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Correlation of renal histology with outcome in children with lupus nephritis

PERRY J. RUSH, REUBEN BAUMAL, ABRAHAM SHORE, J. WILLIAMSON BALFE, and MARTIN SCHREIBER

Departments of Paediatrics and Pathology, The Hospital for Sick Children and the Department of Medicine, Sunnybrook Medical Centre, Toronto, Canada

Correlation of renal histology with outcome in children with lupus nephritis. We assessed renal histological features in 20 children with diffuse proliferative lupus nephritis (DPLN) to determine whether they were useful in predicting clinical outcome. Renal biopsies were analyzed by assigning scores indicating an activity index (AI) and chronicity index (CI). Clinical assessment of renal function at biopsy and outcome were graded according to urinalysis, serum creatinine, need for dialysis and/or transplantation, and/or death from end-stage renal failure. Renal function at biopsy correlated significantly with AI and CI. Serum complement (C3 and C4) correlated significantly with CI but not with AI. The usefulness of the clinical grading system was confirmed in ten patients who underwent repeat biopsies. Of these, four converted from DPLN to mesangial or membranous lupus and showed improvement in their grade, while only one of the six with DPLN on both biopsies improved. After a mean follow-up of 4.0 years, 14 of the 20 patients showed clinical improvement, four were unchanged, and two were worse. CI predicted clinical outcome ($P < 0.01$) but AI did not. Histologic scores of AI and CI obtained from renal biopsies showing DPLN may be useful in predicting therapeutic responses and designing prospective clinical trials to determine optimum management of children with DPLN.

Renal involvement is a major cause of morbidity and mortality in systemic lupus erythematosus (SLE). Consequently, in some centers, renal biopsies are performed on all patients with SLE and the morphological findings are used as a guide for therapy and prognosis. In other centers, therapy and prognosis are based entirely on clinical assessment of renal function. Because of this difference in practice, we analyzed the renal biopsies of 20 children with SLE that showed diffuse proliferative lupus nephritis (DPLN), using histologic scores based on an activity index (AI) and a chronicity index (CI). We correlated these scores with renal function and serum levels of C3 and C4 at the time of renal biopsy and at outcome to determine whether the renal biopsy was useful in predicting the course of SLE.

Methods

The medical histories of all children with SLE who were hospitalized at The Hospital for Sick Children (HSC), Toronto, between 1970 and 1984 and had renal biopsies showing DPLN were reviewed. We elected to include only patients with DPLN since this is the worst form of SLE and the most difficult to treat. In addition, decisions about therapy are critical for management of DPLN, yet there is considerable controversy about treatment. Our goal was to determine the relationship of renal biopsies to renal function and outcome in DPLN patients, whose course must be considered to be guarded.

All of the children in this study fulfilled at least four of the criteria for diagnosis of SLE established by the American Rheumatism Association [1]. Renal status was evaluated at the time of renal biopsy to assess the extent of kidney involvement from lupus. Assessment of outcome was based on the most recent physical examination, urinalysis, renal function tests and SLE serology.

All of the children with SLE described in the present paper were treated at the onset of their disease with daily oral prednisone in a dose of 2 mg/kg body wt per day (maximum 80 mg) given in 3 to 4 divided doses, without regard for the changes seen on renal biopsy. After four to eight weeks, the prednisone was gradually reduced to alternate day therapy. All of the children also received azathioprine as a prednisone-sparing drug in a single daily dose of 1 to 2 mg/kg body wt. Depending on disease activity, prednisone was reduced to the lowest dose that would maintain a biochemical and clinical remission. A relapse was usually indicated by an increase in proteinuria and an active urinary sediment associated with a fall in serum C3 and/or C4 and increasingly positive serology (ANF or anti-DNA). Relapses were managed by daily prednisone in divided doses, followed by gradual tapering to alternate day therapy. In occasional cases, bolus intravenous methylprednisolone (10 mg/kg body wt per day × 3 days) or plasmapheresis was used.

