Clinical course of patients with major histocompatibility complex class II deficiency

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Abstract

The clinical course of 10 children who have been diagnosed with major histocompatibility complex (MHC) class II deficiency (bare lymphocyte syndrome) in the UK over the past eight years is described. They have had a generally poor prognosis, with only two of the 10 still alive despite eight attempts at bone marrow transplantation in six patients. Overwhelming viral infection was the predominant cause of death. Alternative transplant strategies or novel therapies are required for these patients.

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Keywords: bone marrow transplantation; MHC II deficiency; viral infections, outcome

Defective expression of major histocompatibility complex class II (MHC II) molecules account for 5% of severe combined immunodeficiency (SCID).¹ Despite the great advances in our understanding of the molecular basis of this condition in recent years, most patients still die in early childhood. Using complementation studies on cell lines from MHC class II deficient patients, four distinct variants have been recognised, involving regulatory proteins, which have been defined as CIITA and subunits of RFX, which act on the class II promoter region.²⁻⁴

Functionally, the lack of MHC II on antigen presenting cells results in defective maturation and activation of CD4⁺ T lymphocytes and extreme susceptibility to infections with a variety of microorganisms. CD8⁺ T lymphocyte activity in these patients is usually normal, as their activation depends on MHC I expression which is often unaffected.⁵ This study summarises the experience of 10 children with MHC class II deficiency who were treated in two UK supraregional paediatric immunology units. It describes the spectrum of infections and the poor clinical outcome despite modern therapies. The ethnic groupings of the patients reported to date have been relatively confined to the Mediterranean Basin, Northern Europe, and Turkey. We present the first patients to be reported from the United Kingdom, whose ethnic backgrounds are dissimilar to the currently known groups.

Patients

Ten children (five boys, five girls) from eight kindreds presented to either Great Ormond St Hospital for Sick Children, London or Newcastle General Hospital between 1991 and 1999. Two families were white (of non-

Mediterranean origin), five were from the Indian subcontinent (Pakistan and Bangladesh), and one was from Kuwait. Parents from the latter two groups were all first cousins. In two cases HLA class II deficiency was detected in siblings. One further family had a family history suggestive of immunodeficiency.

Clinical manifestations

INFECTIONS

Table 1 presents infection history. The median age of the first serious infection was 4 months (range 2 weeks to 12 months). One patient was diagnosed at 1 day of age, as his brother had previously died of MHC class II deficiency and thus was free of infection at diagnosis. The infections prompting diagnosis were: viral (n = 2); cytomegalovirus (CMV) pneumonitis (n = 1), severe chickenpox (n = 1), bacterial (n = 3); *Escherichia coli* meningitis (n = 1), persistent otitis media and sinusitis (n = 1), recurrent upper respiratory tract infections (n = 1), fungal (n = 4), persistent candidiasis (n = 2), and *Pneumocystis carinii* (n = 2). Significant respiratory tract infections occurred in all but one of the patients. CNS infections were also common with enterovirus meningoencephalitis occurring in four children, two of which also developed *E coli* meningitis. Fungal infections, mainly candidiasis were present in six of the children and in three of these children directly contributed to their death. Eight of the ten children have died (median age 8 months; range 6 months to 17.5 years). The cause of death was overwhelming viral infections (parainfluenza III, adenovirus, cytomegalovirus, human herpes virus 6 (HHV-6), enterovirus encephalitis) in six children, three of which occurred post bone marrow transplantation (post-BMT); overwhelming candidiasis in one child; and the remaining child died of acute pulmonary graft versus host disease (GVHD) post-BMT.

SKIN RASHES PRIOR TO BMT

Three of our patients (6, 7, and 8) had generalised erythematous rashes prior to BMT. The possibility of maternofetal engraftment (MFE) was considered and skin biopsies were performed. In all three cases, a T lymphocyte infiltrate was noted in the epidermis and the dermis, but in all cases staining for MHC II expression was negative. In one case (patient 6) HHV-6 DNA was found on the skin biopsy by polymerase chain reactin (PCR). All three patients had evidence of disseminated Herpesviridae infection (patient 6: HHV-6; patients 7 and 8: CMV).

