Pediatr Nephrol (2001) 16:346–349

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Familial steroid-responsive nephrotic syndrome and HLA antigens in Bengali children

Received: 14 July 2000 / Revised: 15 November 2000 / Accepted: 15 November 2000

Abstract We investigated the major histocompatibility complex class I and II loci in three Bengali families with nine children affected with steroid-sensitive nephrotic syndrome (SSNS). A sequence-specific primer (SSP) of DNA typing method was used to detect human leukocyte antigens (HLA). The unaffected siblings and their parents were also studied. Similar to previous reports, there was a high frequency of HLA-DR7.1 (DRB1*0701), DR53 (DR B4*01011–0104) and DQ2 (DQB2*0201–3) antigens in the affected children. However, there was a similar finding in the unaffected children and their parents. HLA-DR7.1 probably was not a causative factor, since it had no predictive value for the occurrence or the severity of SSNS in the affected families. Siblings with identical HLA typing behaved differently (they either had or did not have SSNS). In these families there was no correlation between predisposition to the nephrotic syndrome and the genetic determinant responsible for HLA.

Keywords Familial · Steroid-responsive nephrotic syndrome · Bengali · HLA-DR7

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Introduction

Idiopathic nephrotic syndrome (INS) is uncommon in European children, with an annual incidence of 2–7/100,000 children per year [1]. The most common form of INS is characterised by minimal change histology (MCNS), which is usually SSNS. It is more common in Asian children, with an annual incidence of 16/100,000 children [2]. The other type of INS is steroid-resistant nephrotic syndrome (SRNS), which is usually associated with focal segmental glomerulosclerosis (FSGS).

Familial SSNS is rare, and only about 3% of patients have affected siblings [3]. Nonetheless, the occasional familial occurrence points to a genetic predisposition. Reports on associations between certain HLA class II antigens and SSNS support this hypothesis [4]. A close association has been found between SSNS in Caucasians and human leukocyte antigen (HLA)-DR, especially DR7 [5, 6], and the combined occurrence of HLA DR3 and DR7 [7]. HLA DR7 is associated with a more severe clinical course [8]. There are no reports of any association of familial SSNS with HLA antigens apart from a single report of two French infants who had SSNS and were not HLA identical but had in common the A2-B 12-DR4 haplotype [9].

Recently some familial forms of idiopathic SRNS with FSGS have been identified with an autosomal dominant or recessive mode of inheritance. Linkage analysis has permitted the localisation of several genes on chromosomes 1, 11, 17 and 19 [10–15], but not on chromosome 6, which carries the HLA locus.

We observed three Bengali families living in east London with nine children affected with SSNS. We report the HLA typing in these children, their unaffected siblings and their parents. Our results are consistent with those previously reported in idiopathic SSNS of a higher prevalence of HLA-DR7. However, we also found that unaffected children and parents were similar, indicating that HLA-DR7 is not the single cause of familial SSNS. These and other contributors remain unknown.

Materials and methods

The study group consisted of three unrelated Bengali families with nine children affected with SSNS. Two of them were large families with seven siblings each. There were three affected children in the first family, four in the second, and two in the third.

The families were investigated with the help of a home care team. The notes from the affected children were reviewed and the following information obtained: age at presentation, details of clinical presentation (hypertension, haematuria), results of investigations done (renal function, complement, ANA, hepatitis B and renal biopsy if performed), days taken to respond to steroid therapy, details of any further relapses and the use of steroid-sparing agents (cyclophosphamide, cyclosporin) or other medications (e.g. antihypertensive drugs).

The parents consented to their children and themselves having blood taken for HLA typing. Children above 12 years of age also gave separate consent. The Research Ethical Committee at the Royal London Hospital approved the protocol of the study.

The absence of proteinuria was confirmed in the parents and the unaffected siblings, and thus the absence of nephrotic syndrome was confirmed by lack of all the features common with nephrotic syndrome including proteinuria.

HLA typing was performed using the DNA typing method with sequence-specific primer (SSP) reaction [16].

Results

Family 1

Three children out of seven were affected as shown in the pedigree (Fig. 1). Their clinical details are summarised in Table 1. There was no history of consanguinity between parents and only the first affected girl had a renal biopsy, which showed a minimal change histology (MCNS). All the affected children had HLA-DR7 antigens, but siblings (4 and 5) inherited DR7 in both haplotypes without developing SSNS (Fig. 1).