The grading system to measure renal function at the time of renal biopsy and at outcome was employed previously [2], and consisted of simple measurements of renal function which could easily be obtained from the patients' charts: *grade 1*, normal urinalysis or up to trace proteinuria and normal serum (true) creatinine (that is, ≤ 1.0 mg/dliter); *grade 2*, proteinuria of 1 to 2+ (30 to 100 mg/dliter), or hematuria or occasional granular or cellular casts, and a normal serum creatinine; *grade 3*, proteinuria of 3 to 4+ (> 300 mg/dliter) and a serum creatinine (> 1.0 but ≤ 1.4 mg/dliter); *grade 4*, nephrotic range proteinuria (> 100 mg/kg body wt per day) and/or an abnormal serum

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creatinine (> 1.4 mg/dliter); and *grade 5*, institution of dialysis and/or transplantation or death from end-stage renal failure. Children who fell by at least one grade, remained unchanged, or rose by at least one grade between the time of renal biopsy and outcome were considered to have shown improvement, no change, or a worsening of their renal status respectively.

Closed renal biopsies were performed at the time of diagnosis of SLE, before treatment was begun, in nine patients. Nine other patients had received prednisone for less than one week, while the remaining two had been taking prednisone for more than one month prior to biopsy. Biopsies containing at least six glomeruli were examined by two pathologists (MS and RB) using light microscopy (LM); neither pathologist had any knowledge of the patients' renal function or serum levels of C3 or C4. Both qualitative (modified World Health Organization [WHO]) and semi-quantitative (AI and CI) classifications were used to analyze the renal biopsies [3–5]. The original WHO classification of lupus nephritis (normal, mesangial, focal segmental proliferative, diffuse proliferative, and membranous) has been modified slightly to include these as well as an advanced sclerosing category [3]. The modified classification also stressed that some cases of lupus nephritis could be active, active and inactive, or inactive only, and that one form of nephritis might convert into another. DPLN (class 4) was divided into the following categories: 4A, no segmental lesions; 4B, active necrotizing lesions; 4C, active and sclerotic lesions; and 4D, sclerotic lesions. A semi-quantitative pathologic scoring system, based on methods derived originally by Pirani, Pollak, and Schwartz [4] and adapted later at the National Institute of Health [5], was also used. This system involved assignment of scores of 0, 1, 2, or 3 to individual morphological features of the biopsy.

The LM features which were evaluated included: 1) mesangial and endothelial cell proliferation, 2) leukocyte exudation, 3) karyorrhexis and/or fibrinoid necrosis, 4) cellular crescents, 5) hyaline deposits, 6) interstitial inflammation, 7) glomerulosclerosis, 8) fibrous crescents, 9) tubular atrophy, and 10) interstitial fibrosis. These features were assessed using slides stained with hematoxylin and eosin, hematoxylin phloxine and saffron, and Masson trichrome. An AI was calculated on the basis of the sum of the first six items. The scores for karyorrhexis/fibrinoid necrosis and cellular crescents were multiplied by two so that the total maximum score for AI was 24. The sum of the last four items provided a maximum score of 12 for the CI.

The renal biopsies were also processed by immunofluorescence (IMF) and electron microscopy (EM). IMF was performed using fluorescent-labelled anti-IgG, anti-IgM, anti-IgA, and anti-C3 antisera. EM was performed using tissue which had been fixed in universal fixative, dehydrated in graded ethanols, embedded in Epon, cut using a cryostat, and stained with osmium tetroxide and uranyl acetate. The results of the LM examination were used to reach a diagnosis of DPLN on the renal biopsies, while data from IMF and EM provided confirmation.

Statistical analysis was performed using non-parametric tests of significance (that is, the Spearman–Rank correlation coefficient and the Mann–Whitney–U-test) [6]. P values > 0.05 were considered not significant. To determine the influence of various factors on outcome, the patients were divided into two groups on the basis of sex, mean serum levels of C3 and C4 obtained at the time of renal biopsy, the mean pathological scores of AI and CI, and the mean scores for the individual histological features of the AI and CI.