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Table 1 Infection history

Patient	Sex	Age at presentation	Presenting infection	Predominant infections	Outcome (cause of death)
1	F	4 months	Chickenpox	<i>E coli</i> meningitis Enterovirus encephalitis (persistent poliovirus in stools) <i>Pneumocystis carinii</i> pneumonia	Alive at 7 years (post 2 BMTs)
2	F	5 months	<i>E coli</i> meningitis	Varicella pneumonia Disseminated candidiasis Enterovirus encephalitis	Died at 7.5 years (enterovirus encephalitis)
3	F	4 months	Oral candidiasis Failure to thrive ?cause	RSV pneumonitis Disseminated candidiasis	Died at 6 months (candidiasis)
4	M	2 weeks	Oral candidiasis	Chickenpox CNS echovirus, measles Cryptosporidium CMV/adenovirus pneumonia	Died at 15.8 years (CMV/adeno pneumonia) (following BMT)
5	F	12 months	Chronic otitis media and maxillary sinusitis (sister of patient 4)	Enterovirus encephalitis Disseminated aspergillosis Cryptosporidium enteritis Chickenpox	Died at 6.5 years (enterovirus encephalitis)
6	M	5 months	<i>Pneumocystis carinii</i> pneumonia	Disseminated HHV-6 <i>Pneumocystis carinii</i>	Died at 7 months (disseminated HHV-6)
7	M	4 months	Disseminated CMV <i>Haemophilus influenzae</i> pneumonia	Disseminated CMV Rotavirus enteritis	Died at 7 months (disseminated CMV) (following BMT)
8	M	1 day	(brother of patient 7)	<i>Staphylococcus aureus</i> umbilical stump infection CMV viraemia (asymptomatic) Rotavirus gastroenteritis	Died at 8 months (acute pulmonary GVHD) (2 BMTs)
9	M	3 months	<i>Pneumocystis carinii</i> pneumonia	Parainfluenza III pneumonia Candida nappy rash	Died at 6 months (Parafu III pneumonia) (following BMT)
10	F	2 months	Chronic diarrhoea Bronchiectasis	Vulval candidiasis CMV viraemia (asymptomatic) Adenovirus/Cryptosporidium gastroenteritis	Alive at 7 years (5 months post-BMT)

ASSOCIATED FEATURES

Patient 8 developed hypertrophic pyloric stenosis which was treated with a pyloromyotomy at 3 months of age. Patient 9 was born with a congenital retinal dystrophy (grossly abnormal visual evoked potentials, and electroretinogram); chromosome analysis revealed 47XY, +mar.ish der (14) or der (22) inherited from his mother. A brother also has the same karyotype but does not have MHC II deficiency.

Immunology

Absent expression of HLA class II molecules on peripheral blood leucocytes confirmed the diagnosis in all cases (table 2). Stimulation of peripheral blood mononuclear cells with γ interferon in vitro did not result in MHC II expression. The absence of HLA class II was associated with a CD4 lymphopenia. HLA class I expression was normal in the patients tested and CD8 lymphocyte numbers were not reduced. Consistent with the findings of other studies, lectin induced lymphocyte mitogenesis was found to be normal, antigen induced (PPD, Candida, VZV) or anti-CD3 responses were low. The exact molecular mutations caus-

ing the MHC class II deficiency in these patients are yet to be determined.

Bone marrow transplantation

Four children died without receiving a BMT. All BMTs were done using bone marrow cells aspirated from iliac crests of donors (table 3). In cases where T cell depleted grafts were infused, in vitro T cell depletion was accomplished using Campath antibody treatment.⁶ Three BMT recipients died within six weeks of transplantation of overwhelming viral (CMV, parainfluenza III pneumonitis, enterovirus encephalitis). Two other recipients received a second graft as the first was rejected. One of these children died of pulmonary acute GVHD after a DQ mismatched T cell depleted BMT (patient 8), but the other has gone on to have a successful matched unrelated donor BMT (patient 1). Patient 10 was recently transplanted with the novel, non-myeloablative conditioning protocol of fludarabine and melphalan.⁷ Despite significant bronchiectasis and colitis prior to BMT, and recurrent problems of adenovirus and cryptosporidium colitis and CMV reactivation post-BMT, the

Table 2 Immunological tests at presentation

Patient	1	2	3	4	5	6	7	8	9	10
HLA class II expression (%)	0	0	0	<1	0	0	<1	0	0	<1
CD4 count (cells/ μ l)	264	153	784	307	1365	319	400	372	221	414
HLA class I expression (%)	89	100	54	NT	NT	NT	N	96	N	NT
CD8 count (cells/ μ l)	205	221	1960	1434	1235	392	4676	2836	390	2104
Lymphocyte proliferation										
PHA	N	L	N	L	N	NT	N	N	N	NT
Antigen	L	L	NT	NT	NT	NT	L	L	NT	NT
Serum Igs (g/l)										
IgM	0.07	0.10	0.43	0.32	0.09	0	0.11	0.02	0.13	0.54
IgG	0.52	7.22	0	1.39	0.87	0.1	1.64	6.16	0.77	15.5
IgA	0.02	0.02	0	0.08	0.21	1.7	1.76	0.18	0.08	<0.03

NT, not tested; N, normal; L, low.

