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Dense Deposit Disease in Korean Children: A Multicenter Clinicopathologic Study

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The purpose of this study was to investigate the clinical, laboratory, and pathologic characteristics of dense deposit disease (DDD) in Korean children and to determine whether these characteristics differ between Korean and American children with DDD. In 2010, we sent a structured protocol about DDD to pediatric nephrologists throughout Korea. The data collected were compared with previously published data on 14 American children with DDD. Korean children had lower 24-hr urine protein excretion and higher serum albumin levels than American children. The light microscopic findings revealed that a higher percentage of Korean children had membranoproliferative glomerulonephritis patterns (Korean, 77.8%; American, 28.6%, $P = 0.036$), whereas a higher percentage of American children had crescents (Korean, 0%; American, 78.6%, $P < 0.001$). The findings from the electron microscopy revealed that Korean children were more likely to have segmental electron dense deposits in the lamina densa of the glomerular basement membrane (Korean, 100%; American, 28.6%, $P = 0.002$); mesangial deposit was more frequent in American children (Korean, 66.7%; American, 100%, $P = 0.047$). The histological findings revealed that Korean children with DDD were more likely to show membranoproliferative glomerulonephritis patterns than American children. The degree of proteinuria and hypoalbuminemia was milder in Korean children than American children.

Key Words: Dense Deposit Disease; Membranoproliferative Glomerulonephritis; Electron-Dense Deposit

INTRODUCTION

Dense deposit disease (DDD) is a rare glomerulonephritis that typically affects children between the ages of 5 and 15 yr old (1). The prevalence of DDD is estimated at only two to three people per million, but about 50% of these patients proceed to end-stage renal failure within 10 yr of diagnosis (2, 3). Although the following findings are nonspecific, DDD is clinically characterized by hematuria, proteinuria, acute nephritic syndrome, or nephrotic syndrome. Spontaneous remission is extremely rare (1).

DDD has previously been referred to as membranoproliferative glomerulonephritis (MPGN) type II, but it differs markedly from other MPGN types in pathogenesis. When Galle (4) first described DDD in 1962, he reported an electron dense transformation of the glomerular basement membranes (GBM). However, under electron microscopy, the morphologic hallmark of DDD is the transformation of the lamina densa of the GBM, which shows an intense deposition of C3 in a ribbon-like pattern along the GBM, tubular basement membrane, and the wall of Bowman's capsule.

A few recent studies have examined the clinicopathologic characteristics of patients with DDD (5, 6). For example, one study compared the clinicopathologic features of DDD in children and adults (5). However, it is unknown whether the clinicopathologic course and prognosis differs between Asian and Western children with DDD. Thus, we investigated all DDD cases previously reported and newly recruited the Korean pediatric population and compared the outcomes and clinicopathologic features with those of American children. The aim of this study was to investigate the clinical, laboratory, and pathologic char-

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acteristics of DDD in Korean children, and to determine whether these characteristics differed from those of American children with DDD.

MATERIALS AND METHODS

Study design and patients

In 2010, we sent a structured protocol for this study to pediatric nephrologists working at university hospitals in Korea. Nine patients with DDD were recruited from six hospitals; the study population included 6 males and 3 females (mean age, 9.0 yr; range, 4-13.1 yr). We investigated the clinicopathologic features of DDD from the protocols. The following clinical data were documented: age and gender of patients, peripheral edema, oliguria, hypertension, 24-hr urine protein, nephrotic syndrome, albumin, hematuria, red blood cell casts, serum creatinine at renal biopsy, C3, C4, preceding infection, duration of follow-up, treatment, and outcome. These data were compared with previously published data on 14 American children with DDD (5). Table 1 summarizes the patient demographics.

All participants were native Koreans without any significant previous medical conditions. DDD was diagnosed by the pathologists at each hospital, and the histological photographs and clinical data for each patient were obtained from their pediatric nephrologists.

Histological data

The diagnosis of DDD was based on the ultrastructural finding of a transformation of the glomerular basement membranes by ribbon-like, highly electron-dense material and a high degree of immunofluorescence staining for C3. Initial renal biopsy slides and photographs were reviewed by a pathologist at Yonsei University Severance Hospital to assess the pathological features of DDD using light microscopy (LM), immunofluorescence (IF), and electron microscopy (EM). A diagnosis of DDD was confirmed for all nine patients.

When using LM, DDD exhibited 4 different histologic patterns; mesangial proliferative glomerulonephritis (GN), endocapillary proliferative GN, MPGN, and crescentic GN. LM findings included the number of glomeruli and crescents, the percentage of globally and segmentally sclerotic glomeruli, necrosis, endocapillary hypercellularity, intracapillary neutrophil infiltration, interstitial inflammation, tubular atrophy, and interstitial fibrosis. Staining intensity was graded 0 (negative) to 3+ (severe) on a semiquantitative scale for IgG, IgA, IgM, C3, and C1q. Ultrastructural evaluation was performed with a transmission electron microscope.