Table 1. Clinical features in 20 children at first renal biopsy showing diffuse proliferative lupus nephritis and at outcome[a,b]

Clinical features	Time of biopsy number %	Outcome number %
A) Renal features		
Proteinuria		
present	17 (85)	12 (60)
≥3.0 gm/24 hr	7 (35)	2 (10)
Hematuria	8 (40)	0 (0)
Hypertension	8 (40)	0 (0)
B) Renal status		
Grade 1	0 (0)	7 (35)
Grade 2	4 (20)	3 (15)
Grade 3	4 (20)	5 (25)
Grade 4	12 (60)	4 (20)
Grade 5	0 (0)	1 (5)
C) Extra-renal features		
Arthritis	9 (45)	0 (0)
CNS	2 (10)	0 (0)
Skin	15 (75)	2 (10)
Serositis	5 (25)	0 (0)
D) Therapy[c]		
Nil	—	3 (15)
Prednisone	—	8 (40)
Prednisone & azathioprine	—	8 (40)
Plasmapharesis	—	1 (5)
E) Renal biopsies[d]		
WHO 4A	3 (15)	
4B	12 (60)	
4C	5 (25)	

[a] Mean serum creatinine (± SD was 1.1 ± 0.4 mg/dliter at biopsy and 1.5 ± 0.4 at outcome.

[b] Serum levels of C3 were 43 ± 16 mg/dliter at biopsy and 90 ± 30 mg/dliter at outcome. The C4 levels were 7 ± 2.6 mg/dliter at biopsy and 17 ± 7 mg/dliter at outcome.

[c] Therapy at time of biopsy is described in the **Methods.**

[d] Renal biopsies not done at outcome.

Results

Clinical features of the group and individual children at first renal biopsy

The 20 children (mean age 13.7 years, range 6 to 18 years) included nine boys and 11 girls (Table 1). At the time of biopsy, most (17 patients, 85%) showed proteinuria (≥ 3.0 g/24 hr in 7), while hematuria and hypertension were each seen in eight. Serum creatinine was ≥ 1.4 mg/dliter in five children. Renal function was classified as grade 2 in four children, grade 3 in four, and grade 4 in 12 children. The grades for each child's renal function at biopsy are shown in Table 2. Extra-renal manifestations of SLE, including articular, neurological, cutaneous, and serosal signs and symptoms, occurred in ten to 75% of the children. Active disease was indicated by reduced mean serum levels of C3 and C4 (43 ± 16 and 7 ± 2.6 mg/dliter respectively).

Pathological features of the entire group and individual children at first renal biopsy

Renal biopsies of three children showed DPLN class 4A (no segmental lesions), those for 12 showed class 4B (with active

Table 2. Renal biopsy findings and grade of renal function in 20 children with lupus nephritis

Patient	Biopsy 1			Grade		Biopsy 2			Grade		Time between biopsies, *months*
	WHO	AI	CI	Biopsy 1	Outcome	WHO	AI	CI	Biopsy 2	Outcome	
1	4B	8	0	3	1						
2	4A	8	0	3	2						
3	4B	11	3	4	3						
4	4A	3	1	2	1						
5	4B	9	0	4	1						
6	4C	11	8	4	1						
7	4C	16	8	4	2						
8	4B	13	3	4	3						
9	4B	13	3	3	3						
10	4B	11	0	2	2						
11	4B	16	3	4	1	2	0	0	1	1	33
12	4B	9	5	4	3	4D	5	9	3	3	32
13	4B	19	4	4	2	2	0	0	2	2	18
14	4B	6	0	2	1	2	0	0	1	1	33
15	4C	11	5	4	4	4D	6	9	4	4	31
16	4B	9	3	4	4	4B	8	3	4	4	27
17	4A	7	1	4	3	5	0	0	3	3	26
18	4C	9	5	2	5	4C	12	7	4	5	24
19	4B	9	2	4	1	4D	6	7	4	1	48
20	4C	13	6	3	4	4D	12	10	4	4	30

Table 3. Correlations in 20 children at first renal biopsy showing diffuse proliferative lupus nephritis

Parameters	Spearman–Rank correlation coefficient	*P* value
AI/grade	+0.41	<0.05
CI/grade	+0.46	<0.05
AI/CI	+0.23	NS
C3/grade	+0.24	NS
C4/grade	+0.23	NS
C3/C4	+0.54	<0.05
C3/AI	−0.32	NS
C3/CI	+0.52	<0.05
C4/AI	−0.15	NS
C4/CI	+0.42	<0.05
Serum creatinine/grade	+0.63	<0.01
Serum creatinine/AI	+0.23	NS
Serum creatinine/CI	+0.47	<0.05

necrotizing lesions, including disruption of capillary walls, glomerular cell proliferation, polymorphs, karyorrhexis, fibrinoid necrosis, hematoxylin bodies, cellular crescents, wire loops, hyaline thrombi, fibrin thrombi, and segmental fibrin deposition), while the remaining five showed class 4C (active and sclerotic lesions). The WHO pathological category and the AI and CI of the renal biopsies of individual children are shown in Table 2.

