 (16)	13 (10.2)
Waldherr, et al. (1992)	3	210	1 (0.5)	1 (0.5)
Richards, et al. (1992)	10	68	25 (37)	1 (1.5)
Parving, et al. (1992)	1	35	8 (23)	2 (5.7)
Gambara, et al. (1992)	8	52	17 (33)	2 (3.8)
John, et al. (1994)	8	80	65 (81)	6 (7.5)
Olsen, et al. (1995)	7	33	4 (12)	1 (3.0)
Our series	15	313	31 (10)	10 (3.2)

*These two cases exhibited purpura nephritis with IgA deposition.

laboratory features of diabetic nephropathy, found hematuria in 30 % and red cell casts in 13 %. Taft et al.[6] also reported that more than half of the diabetic patients had significant microscopic hematuria, and concluded that the presence of hematuria was a poor predictor of the coexistence with glomerulonephritis.

Overt proteinuria and renal insufficiency do not usually occur prior to the first decade of diabetes. In our study, seven of 10 patients with IgA nephropathy superimposed on diabetes had a duration of diabetes of less than 5 years. Absence of diabetic retinopathy is also an indication for renal biopsy in proteinuric diabetic subjects. Kasinath et al.[2] reported that one of ten diabetic patients with a non-diabetic renal disease had diabetic retinopathy. Parving et al.[10] also reported that none of the eight diabetic patients with primary glomerulonephritis had diabetic retinopathy. In our study, diabetic retinopathy was found in only three of the ten diabetic patients with IgA nephropathy. Therefore, short duration of diabetes and/or absence of diabetic retinopathy are reliable indicators of the co-existence of non-diabetic renal disease.

In conclusion, IgA nephropathy in diabetic patients is reported to occur frequently. Therefore, renal biopsy should be considered whenever clinical findings do not fit the natural course of diabetic nephropathy.

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