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Serum immunoglobulin G subclass dysbalances in the lymphadenopathy syndrome and acquired immune deficiency syndrome

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SUMMARY

Serum IgG subclass levels were measured by an indirect competitive immunoenzymatic assay with monoclonal antibodies in 61 adult patients of different geographic origins affected either with the lymphoadenopathy syndrome (LAS, 46 cases) or with the acquired immune deficiency syndrome (AIDS, 15 cases). In spite of considerable variations from patient to patient, IgG-1 and IgG-3 levels were higher than in normal Caucasians, with IgG-1 levels much more elevated in LAS than in AIDS patients. In Caucasians with AIDS or LAS, IgG-4 levels were low. IgG-2 levels tended to be low and correlated negatively with IgG-1 levels. IgG subclass imbalances were especially striking in patients with lymphoid interstitial pneumonitis. The results suggest that the IgG increase predominantly affects the less T-dependent subclasses. The low levels of the more T-dependent isotypes do not appear to play a clear role in the occurrence of pyogenic infections in certain patients.

Keywords acquired immune deficiency syndrome (AIDS) IgG subclasses lymphadenopathy syndrome (LAS) serum immunoglobulins

INTRODUCTION

A profound T cell defect is the hallmark of the acquired immune deficiency syndrome (AIDS). A diffuse hyperimmunoglobulinaemia also occurs in most cases of AIDS and lymphadenopathy syndrome (LAS) (Seligmann *et al.*, 1984; El-Sadr *et al.*, 1984, reviews). Its mechanism is not yet fully understood (Zolla-Pazner, 1984) and it affects all immunoglobulin (Ig) classes (Amman *et al.*, 1982; Stahl *et al.*, 1982; Lane *et al.*, 1983; Chess *et al.*, 1984; El-Sadr *et al.*, 1984; Seligmann *et al.*, 1984).

The hyperimmunoglobulinaemia is probably due to polyclonal B cell activation, although a recent study of AIDS sera using immunofixation electrophoresis showed the additional presence of small amount of monoclonal immunoglobulins in some cases, especially those with Kaposi's sarcoma (Papadopoulos *et al.*, 1985). In contrast to this B lymphocyte hyperactivity, the existence of a B cell defect is well documented in AIDS (Lane *et al.*, 1983; Amman *et al.*, 1984; Pahwa *et al.*,

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1984) and impaired antibody response may play a role in certain infections, especially pneumococcal (Amman *et al.*, 1984) and perhaps cryptococcal (Dromer *et al.*, 1985) infections. Antibodies directed against certain pathogens predominantly belong to a given IgG subclass: there is an IgG-1/IgG-3 predominance of antibodies to viral proteins (Morell, Roth-Wicky & Skvaril, 1983; Linde *et al.*, 1983; Kaschka *et al.*, 1984; Skvaril & Schilt, 1984; Sundqvist, Linde & Wahren, 1984) and an IgG-2 predominance of anti-bacterial carbohydrate antigen antibodies (Yount *et al.*, 1968; Siber *et al.*, 1980; Bird *et al.*,1984; Hammarstrom *et al.*, 1984; Freijd *et al.*, 1984). IgG subclass dysbalances are frequently observed in normo- or hyperimmunoglobulinaemia patients affected with primary immunodificiency syndromes and may explain their predisposition to certain pyogenic infections (Oxelius, 1984, review). To our knowledge, there is no published data on IgG subclass levels in adult patients with AIDS and LAS, and only limited data available for children (Rubenstein *et al.*, 1983; Church, Lewis & Spotkov, 1984).

MATERIALS AND METHODS

Serum samples from 61 patients were collected in several hospitals in Paris and Poitiers (France). Fifteen patients (all males, 11 Caucasians, 3 Central Africans and 1 Haitian) had AIDS as defined by the Centers for Disease Control (MMWR, 1982b; Fauci *et al.*, 1984). Eleven had opportunistic infections, two had Kaposi's sarcoma and two both. Clinical and laboratory findings in the 46 other patients fullfilled the definition of LAS (MMWR, 1982a). They included 31 Caucasians (28 male homosexuals, a female and a male intravenous drug user and a male patient without a known risk factor), two North Africans (a drug user and a haemophiliac), seven Haitians and six Central Africans (10 males & 3 females). Among these patients, six (1 woman & 5 men) presented with lymphoid interstitial pneumonitis (LIP), a syndrome known to be associated with AIDS and LAS, particularly in children (Rubinstein *et al.*, 1983; Kradin & Mark, 1983; Oleske *et al.*, 1983; Church *et al.*, 1984; Solal-Celigny *et al.*, 1985). Interestingly, the patients with LIP were all either Central Africans (4 cases) or Haitians (2 cases), they all had LAS and they included the only three patients with severe recurrent bacterial infections in the whole series.

IgG subclass levels were determined in coded samples, without knowledge of the clinical condition, by a competitive indirect immunoenzymatic assay with monoclonal antibodies as previously described (Aucouturier *et al.*, 1984). Normal values were established in a study of 122–179 sera from normal blood donors aged 20 to 59 years (Aucouturier, Mounir & Preud'homme, 1985). These normal subjects were all Caucasians (we lack personal data on normal Haitians and Africans). For this reason, statistical comparison between normal and diseased individuals was performed in Caucasians only. IgG, IgA and IgM levels were determined by the Mancini method or by laser nephelemetry. Serum proteins were studied by conventional electrophoretic and immunoelectrophorectic analyses. A number of sera from healthy relatives or household members were included in the study. Since the results in the latter subjects were normal, they will not be mentioned. Statistical analysis was performed by linear regression and by the Student's *t*-test when the number of patients was large enough.