Clinicopathologic correlations at first renal biopsy

Using the Spearmann–Rank correlation coefficient, there was a significant correlation between the AI and CI on the one hand and the grade of lupus nephritis on the other, but not between the serum levels of C3 or C4 (obtained at renal biopsy) and the grade (Table 3). In addition, C3 and C4 correlated with each other and with the CI but not with the AI. Finally, the serum creatinine correlated with the grade and with the CI but not the AI.

Clinical and pathological features of children undergoing repeat renal biopsies

Ten of the children underwent repeat renal biopsies, eight for purposes of clinical follow–up because they showed either improvement or deterioration, and two because they were part of a prospective study of therapeutic agents in SLE. Of the ten, three showed conversion to mesangial and one to membranous lupus nephritis (patients 11, 13, 14, 17), while six (patients 12, 15, 16, 18, 19, 20) still showed DPLN on a second biopsy (Table 2). At the time of the second biopsies, all children converting from DPLN to either mesangial or membranous lupus showed an improvement in their grade relative to the first biopsy. In contrast, only one of the six with DPLN on both biopsies showed an improved grade (patient 12), three had a similar grade (patients 15, 16, 19), and two were worse (patients 18, 20). The child whose grade improved showed a fall in AI but a rise in CI. Of those with similar grades, two behaved similarly and the other showed a slight fall in AI and no change in CI. The children whose grades became worse showed either an increase or slight fall in AI and a worse CI. Therefore, there was a reasonably good correlation between change in grade and change in AI and CI in the children undergoing repeat renal biopsies.

Clinical features of the group and individual children at outcome

The mean follow–up time of the 20 children was 4.0 years (range 1 to 12 years). At outcome, 12 showed proteinuria ($\geq$ 3.0 g/dliter in two) but none had hematuria or hypertension (Table 1). The serum creatinine was $\geq$ 1.4 mg/dliter in four. Renal function at outcome showed improvement in that ten (50%) of the children were now in grades 1 or 2, as opposed to four at initial biopsy. One child had died. Only two of the children had cutaneous SLE; no other extrarenal manifestations of SLE were present. Mean serum levels of C3 and C4 (90 ± 30 and 17 ± 7 mg/dliter respectively) were now more than twice as high

as they had been at initial renal biopsy. Treatment at outcome invariably involved a lower dose of daily or alternate day prednisone.

Correlation between clinical and pathological features at initial renal biopsy and the time of follow-up with outcome

Between the initial renal biopsy and the outcome, 14 children showed an improved, four a similar, and two a worse grade (Table 2). Outcome was not predicted by the sex of the child, a reduced serum level of C3 or C4, the time of follow-up, the total pathologic score, or the AI at initial biopsy (Mann–Whitney–U-test) (Table 4). However, a CI ≥ 3 was predictive of progression to a more severe grade ($P < 0.01$). The components of the CI which proved to be predictive were glomerulosclerosis ($P < 0.01$) and interstitial fibrosis ($P < 0.05$).

Discussion

Our goal in the present study was to determine whether there was a correlation between the features of DPLN on renal biopsies in children and the clinical outcome, as shown previously in adults [7]. Although lupus nephritis in children and adults has many similar clinical features, SLE demonstrates a number of features, such as lymphadenopathy and splenomegaly, which are more prevalent in children, suggesting that there may be significant qualitative differences in these age groups. Furthermore, in our study, renal biopsies showed that many of the children already had a high CI even though their SLE was of short duration, a situation not previously described in adults. Since all of our patients were treated with prednisone and azathioprine according to a protocol, these agents presumably exerted a similar influence on AI and CI in all patients.

We used a previously described grading system [2] which allowed analysis of all patients with DPLN rather than only those progressing to end-stage renal failure as in previous reports [8–11]. In our experience, most children with DPLN do not progress to chronic or end-stage renal failure. The reliability of our grading system was supported by the significant correlation of grade with AI, CI, and serum creatinine, and the improvement in grade of all patients converting from DPLN to mesangial or membranous lupus on repeat biopsies. In contrast, improvement occurred in only one of the six patients with DPLN on both biopsies.