Table 1. Demographics of nine Korean patients with dense deposit disease

Parameters	Number (%)
Female:male	3:6
Age (yr)	
0 to 5	2 (22.2)
6 to 10	5 (55.5)
11 to 15	2 (22.2)
Body surface area (m^2)	
0 to 0.5	0 (0)
0.6 to 1.0	3 (33.3)
> 1.0	6 (66.6)
Body mass index (kg/m^2)	
10 to 14	5 (55.5)
15 to 19	2 (22.2)
20 to 24	2 (22.2)

Definitions

Nephrotic syndrome was defined as the presence of nephrotic range proteinuria, hypoalbuminemia, hyperlipidemia, and peripheral edema. Nephrotic range proteinuria was defined as a 24-hr urine protein > 40 mg/m^2/hr, or a spot urine protein-to-creatinine ratio ≥ 2. Hypoalbuminemia was defined as a serum albumin level ≤ 2.5 g/dL. Hematuria was defined as ≥ 5 red blood cells per high power field on microscopic examination of the urinary sediment or positive blood identification by dipstick. The terms "focal" and "diffuse" refer to disease infiltration of $\leq 50\%$ or $> 50\%$ of glomeruli, respectively.

The pathological features of MPGN were classified into three subtypes. Type I classical MPGN is the most common variant characterized by subendothelial immune deposits in the capillary wall and is associated with an activation of the classical complement pathway (7). In type II MPGN (DDD), intramembranous electron dense deposits are seen within the glomerular, tubular and Bowman's capsular basement membrane, which is associated with C3 nephritic factor and persistent activation of the alternative complement pathway (7). Type III MPGN is considered a morphologic variant of type I characterized by subepithelial as well as subendothelial deposits. (7)

Statistical analysis

Statistical analyses were performed with SPSS for Windows version 18.0 (SPSS, Chicago, IL, USA). Descriptive statistics are expressed as mean ± standard deviation. As appropriate, additional analyses were performed with nonparametric statistical methods, including Mann-Whitney test, Fisher's exact test and the Wilcoxon rank-sum test. $P < 0.05$ was considered statistically significant.

Ethics statement

This study was approved by the institutional review board of Yonsei University Severance Hospital (IRB approval number: 4-2011-0106). The board exempted written informed consent from all study participants.

RESULTS

The subject population included nine children: two children

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Table 2. Clinical characteristics at presentation and follow-up in Korean patients

No.	Preceding infection	Peripheral edema	Oliguria	Hyper-tension	24 hr urine protein (mg)	Gross hema-turia	Serum albumin (g/dL)	Serum creatinine at biopsy (mg/dL)	C3 (mg/dL)	C4 (mg/dL)	Treatment	Outcome	Duration of follow-up (months)
1	-	-	-	-	49	-	5.0	0.6	15	15.9	ACEi	PRD*	14
2	-	-	-	-	5,000	-	2.7	0.5	49.6	16.8	Combined†	PRD	54
3	-	+	+	-	2,625	+	2.3	1.17	125	71.7	Combined	CR‡	87
4	-	-	-	-	583	-	3.6	0.59	60	25.4	Combined	PRD	54
5	+	-	-	-	350	+	3.5	0.4	8	33	ACEi	PRD	204
6	-	-	-	-	197	-	4.1	0.7	17	8.3	ACEi	PRD	8
7	+	-	-	-	78	-	3.9	0.9	12.5	21.3	Combined	CR	126
8	+	+	-	-	2,200	+	3.4	0.6	26	48	IS	CR	156
9	-	-	-	-	120	-	4.2	0.46	16.1	7.7	ACEi	PRD	1

*Persistent renal dysfunction; †Immunosuppressive agents/renin angiotensin system blockade; ‡Complete response.