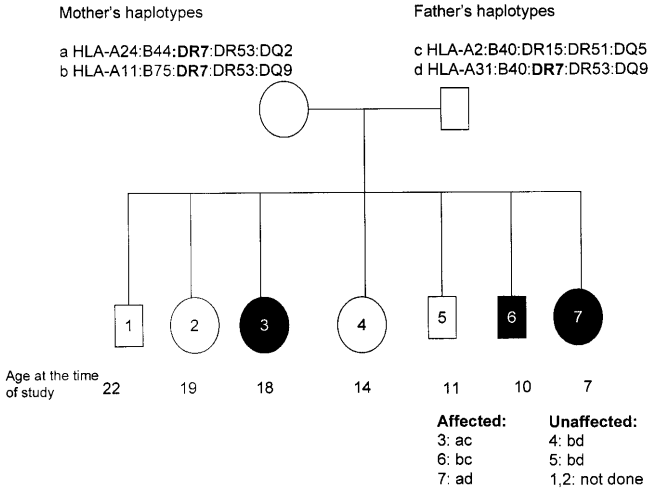

Fig. 1 HLA typing of family 1

Family 2

Four children out of seven were affected as shown in the pedigree (Fig. 2). Their clinical details are summarised in Table 1. There was no history of consanguinity between parents. The details of the first affected boy are not complete because he was diagnosed while the family were living in Bangladesh. He responded within a few weeks following unknown treatment (presumably steroids). He had a few relapses, but has been in remission for the last 8 years.

The second affected child was a girl who had two renal biopsies because she presented with a mixed nephritic-nephrotic picture (macroscopic haematuria, pro-

Table 1 Clinical details and HLA typing of all patients

Family (patient)	Presentation age (years)	Atypical features	Responds to steroid	Relapses	Follow-up (years)	HLA typing
One (1)	13.3	Age	3 weeks	Frequent until cycloph.	6	HLA-A24:B44:**DR7**:DR53:DQ2 HLA-A2:B40:DR15:DR51:DQ5
One (2)	2	None	5 weeks	Frequent	8.5	HLA-A11:B75:**DR7**:DR53:DQ9 HLA-A2:B40:DR15:DR51:DQ5
One (3)	6.5	None	4 weeks	One relapse	1.3	HLA-A24:B44:**DR7**:DR53:DQ2 HLA-A2:B40:**DR7**:DR53:DQ9
Two (1)	2	None		? Frequent	14	HLA-A33:B75:DR15:DR51:DQ5 HLA-A33:B44:**DR7**:DR53:DQ9
Two (2)	8	Ma.haem, hypertensive	5 weeks	Infrequent	2	HLA-A24:B44:**DR7**:DR53:DQ HLA-A11:B57:**DR7**:DR53:DQ2
Two (3)	2	None	7 weeks	Frequent	3	HLA-A33:B75:DR15:DR51:DQ5 HLA-A33:B44:**DR7**:DR53:DQ9
Two (4)	1.5	None	3 weeks	Frequent	1.5	HLA-A33:B75:DR15:DR51:DQ5 HLA-A11:B57:**DR7**:DR53:DQ2
Three (1)	2.5	None	1 week	One relapse	9.5	HLA-A3:B52:DR4:DR53:DQ3 HLA-A68:B60:DR17:DR52:DQ2
Three (2)	1.5	None	3 weeks	Infrequent	7	HLA-A3:B52:DR4:DR53:DQ3 HLA-A68:B60:DR17:DR52:DQ2

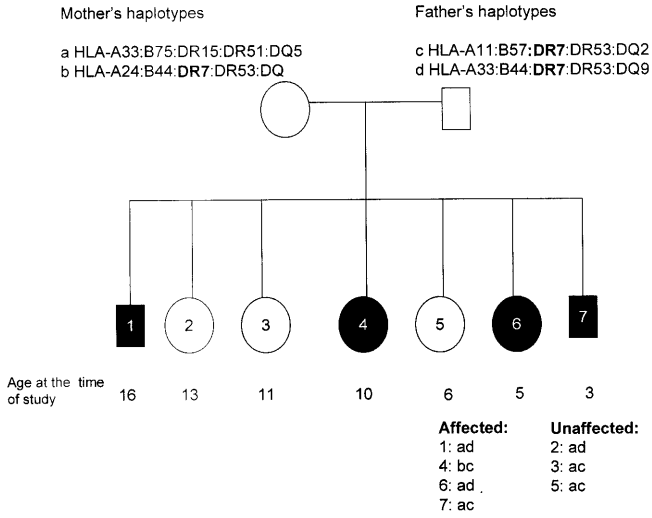

Fig. 2 HLA typing of family 2

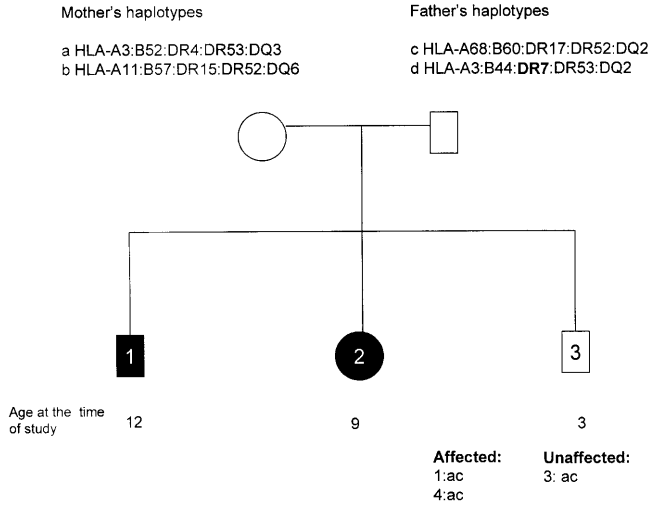

Fig. 3 HLA typing of family 3

teinuria and hypertension). She was a frequent relapser and steroid dependent. Her renal biopsy showed mesangial proliferation on both occasions.