The children with DPLN described in this paper showed a number of pathological and clinical features which deserve comment. First, the initial renal biopsies of our patients generally showed high values for CI (≥ 3 in 12 patients), even though most of these biopsies were performed at or close to the onset of their disease. This is at variance with other experience in adult DPLN. On the other hand, SLE may occur in an insidious fashion with non-specific symptoms, perhaps accounting for the substantial progression of this disease in children before a diagnosis has been made. Indeed, some of the children in our study did appear to have persistently active renal disease despite having received continuous therapy with prednisone and azathioprine. In addition, our hospital is a tertiary referral center for pediatric nephrology and our patients may represent an aggressive subgroup of SLE patients with chronic renal changes early on in their disease. In the ten children undergoing repeat renal biopsies, the AI diminished in nine (90%), while the CI increased in five (50%), suggesting that some patients had ongoing active lupus nephritis, tending towards glomerulosclerosis, tubular atrophy, and interstitial fibrosis. Despite this, 14 (70%) of the 20 were clinically better at outcome (that is, improved by at least one grade), while four (20%) remained unchanged and only two (10%) became worse. Seven of eight patients (88%) with a CI < 3 were clinically better and five (63%) were in grade 1 at outcome. In contrast, only seven of 12 (58%) patients with a CI ≥ 3 were clinically better and only two (17%) were in grade 1 at the outcome. These observations

Table 4. Prognostic value of indices of 20 children showing diffuse proliferative lupus nephritis at first renal biopsy

Parameter	Number of children	Mann–Whitney U-test	*P* value
Sex *male*	9	55	NS
female	11		
C3 <43 mg/dliter	7	53.5	NS
≥43 mg/dliter	13		
C4 < 7 mg/dliter	13	55	NS
≥7 mg/dliter	7		
Time of follow-up			
<4.0 years	14	46.5	NS
≥4.0 years	6		
Total pathologic score (AI + CI)			
<13.9	10	70	NS
≥13.9	10		
AI <10.6	10	56	NS
≥10.6	10		
Glomerular cell proliferation			
<2.35	10	69	NS
≥2.35	10		
Leukocyte exudation			
<1.5	10	65.5	NS
≥1.5	10		
Karyorrhexis/fibrinoid necrosis			
<2.1	17	26.5	NS
≥2.1	3		
Cellular crescents			
<1.5	11	55	NS
≥1.5	9		
Hyaline deposits			
<2.1	10	55.5	NS
≥2.1	10		
Interstitial inflammation			
<1	4	48	NS
≥1	16		
CI <3	8	81	<0.01
≥3	12		
Glomerulosclerosis			
<0.7	7	81	<0.01
≥0.7	13		
Interstitial fibrosis			
<1	7	72	<0.05
≥1	13		
Tubular atropy			
<1.05	15	57	NS
>1.05	5		
Fibrous crescents			
<0.25	16	38	NS
≥0.25	4		

support our conclusion that a CI ≥ 3 was significantly predictive of progression ($P < 0.01$) to a more severe grade (Table 4).

A semi-quantitative scoring system, based on AI and CI, has been utilized to a limited extent to analyze renal biopsies of adults with lupus nephritis [12–16]. First, Austin et al [12, 13] studied renal biopsies of 102 lupus patients, of which 72 showed DPLN or membranoproliferative lupus nephritis. The AI, especially cellular crescents and fibrinoid necrosis, was found to be more predictive of progression to renal failure than other individual histological features of AI. In addition, CI and its individual histological features, especially tubular atrophy, were predictive of development of renal failure. Second, Carette et al [14] assigned a CI to the renal biopsies of 53 lupus nephritis patients, most of whom had DPLN. The CI was useful in predicting outcome and response to immunosuppressive therapy, since nine of ten patients with a high CI, but only three of 21 with a low CI, doubled their plasma creatinine levels. Moreover, of 14 patients with an intermediate CI, one of 11 treated with azathioprine or cyclophosphamide plus prednisone doubled his plasma creatinine, while all three patients treated with prednisone alone progressed to end-stage renal failure. Third, in a study of 62 patients with lupus nephritis who were treated for more than 18 months with prednisone or cytotoxic drugs and underwent two renal biopsies, Balow et al [15] found that CI increased with time in patients taking prednisone but not in those taking cytotoxic drugs. They suggested that cytotoxic drugs reduced the likelihood of developing chronic renal damage in lupus nephritis. It should be noted that the patients studied in these three previous reports were usually treated at a very late stage in their disease and consequently often had high values for CI. Nevertheless, many of the children described in the present paper also had high CI values, although their disease was likely present for a shorter time. Fourth, Magil et al [16] showed that the total pathologic score (sum of AI and CI) was not predictive of the development of renal failure in 35 patients with biopsy-proven DPLN. Since values for AI and CI alone were not shown, the possibility remains that either the AI or CI was predictive of progression to renal failure but was negated by the other. Indeed, in the present study, the statistical significance of the CI for predicting the clinical outcome was lost when the total pathologic score was used (Table 4).