Table 3. Clinical characteristics at presentation of DDD

Characteristics	American children (5) (n = 14)	Korean children (n = 9)	*P* value
Peripheral edema	6 (42.8)	2 (22.2)	0.400
Mean 24-hr urine protein	4.0	1.25	0.001
Proteinuria < 1 g/24 hr	2/13 (15.4)	6 (66.7)	0.026
Proteinuria 1 to 3 g/24 hr	4/13 (30.8)	2 (22.2)	0.999
Proteinuria > 3 g/24 hr	7/13 (53.8)	1 (11.1)	0.074
Full nephrotic syndrome	4/13 (30.8)	2 (22.2)	0.999
Mean serum albumin (g/dL)	2.7	3.65	0.021
Hematuria (microscopic or macroscopic)	13/13 (100)	9 (100)	0.999
Macroscopic hematuria	3/13 (23.1)	3 (33.3)	0.655
Red blood cell casts	6/13 (46.2)	1 (11.1)	0.165
Mean serum creatinine at biopsy (mg/dL)	0.8	0.65	0.340
Renal insufficiency at presentation	5 (35.7)	1 (11.1)	
Low C3	13/13 (100)	8 (88.9)	0.409
Low C4	0/13 (0)	2 (22.2)	0.156
Preceding infection	8 (57.1)*	3 (33.3)†	0.400

Numbers in parentheses are percentages. *Pneumonia in four patients, upper respiratory tract infection in three patients, and bronchitis in one patient; †Upper respiratory tract infection in three patients.

Table 4. Histological pattern by light microscopy

Pattern of histology	American children (5) (n = 14)	Korean children (n = 9)	*P* value
Mesangial proliferative GN	4 (28.6)	0 (0)	0.254
Endocapillary proliferative GN with or without exudative features	3 (21.4)	2 (22.2)	0.999
Membranoproliferative GN	4 (28.6)	7 (77.8)	0.036
Crescentic GN*	3 (21.4)	0 (0)	0.273

Numbers in parentheses are percentages. *Defined by the presence of crescents affecting ≥ 50% of glomeruli.

≤ 5 yr of age and seven children > 6 yr of age (Table 1). The ratio of males to females was 2.0, and the mean age was 9.0 yr (range 4-13.1 yr). No children were overweight or obese, and none had a history of comorbid conditions, such as hypertension. The development of renal symptoms was preceded by an acute infection in 33.3% of patients (Table 2).

Although all patients had proteinuria at presentation, only three children (33.3%) developed nephrotic range proteinuria. The mean 24-hr urine protein was 1.25 g. Decreased C3 levels were present in eight patients (88.9%), whereas C4 was depressed in only two patients (22.2%) (Table 3). Gross and microscopic hematuria were present in 33.3% and 100% of patients, respectively. The mean serum albumin level was within normal limits. At presentation, renal insufficiency was documented in only one patient (11.1%), and the mean serum creatinine at biopsy was 0.65 mg/dL. There were no differences between Korean and American children in age, gender, hematuria, generalized edema, and serum creatinine levels at presentation. However, Korean children had lower mean 24-hr urine protein excretion (Korean, 1.25 g; American, 4.0 g, $P < 0.001$) and higher mean serum albumin levels (Korean, 3.7 g/dL; American, 2.7 g/dL, $P = 0.021$) than American children (Table 3).

The light microscopic findings revealed that the most common histological pattern for DDD was MPGN, found in 77.8% of Korean patients; the next most common pattern was endocapillary proliferative GN with or without exudative features (22.2%) (Table 4). One patient had MPGN that resulted from mesangial proliferative GN. One other patient had MPGN that resulted from endocapillary proliferative GN. The MPGN pattern was associated with more endocapillary hypercellularity and intracapillary neutrophil infiltration than other patterns. No crescentic GN was observed (Fig. 1A, B). A significantly higher percentage of Korean patients had MPGN patterns (Korean, 77.8%; American, 28.6%, $P = 0.036$), whereas a significantly higher percentage of American children had crescents (Korean, 0%; American, 78.6%, $P < 0.001$) (Table 5). Segmentally sclerotic glomeruli were observed in 13.4% of Korean patients; however, none was observed in the American children.

Using immunofluorescence (Fig. 1C), we detected intense C3 staining along the glomerular capillary wall of 87.5% of Korean patients (mean intensity 1.7+). C1q and IgA positivity were absent. There were no differences in C3, C1q, IgG, IgM, and IgA depositions between Korean and American children (Table 6).

