Dense Deposit Disease in Korean Children: A Multicenter Clinicopathologic Study

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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-
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.

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/m²/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 ≤ 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
Table 2. Clinical characteristics at presentation and follow-up in Korean patients

| No. | Preceding infection | Peripheral edema | Oliguria | Hypertension | 24 hr urine protein (mg) | Gross hematuria | 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   |
| Microscopic 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.

≤ 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 and American children in age, gender, hematuria, generalized edema, and serum creatinine levels at presentation. However, there were no differences between Korean and American children in age, gender, hematuria, generalized edema, and serum creatinine levels at presentation.
Characteristic 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%...
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.

### 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 clinicopathologic 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

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**Table 6. Immunofluorescence findings**

| Target molecules | American children (5) | Korean children (n = 8) | \( P \) value |
|------------------|-----------------------|------------------------|---------------|
| C3 (100)         | 7/8 (87.5)            | 1 (12.5)               | 0.364         |
| C1q (21.4)       | 0/8 (0)               | 1.3 (0.5)              | 0.273         |
| IgG (35.7)       | 1/8 (12.5)            | 0 (0)                  | 0.351         |
| IgM (57.1)       | 2/8 (25)              | 0.8 (0)                | 0.204         |
| IgA (7.1)        | 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) | 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. \( \ast \) GBM, glomerular basement membranes; \( \dagger \) Segmental, involving < 50% of the glomerular loops; global, involving ≥ 50% of glomerular loops.

**Table 8. Clinical follow-up**

| Parameters                              | American Children (5) | 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)                  |               |
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 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 poststreptococcal GN and in DDD without membranoproliferation. Therefore, EM examination through renal biopsy is necessary to distinguish between them. Intramembranous 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 immunglobulin 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 clinicopathologic 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.

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