Siblings 1, 2 and 6 had identical HLA typing; however, sibling 2 did not have the disease while siblings 1 and 6 did. Siblings 3, 5 and 7 had identical HLA typing but only sibling 7 developed SSNS (Fig. 2).

Family 3

Two children were affected. Neither had atypical features. Table 1 summarises the clinical details and HLA haplotypes of the affected children. The three children had identical HLA typing with no HLA-DR7 antigen inherited (Fig. 3).

Discussion

The increased incidence of NS in siblings of affected patients, who have a 1000 times greater risk of developing the condition than the general population [17], could be explained either by a shared genetic background and/or by exposure to common environmental factors. Siblings with identical HLA typing behaved differently (some developed SSNS while others did not). In these Bengali families there was no correlation between a predisposition to NS and the genetic determinant responsible for HLA.

All our patients were steroid responsive (SSNS); however, the histopathology showed MCNS in one patient in family 1 and mesangial proliferation in another patient in family 2. It is expected that the rest of the patients in family 1 had MCNS and in family 2 mesangial proliferation since histopathological findings in siblings with familial NS show close to a 100% concordance rate [18]. The histopathology of the patients in family 3 was unknown as there was no clinical indication for renal biopsy, but they fulfilled our criteria for a diagnosis of SSNS.

Previous reports indicate an association between HLA-DR7 antigen and idiopathic SSNS in Caucasian [5, 19, 20], Chinese [21] and Arab [22] patients. However, there are contradictory reports from South Africa indicating a higher frequency of HLA Bw44, which is part of HLA-B12 in Indian children with SSNS [23].

It has been found previously that there is an association between HLA-B12 and a short interval to relapse after cyclophosphamide therapy [24]. Lenhard et al. reported that HLA-B12 was remarkably increased in FSGS patients with a persistent or progressive nephrotic syndrome [25]. None of our patients were positive for HLA-B12 antigen.

Bouissou et al. found that the presence of HLA-DR7, DR3/7 or DQ2 suggests that SSNS patients are highly likely to relapse frequently, become steroid dependent and have a prolonged course [7]. We have observed this in our patients as shown in Table 1. Five out of seven (71.4%) of those who had HLA-DR7 were frequent relapsers. One patient had incomplete data. Furthermore, looking at the time to respond to therapy, the patients with DR7 antigen took a mean of 3.85 weeks to respond, where the patients without DR7 took an average of 2 weeks to respond. While this may not be statistically significant, the descriptive differences are quite noticeable. Bensman et al. reported two siblings with SSNS who were not HLA identical but shared the A2-B 12-DR4 haplotype [9]. None of these antigens were shared in our patients.

In our cohort there was a high incidence of HLA-DR7 (seven out of nine) in both affected and unaffected children (five out of six). Therefore, there was no clear cause and effect relationship between HLA-DR7 and the occurrence of the disease, which is most likely caused by other genetic and environmental factors. We found also a high frequency of HLA-DQ2 (66%) in the affected children, which is again similar to previous reports in idiopathic SSNS [5, 7, 19]. However, the same was found in the unaffected children (50%).

HLA-DR5 was thought to play an important role in familial NS as it was reported in two unrelated families

with two different types of nephrotic syndrome (SSNS and SRNS) [26]. Different associations between familial FSGS and HLA antigens have been reported [26, 27], but Chandra et al. found no common HLA antigens in three siblings with FSGS [28]. Recently, familial FSGS identified with an autosomal dominant or recessive mode of inheritance and linkage analysis has allowed localisation of several genes on chromosomes 1, 11, 17 and 19 [10–14].

Our findings support the hypothesis that even if familial SSNS is caused by autosomal recessive genes, the disease susceptibility and/or resistance gene(s) are not located in close proximity to the DRB1 and the DQ region of chromosome 6. In these families the presence of HLA-DR7 or DQ 2 was unhelpful in predicting the occurrence of SSNS. These gene loci might control steroid sensitivity or resistance and disease severity when the condition had been precipitated by other factors (genetic or environmental) and this could explain the high prevalence of these antigens in SSNS patients.

In conclusion: HLA typing in familial autosomal recessive SSNS in Bengali children is similar to that of idiopathic SSNS in other ethnic groups with a high frequency of DR7.1 and DQ2 antigens. However, the same findings were found in the unaffected siblings. In these families there was no correlation between predisposition to the nephrotic syndrome and the genetic determinant responsible for HLA antigens.

Acknowledgement We would like to thank Professor Martin T. Barratt for his invaluable advice, Dr. Judy Taylor for her assistance in providing patient information and the home care team at the Royal London Hospital for their help in localising the families and for doing the blood and urine tests.

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