Electron microscopy confirmed the distinguishing character-

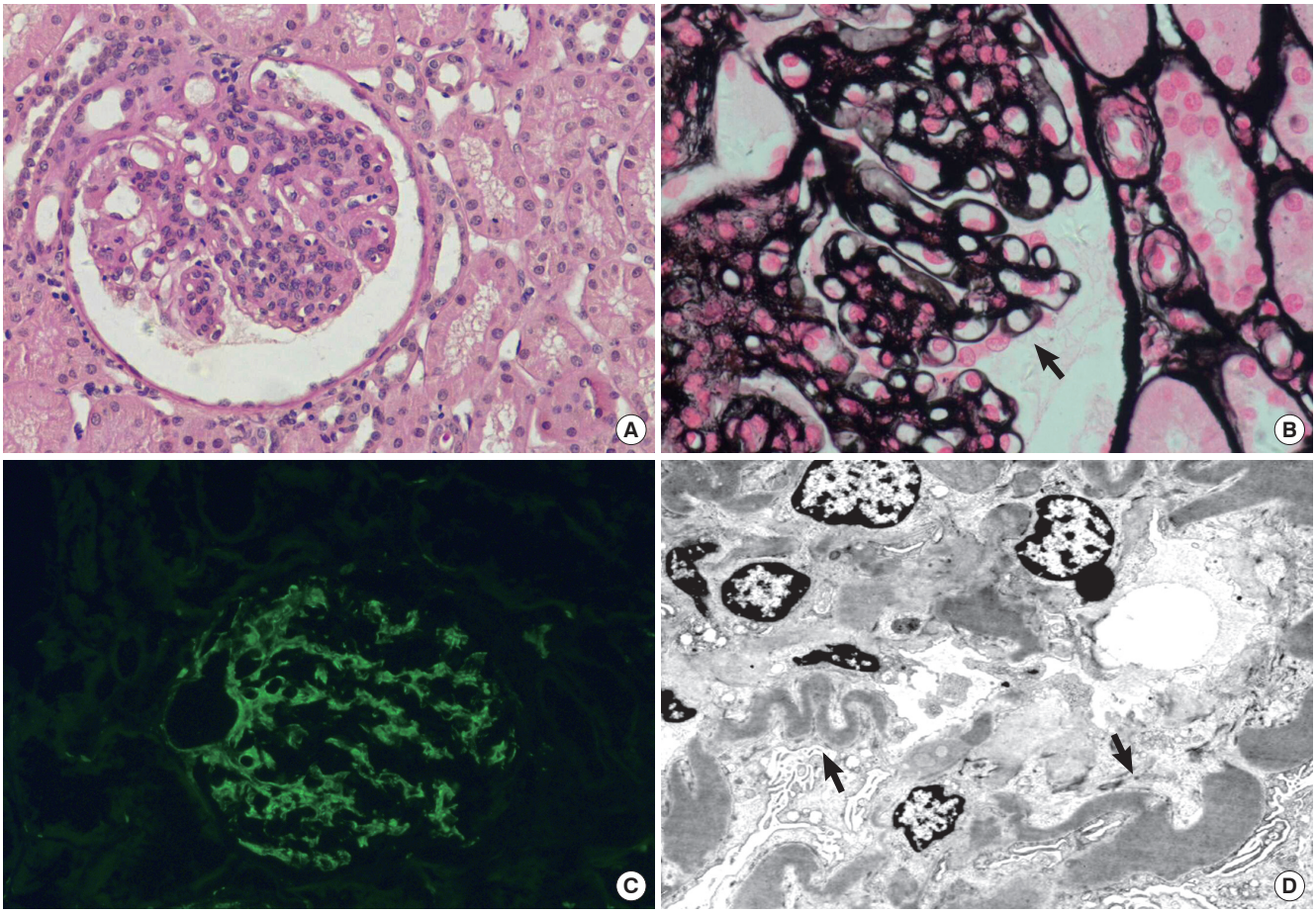

Fig. 1. Light, immunofluorescence, and electron microscopy findings in a Korean case of dense deposit disease. (**A**) Cellular proliferation leads to lobule formation in the glomerulus (H&E, × 200). (**B**) The glomerular capillary wall is thickened focally, but the doubling or splitting observed in type I MPGN is not observed (arrow) (Periodic acid methenamine silver, × 400). (**C**) C3 immunofluorescence deposits along the glomerular capillary wall have a linear rather than a granular pattern (× 200). (**D**) Intramembranous electron dense deposits with a ribbon or sausage shape (arrows) are visible under the electron microscope (× 4,000).

Table 5. Light microscopic findings

Pathologic findings	American children (5) (n = 14)	Korean children (n = 9)	*P* value
Mean number of glomeruli	24.4	37.0	0.207
Percent of globally sclerotic glomeruli	2.9	8.6	0.304
Percent of segmentally sclerotic glomeruli	0	13.4	0.068
Percent of cases with crescents*	11 (78.6)	0 (0)	< 0.001
Focal	8	0	0.007
Diffuse	3	0	0.253
Number of cases with necrosis	1 (7.1)	0 (0)	0.999
Number of cases with endocapillary hypercellularity*	10 (71.4)	6 (66.7)	0.999
Focal	6	5	0.680
Diffuse	4	1	0.611
Number of cases with intracapillary neutrophil infiltration*	8 (57.1)	5 (55.6)	0.999
Focal	6	3	0.691
Diffuse	2	2	0.999
Interstitial inflammation: none/focal/diffuse†	5/7/2	8/1/0	0.041
Tubular atrophy and interstitial fibrosis (none/mild/moderate/severe)‡	8/5/1/0	6/3/0/0	0.999
Arteriosclerosis and arteriolar hyalinosis (none/mild/moderate/severe)	13/1/0/0	8/1/0/0	0.999