Table 3 Bone marrow transplantation

Patient	Type of BMT (nucleated cells/kg)	Age at BMT	Conditioning	Engraftment	Complications
1	Parental (1)	2.3 years	Bu 16 Cy 200 CyA AZX	No	Graft rejection
	MUD (2) (5.0×10^8 /kg)			Yes	Alive and well at 5 years
4	HLA identical MSD (3.9×10^8 /kg)	15.6 years	Bu 16 Cy 200 CyA AZX	Yes	CMV/adenovirus pneumonitis Cryptosporidium (died D +93)
7	HLA identical paternal uncle (4.0×10^8 /kg)	7 months	Campath 1G (D -10 to -6) Bu 20 Cy 200 CyA	No	Acute renal failure (Foscarnet) Toxic epidermal necrolysis Disseminated CMV (died D +17)
8	HLA identical great uncle (1) (11.5×10^8 /kg)	1 month	Bu 16 Cy 200 ATG (D -4 to -1) CyA, MTX $\times$ 3	Yes transient (D +21)	Transplant associated pneumonitis Transplant rejection
	DQ mismatched paternal uncle (2) (T cell depleted) (5.5×10^8 /kg)	5 months	Bu 20 Cy 200 anti-LFA-1/CD2 (D -3 to +10)	Yes (D +14)	Transplant associated pneumonitis Rotavirus enteritis (died D +87)
9	HLA identical sister (7.8×10^8 /kg)	6 months	Bu 20 Cy 200 CyA MTX $\times$ 2	No	Parainfluenza III pneumonitis (died D +19)
10	HLA identical father (whole marrow) (8.4×10^8 /kg)	6 years	Flu, Mel	Yes	Severe gastroenteritis Cryptosporidium, adeno CMV viraemia (asymptomatic) (alive 5 months post-BMT)

Bu 20, busulphan total dose 20 mg/kg given as 4 divided doses (5 mg/kg) over 4 days; Cy 200, cyclophosphamide total dose 200 mg/kg given as 4 divided doses (50 mg/kg) over 4 days; AZX, azathioprine; MTX, methotrexate; Flu, fludarabine 30 mg/m²; Mel, melphalan 140 mg/m².

child is now well and engrafted five months post-BMT. Antithymocyte globulin was used as prophylaxis against GVHD and the CD4 count at present is 300 cells/ μ l.

Discussion

These patients represent an experiment of nature, which shows the importance of antigen presentation by MHC II molecules to CD4⁺ T lymphocytes, in protecting the human host from infection with the spectrum of micro-organisms ranging from viruses to parasites. Six of the eight deaths in our series were caused by virus infections, confirming the critical role of these CD4⁺ lymphocytes in controlling the spread of these pathogens. In a seventh patient (patient 8), CMV infection (blood CMV PCR positive) may have predisposed to the severe inflammatory pneumonitis associated with engraftment which led to the patient's death. The spectrum of infections and the high mortality as a result of virus infections is in keeping with previously published reports.⁸ Transplantation remains the only curative therapy for MHC class II deficiency, though viral infections in the peri-BMT period continue to be a significant cause of morbidity and mortality.

Ideally, BMT before the acquisition of viral infection would be advantageous but there are other problems. Patient 8 (sib of patient 7) was diagnosed and isolated from day 1 of life; he was uninfected at the time of first BMT, nevertheless engraftment was not achieved, even with additional immunosuppressive conditioning to destroy competent host CD8⁺ T cells. Expression of MHC II molecules is said to be the most important factor in graft rejection following BMT for other conditions,⁹ yet in patients with no MHC II expression, graft rejection may still occur, raising the question as to what other factors are involved in this process. It also raises the question of why we should have to match these patients for MHC II compatibility when looking for a donor, if in

theory host CD4⁺ lymphocytes have no MHC II molecules to educate them in the thymus. It is known that up to 20% of patients have detectable but reduced amounts of MHC II expression and obviously require MHC class II matching. The ability of patients with MHC II deficiency to recognise and reject foreign cells is noted by Grisicelli *et al* who comment that none of 11 patients in their series given non-irradiated blood transfusions prior to diagnosis developed transfusion versus host reactions.⁵ In our series a number of patients had an erythematous rash suggestive of maternofetal engraftment, but this was not confirmed on histology as there was no staining for MHC II antigens in skin biopsy specimens. Although maternally derived T cells may be MHC II negative, we also found no evidence of maternal T cells in patients blood using cytogenetics and molecular linkage studies. Thus leucocytes from the mother prior to birth, from blood transfusions prior to conditioning, and from bone marrow post-conditioning can be repelled by the host, presumably by CD8⁺ T lymphocytes.

In a summary of 23 patients who underwent BMT for MHC II deficiency in Europe up to 1996, disease free survival was 40% for HLA matched transplants (n = 9) but only 20% for HLA mismatched transplants (n = 14).^{1-5,10} Of the eight patients who remained well post-transplantation, all had persistently low CD4⁺ T lymphocytes (105–650 cells/ μ l), consistent with impaired thymic maturation caused by defective HLA class II expression on thymic epithelia. It is well known that positive T lymphocyte selection in the thymus depends on interaction of these cells with thymic cortical epithelial cells of non-bone marrow origin expressing MHC II.

Unlike other forms of SCID, MHC II deficiency does not only affect marrow derived cells. The lack of MHC II expression on thymic epithelium leading to delayed/incomplete

maturation of immature T cells results in a window through which opportunistic infections often develop and kill the host. This study of UK patients with different ethnic backgrounds from those previously reported, shows the problems of viral infection and stresses that these complications relate to matched as well as mismatched BMT. Transplant conditioning regimens containing alternative immunosuppressive agents are required to improve the prognosis of this group. Our favourable early post-BMT result using the novel, non-myeloablative conditioning regimen in patient 10, may provide an alternative to the conventional BMT performed to date on patients with this condition.

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