Many previous studies, both those performed early on and in recent years, have attempted to draw correlations between the histological findings seen on a renal biopsy and the clinical course and outcome of lupus [17–21]. One example is the report of Hecht et al [22] on 31 patients with SLE, most of whom underwent repeat renal biopsies. However, these studies were not performed using a scoring system based on AI and CI. Nevertheless, most studies have shown that DPLN is a more serious disease than mesangial or membranous lupus. Morel-Maroger et al [23] reported that 40 SLE patients with DPLN, especially those with sclerotic lesions, had a poorer outcome than lupus patients with minimal glomerular lesions. Appel et al [7] showed in 56 lupus patients that the WHO classification of lupus nephritis was the single most important prognostic indicator. Outcome for patients with mesangial and membranous lupus was favorable, while that for patients with DPLN was worse. Finally, in 74 lupus patients, Tateno et al [24] reported that those whose renal biopsies showed mesangial lupus or minor changes of DPLN had a benign clinical course. However, renal function was slightly decreased in patients with moderate DPLN and markedly abnormal in seven of ten patients with severe DPLN. Contrary to all of the foregoing studies, Cameron et al [25] reported no difference in the outcome of patients with different WHO histological forms of lupus nephritis. The divergence of opinion reported to date might be overcome by employing scoring systems of AI and CI for examining renal biopsies, instead of relying entirely on the WHO classification.

Most of the children with biopsy-proven DPLN in the present study were better at outcome than at biopsy; not as many showed severe proteinuria, none had hematuria or hypertension, the renal status showed improvement, and mean serum levels of C3 and C4 more than doubled. In addition, extra-renal manifestations of SLE had almost completely disappeared. This improvement belies the widely held view that the outcome in DPLN is usually poor, especially in adults [7]. Furthermore, of the children undergoing repeat renal biopsies, the four who converted from DPLN to mesangial or membranous lupus all showed improvement in AI, emphasizing that AI is reversible. The fact that CI also fell in two (patients 11 and 13) has been interpreted as a consequence of the limited size of the renal biopsies and not necessarily evidence of reversibility.

For some time physicians have argued about the value of performing renal biopsies in patients with SLE [26]. Biopsies are traditionally performed for three reasons. First, histological findings on renal biopsies in patients with lupus nephritis may change over time. A recent study indicated that the incidence of conversion from one WHO class to another was high [27]. Second, some patients with lupus nephritis may not show abnormalities of renal function, although histological examination of their renal biopsies may show involvement of the kidneys [28, 29]. Third, qualitative examination of a renal biopsy using the WHO or modified WHO classifications may tell the clinician whether a patient with lupus nephritis ought to be treated with steroids and/or cytotoxic drugs and what the ultimate outcome is likely to be. Based on the findings of the present study, we suggest that additional information is derived from performing renal biopsies and examining them semi-quantitatively by determining the AI and CI. We have shown that our standard therapy for DPLN of prednisone and azathioprine could lower the AI, but generally could not reverse the CI. Although a longer follow-up period is necessary, it would appear that children with DPLN and a high CI have a downward clinical course which is relatively resistant to therapy with steroids and azathioprine. It is too early to say whether DPLN in these children is resistant to other cytotoxic drugs. We would suggest that determination of the CI from renal biopsies may be a useful instrument for helping to predict therapeutic responses in individual children with DPLN and for designing prospective clinical trials in this disease.

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Reprint requests to Dr. R. Baumal, Department of Pathology, The Hospital for Sick Children, 555 University Avenue, Toronto, Ontario, Canada M5G 1X8

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