Numbers in parentheses are percentages. *Focal, ≤ 50% of glomeruli; diffuse, > 50% of glomeruli; †Focal, ≤ 50% of cortical surface area; diffuse, > 50%; ‡Mild: 0 to 25% of cortical surface area; moderate: 26 to 50%; severe: > 50%.

istic of DDD: electron-dense deposits that had irregularly thickened and transformed the lamina densa (Fig. 1D). In the GBM of all patients, the intramembranous deposits were segmentally interrupted. The deposits also involved the mesangium (66.7%

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Table 6. Immunofluorescence findings

Target molecules	No. (%) of positive patients		*P* value
	American children (5) (n = 14)	Korean children (n = 8)	
C3	14 (100) (2.6+)	7/8 (87.5) (1.7+)	0.364
C1q	3 (21.4) (1.8+)	0/8 (0) (0)	0.273
IgG	5 (35.7) (1.3+)	1/8 (12.5) (0.5+)	0.351
IgM	8 (57.1) (0.9+)	2/8 (25) (0.8+)	0.204
IgA	1 (7.1) (1+)	0/8 (0) (0)	1.000

Data indicate the number (percentage) of positive patients and the mean intensity of staining when positive (scale: 0.5, 1 to 3+).

Table 7. Electron microscopic findings

Location of highly electron-dense deposits	American children (5) (n = 14)	Korean children (n = 9)	*P* value
Lamina densa of GBM*	14 (100)	9 (100)	0.999
Segmental†	4 (28.6)	9 (100)	0.002
Global†	10 (71.4)	0 (0)	0.127
Mesangial	14 (100)	6 (66.7)	0.047
Segmental†	7 (50)	6 (66.7)	0.686
Global†	7 (50)	0 (0)	0.023
Subepithelial hump-shaped deposits	2 (14.3)	2 (22.2)	0.999
Subendothelial	5 (35.7)	2 (22.2)	0.657
Bowman's capsule	6 (42.9)	0 (0)	0.048
Tubular basement membranes	6 (42.9)	1 (11.1)	0.176

Numbers in parentheses are percentages. *GBM, glomerular basement membranes; †Segmental, involving < 50% of the glomerular loops; global, involving ≥ 50% of glomerular loops.

of patients), focal subepithelium (22.2% of patients), subendothelium (22.2% of patients), and tubular basement membranes (11.1% of patients) (Table 7). Korean children were more likely to have segmental electron dense deposits in the lamina densa of the GBM (Korean, 100%; American, 28.6%, $P = 0.002$), but American children were more likely to have mesangial deposits (Korean, 66.7%; American, 100%, $P = 0.047$).

The mean duration of follow-up for Korean patients was 78.2 months (range, 1 to 204 months). Treatment for DDD involved renin angiotensin system (RAS) blockade (angiotensin converting enzyme inhibitor and/or angiotensin II receptor blocker) in four patients; immunosuppression (IS) in one patient; and combined RAS blockade/IS in four patients (Table 8). Steroids were used for IS in all five patients. Among the five patients who received IS therapy, two had nephrotic syndrome in the follow-up period (40%), four had decreased C3 levels (80%), and one had renal insufficiency (20%) on admission. At the final follow-up, no patients had progressed to end-stage renal disease, but 66.7% experienced persistent renal dysfunction, such as microscopic hematuria and proteinuria. The clinical outcomes did not differ significantly between Korean and American children.

Table 8. Clinical follow-up

Parameters	American Children (5) (n = 14)	Korean Children (n = 9)	*P* value
Duration of follow-up: mean (range) in months	79.4 (2 to 288)	78.2 (1 to 204)	0.391
Treatment			0.432
RAS* blockade alone	2 (15.4)	4 (44.4)	
IS* alone (steroid or 2nd agents)	3 (23.1)	1 (11.1)	
Combined IS/RAS blockade	8 (61.5)	4 (44.4)	
Outcome†			0.799
Complete response	6 (46.1)	3 (33.3)	
Persistent renal dysfunction	6 (46.1)	6 (66.7)	
ESRD	1 (7.7)	0 (0)	

Numbers in parentheses are percentages, unless otherwise indicated. *RAS, renin angiotensin system; IS, immunosuppressive agents (steroids with or without a second agent); †Overall comparison, complete response/persistent renal dysfunction/ESRD in American children versus Korean children.

DISCUSSION

The purpose of this multicenter study was to identify the clinicopathologic characteristics and outcomes of Korean children with DDD and to compare these characteristics and outcomes with those of American children. We found that DDD was extremely rare in Korea, with only a small number of DDD cases published during the past 3 decades (8-13). In contrast to the reports from America (5), most patients in our study had a good prognosis, including one case that completely resolved. Unfortunately, the rarity of DDD has resulted in a limited understanding of the clinicopathologic findings and natural course of the disease in the Korean population. Thus, our study focused on the cliniopathologic characteristics of DDD and if these characteristics differed from patients with DDD in America.

Although DDD usually affects patients between the ages of 5 and 15 yr (14), this age range can vary considerably, from 1 to 64 yr (15, 16). In a study by Nasr et al. (5), all 14 children in the cohort were over 5 yr of age. In contrast, 2 children (22.2%) in our study were less than 5 yr at the onset of DDD, and DDD was twice as common in male patients as females. Thus, our data suggest that DDD in Asian children may occur at an earlier age than in American children and that it may occur more frequently in males.

Patients with DDD exhibit various clinical manifestations, such as peripheral edema, nephrotic syndrome, hypertension, gross hematuria, and persistent hypocomplementemia. These findings are not specific to DDD. However, recent efforts have attempted to find an association between clinical predictive factors and poor outcome in DDD (5, 6, 14). Nasr et al. (5) found that older age and higher serum creatinine at biopsy to predict a poor prognosis in DDD patients, while Appel et al. found that glomerular crescents or tubular atrophy at biopsy to predict poor outcomes (14). Another recent study found that a greater percentage of females than males were on dialysis in the 'younger

population' (50% vs 27%, respectively, $P = 0.036$), and renal failure was more common among patients who had DDD for at least 10 yr since diagnosis (53% vs 32%, $P = 0.044$) (6). Previous reports suggest that renal function slowly deteriorates for roughly 50% of patients with DDD, and that patients progress to end-stage renal disease and require dialysis within 10 yr of onset (6, 17, 18). In contrast, all patients with DDD in our study had a good clinical prognosis, and one patient had complete resolution of DDD after a high dose of prednisolone. Although the cause of this difference is unknown, we suggest that it may be due to the younger age of our patients, their milder proteinuria and hypoalbuminemia, the absence of glomerular crescents, relatively well-preserved renal function, normal blood pressure, and lower 24-hr protein excretion. In addition, more segmental electron dense deposits in the lamina densa of the GBM may have favored the resolution of DDD instead of diffuse dense deposits in the GBM and mesangium. Improvements to the urinary screening policy of schools in Korea may also encourage the earlier detection and management of DDD in children. However, further studies are needed in a larger population to investigate these possibilities.

The distinct pathologic features of DDD are the dense intramembranous deposits and transformation of the GBM observed with electron microscopy. These changes are distributed in a segmental, discontinuous, interrupted, or continuous and diffuse pattern in the lamina densa of the GBM (19-21). In our study, the histological patterns of DDD did not differ between Korean and American children. However, the light microscopic findings revealed that the percentage of patients with crescents and interstitial inflammation was higher in American than Korean children. The location of highly electron-dense deposits was more segmental in Korean than American children. Electron-dense deposits in Bowman's capsule were more frequent in American children. In our study, two patients had DDD that resulted from either mesangial proliferative GN or endocapillary proliferative GN. Subepithelial and subendothelial electron dense deposits were also observed, as well as intramembranous deposits. These deposits were associated with mesangial proliferation and interposition. Although MPGN patterns were more prevalent in Korean patients than American children, diverse features of mesangial proliferative change, membranoproliferative change, and minor glomerular alterations were also present.

The clinical and morphological diversity of DDD makes it difficult for clinicians to differentiate DDD from other glomerulonephritic diseases. In children, hematuria and a decrease in C3 levels may lead to a diagnosis of poststreptococcal GN and lupus nephritis. Presentation with acute nephritic syndrome and C3 deposits along the capillary loops can be observed both in poststereptococcal GN and in DDD without membranoproliferation. Therefore, EM examination through renal biopsy is necessary to distinguish between them. Intramemtranous electron dense deposits may be observed in the Anders and Strife variant of MPGN type III, but breaks and lamellations in the intervening lamina densa are usually associated with electron dense deposits (22). Persistent C3 deposits, regardless of morphologic transformation and areas of continuous intramembranous deposits along the lamina densa, can also support the diagnosis of DDD.

Many different treatment options use renin angiotensin system blockade, such as angiotensin converting enzyme inhibitors and angiotensin receptor blockers, immunosuppression with corticosteroids, cytotoxic drugs, anticoagulants, and antiplatelet agents. The knowledge and understanding of the pathophysiology of DDD has grown (14, 17, 23). For example, more specific and effective treatment options have become available, such as plasmapheresis with or without plasma exchange to replace factor H deficiency (24-26), intravenous infusion of immunoglobulin to interrupt the C3 convertase-induced rapid amplification feedback loop (27, 28), and eculizumab to inhibit activation of the terminal pathway of the complement against C5 (29, 30). Similar to other studies (5, 6), we found that renin angiotensin system blockade and prednisolone were the most frequently prescribed medications for DDD - both had good therapeutic responses.

Our study has some limitations. We were only able to enroll a small number of patients due to the extreme rarity of DDD. We also did not repeat biopsies in the study patients, and the follow-up duration was relatively short. In addition, this was a retrospective study; therefore, the accuracy of our data could have been affected by the memory of the informants. A prospective cohort study with a larger number of DDD patients is needed to establish the clinicophathologic course, outcome, and evidence-based practice guidelines for better treatment of DDD, including consideration of any ethnic differences.

In summary, our histological findings revealed that Korean children with DDD were more likely to show membranoproliferative glomerulonephritis patterns than American children. In addition, proteinuria and hypoalbuminemia were milder in Korean than American children, although the clinical outcomes did not differ between groups. These findings should be confirmed through future studies involving a greater number of patients with DDD. Due to the rarity of DDD, such studies will require a collaborative effort between multiple research facilities. To this end, we invite other researchers to contact us about future participation in an international collaborative research survey of patients with DDD.

REFERENCES

1. Sethi S, Sukov WR, Zhang Y, Fervenza FC, Lager DJ, Miller DV, Cornell LD, Krishnan SG, Smith RJ. *Dense deposit disease associated with monoclonal gammopathy of undetermined significance. Am J Kidney Dis 2010; 56: 977-82.*

 http://dx.doi.org/10.3346/jkms.2012.27.10.1215

2. Cameron JS, Turner DR, Heaton J, Williams DG, Ogg CS, Chantler C, Haycock GB, Hicks J. *Idiopathic mesangiocapillary glomerulonephritis. Comparison of types I and II in children and adults and long-term prognosis. Am J Med 1983; 74: 175-92.*
3. Swainson CP, Robson JS, Thomson D, MacDonald MK. *Mesangiocapillary glomerulonephritis: a long-term study of 40 cases. J Pathol 1983; 141: 449-68.*
4. Galle P. *A description of a unique lesion of the glomerular basement membranes seen as a hyaline substance with the electron microscope [in Frence] le´sion singulie` re des membranes basales du rein et de la substance hyaline [thesis]. Paris: Medical School, University of Paris; 1962.*
5. Nasr SH, Valeri AM, Appel GB, Sherwinter J, Stokes MB, Said SM, Markowitz GS, D'Agati VD. *Dense deposit disease: clinicopathologic study of 32 pediatric and adult patients. Clin J Am Soc Nephrol 2009; 4: 22-32.*
6. Lu DF, Moon M, Lanning LD, McCarthy AM, Smith RJ. *Clinical features and outcomes of 98 children and adults with dense deposit disease. Pediatr Nephrol 2012; 27: 773-81.*
7. Alchi B, Jayne D. *Membranoproliferative glomerulonephritis. Pediatr Nephrol 2010; 25: 1409-18.*
8. Sung JH, Kang MJ, Hwang EA, Han SY, Park SB, Kim HC, Park KK. *Two cases of type II membranoproliferative glomerulonephritis. Korean J Nephrol 2004; 23: 335-40.*
9. Kim HJ, Kwak BO, Bae JU, Kim KS, Lim SD. *A case of type II membranoproliferative glomerulonephritis detected by school urinary screening tests. J Korean Soc Pediatr Nephrol 2010; 14: 79-83.*
10. Lee SJ, Moon JH, Kang MS, Song MS, Chung WY. *A case of membranoproliferative glomerulonephritis type II (Dense-Deposit Disease). J Korean Soc Pediatr Nephrol 2003; 7: 204-10.*
11. Kwon HS, Oh SJ, Lee YM, Kim JH, Kim PK, Kang HY, Jeong HJ, Choi IJ. *A case of membranoproliferative glomerulonephritis type II: Dense Deposit Disease, DDD. J Korean Soc Pediatr Nephrol 2001; 5: 188-95.*
12. Kim MS, Hwang PH, Kang MJ, Lee DY. *A case of regression of atypical dense deposit disease without C3 deposition in a child. Korean J Pediatr 2010; 53: 766-9.*
13. Kim MJ, Lim BJ, Shin JI, Lee JS, Lee YH, Joh K, Kim PK, Jeong HJ. *Development of IgA nephropathy after clinical remission of Dense Deposit Disease. Korean J Nephrol 2010; 29: 125-30.*
14. Appel GB, Cook HT, Hageman G, Jennette JC, Kashgarian M, Kirschfink M, Lambris JD, Lanning L, Lutz HU, Meri S, et al. *Membranoproliferative glomerulonephritis type II (dense deposit disease): an update. J Am Soc Nephrol 2005; 16: 1392-403.*
15. Bennett WM, Fassett RG, Walker RG, Fairley KF, d'Apice AJ, Kincaid-Smith P. *Mesangiocapillary glomerulonephritis type II (dense-deposit disease): clinical features of progressive disease. Am J Kidney Dis 1989; 13: 469-76.*
16. Schwertz R, de Jong R, Gretz N, Kirschfink M, Anders D, Scharer K. *Outcome of idiopathic membranoproliferative glomerulonephritis in children. Arbeitsgemeinschaft Padiatrische Nephrologie. Acta Paediatr 1996; 85: 308-12.*
17. Walker PD. *Dense deposit disease: new insights. Curr Opin Nephrol Hypertens 2007; 16: 204-12.*
18. Cameron JS, Turner DR, Heaton J, Williams DG, Ogg CS, Chantler C, Haycock GB, Hicks J. *Idiopathic mesangiocapillary glomerulonephritis. Comparison of types I and II in children and adults and long-term prognosis. Am J Med 1983; 74: 175-92.*
19. Nevins TE. *Lectin binding in membranoproliferative glomerulonephritis. Evidence for N-acetylglucosamine in dense intramembranous deposits. Am J Pathol 1985; 118: 325-30.*
20. Sibley RK, Kim Y. *Dense intramembranous deposit disease: new pathologic features. Kidney Int 1984; 25: 660-70.*
21. Swainson CP, Robson JS, Thomson D, MacDonald MK. *Mesangiocapillary glomerulonephritis: a long-term study of 40 cases. J Pathol 1983; 141: 449-68.*
22. Sethi S, Nester CM, Smith RJ. *Membranoproliferative glomerulonephritis and C3 glomerulopathy: resolving the confusion. Kidney Int 2012; 81: 434-41.*
23. Walker PD, Ferrario F, Joh K, Bonsib SM. *Dense deposit disease is not a membranoproliferative glomerulonephritis. Mod Pathol 2007; 20: 605-16.*
24. Licht C, Heinen S, Józsi M, Löschmann I, Saunders RE, Perkins SJ, Waldherr R, Skerka C, Kirschfink M, Hoppe B, et al. *Deletion of Lys224 in regulatory domain 4 of Factor H reveals a novel pathomechanism for dense deposit disease (MPGN II). Kidney Int 2006; 70: 42-50.*
25. Kurtz KA, Schlueter AJ. *Management of membranoproliferative glomerulonephritis type II with plasmapheresis. J Clin Apher 2002; 17: 135-7.*
26. Jansen JH, Høgåsen K, Harboe M, Hovig T. *In situ complement activation in porcine membranoproliferative glomerulonephritis type II. Kidney Int 1998; 53: 331-49.*
27. Bayary J, Dasgupta S, Misra N, Ephrem A, Duong Van Huyen JP, Delignat S, Hassan G, Caligiuri G, Nicoletti A, Lacroix-Desmazes S, et al. *Intravenous immunoglobulin in autoimmune disorders: an insight into the immunoregulatory mechanisms. Int Immunopharmacol 2006; 6: 528-34.*
28. Lutz HU, Stammler P, Bianchi V, Trüeb RM, Hunziker T, Burger R, Jelezarova E, Späth PJ. *Intravenously applied IgG stimulates complement attenuation in a complement-dependent autoimmune disease at the amplifying C3 convertase level. Blood 2004; 103: 465-72.*
29. Hillmen P, Young NS, Schubert J, Brodsky RA, Socié G, Muus P, Röth A, Szer J, Elebute MO, Nakamura R, et al. *The complement inhibitor eculizumab in paroxysmal nocturnal hemoglobinuria. N Engl J Med 2006; 355: 1233-43.*
30. Hillmen P, Hall C, Marsh JC, Elebute M, Bombara MP, Petro BE, Cullen MJ, Richards SJ, Rollins SA, Mojcik CF, et al. *Effect of eculizumab on hemolysis and transfusion requirements in patients with paroxysmal nocturnal hemoglobinuria. N Engl J Med 2004; 350: 552-9.*