RESULTS

Lymphadenopathy syndrome

In Caucasian patients, clearly increased IgG levels (above 15 mg/ml) were found in 27 cases (87%), whereas elevated IgA (above 3,7 mg/ml) and IgM (above 2,4 mg/ml) levels were observed in four (13%) and five (16%) cases respectively (Table 1). Only two patients showed normal levels of the three main Ig classes. Although IgG subclass levels varied from patient to patient (Table 2), IgG-1 levels were consistently high and this was the main reason for every increase in total IgG. IgG-3 levels were also increased although to a lesser extent. Mean IgG-4 level was significantly lower than in normal controls and the mean IgG-2 level was very slightly decreased (non significant). There was a significant negative correlation ($r = 0{\cdot}46$, $P < 0{\cdot}01$) between IgG-1 and IgG-2 levels and a positive

Table 1. Serum Ig class levels in adults with LAS and AIDS (mg/ml) and percentages of cases with increased values (North African patients not included)

		IgG		IgA		IgM	
		Range Mean ± s.d.	Increased (%)*	Range Mean ± s.d.	Increased (%)*	Range Mean ± s.d.	Increased (%)*
Caucasians	LAS (31)†	10·9 – 31·5 20·4 ± 4·9	87%	0·7 – 5·7 2·37 ± 1·17	13	0·45 – 3·2 1·59 ± 0·70	16
	AIDS (11)	8·1 – 20·4 14·3 ± 3·7	55%	1·3 – 9·6 5·2 ± 2·26	73	0·35 – 4·8 2·17 ± 1·18	27
Central Africans & Haitians	LAS (13)	17·9 – 86·3 47·4 ± 19·5		1·6 – 5·0 3·03 ± 1·01		< 0·1 – 10·2 3·37 ± 2·34	
	AIDS (4)	14·8 – 20·7 17·9 ± 2·16		1·2 – 4·1 2·43 ± 1·09		0·5 – 1·3 1·0 ± 0·32	

* Estimated in Caucasians only due to the lack of data on normal Africans and Haitians.
† Numbers of patients are indicated in brackets.

Table 2. Serum IgG subclass levels in adults with LAS and AIDS (range and mean ± standard deviation, mg/ml). The comparison with normal values (Student's *t*-test) was made in Caucasians only; significant differences are indicated in parentheses

		Number of patients*	IgG-1	IgG-2	IgG-3	IgG-4
Caucasians	LAS	31	7·25 – 29·1 17·2 ± 5·3 ($P < 10^{-9}$)	0·90 – 5·80 2·33 ± 1·34	0·11 – 1·37 0·56 ± 0·30 ($P < 0·02$)	0·01 – 1·60 0·30 ± 0·35 ($P < 0·02$)
	AIDS	11	4·1 – 16·0 11·1 ± 4·0 ($P < 10^{-3}$)	0·55 – 5·00 2·35 ± 1·29	0·25 – 1·98 0·70 ± 0·46 ($P < 0·05$)	0·01 – 0·54 0·15 ± 0·16 ($P < 10^{-5}$)
Central Africans & Haitians	LAS	13	14·8 – 71·0 42·0 ± 15·9	0·40 – 4·20 1·76 ± 1·06	0·35 – 4·20 1·68 ± 1·04	0·09 – 12·50 2·05 ± 3·71
	AIDS	4	12·8 – 19·3 16·2 ± 2·4	0·60 – 1·40 0·88 ± 0·32	0·40 – 0·80 0·52 ± 0·16	0·16 – 0·70 0·36 ± 0·22
Normal values (Caucasians)		122	3·0 – 10·5 6·35 ± 1·50	0·40 – 6·30 2·61 ± 1·36	0·12 – 1·14 0·414 ± 0·170	< 0·01 – 1·87 0·459 ± 0·367 (101 men)

* Data on North African patients not included.

one ($r = 0·44$, $P < 0·02$) between IgG-2 and IgG-4 levels. Clinical features in the five patients (16%) whose serum IgG subclass levels were in the normal ranges were unremarkable. Results in the two patients from the Maghreb were 66·0, 1·2, 0·17 and 0·38 mg/ml for each subclass in the first case and 33·0, 3·8, 0·43 and 0·71 mg/ml in the second patient who had no detectable serum IgA.

Table 3. Serum IgG subclass, IgA and IgM levels in patients with lymphoid interstitial pneumonitis (mg/ml)

Patient N°	Sex	Age (years)	Geographical origin	IgG-1	IgG-2	IgG-3	IgG-4	IgA	IgM
1*	F	29	Haiti	47·5	0·55	2·4	0·09	4·1	<0·1
2	M	34	Haiti	42·5	0·8	2·2	0·34	3·65	4·25
3*	M	57	Congo	60	1·7	1·8	0·16	4·1	3·3
4	M	26	Benin	71	4·2	2·7	8·4	3·3	3·2
5*	M	38	Zaire	65	2·0	4·2	12·5	3·2	10·2
6	M	26	Zaire	32	1·9	2·4	0·3	3·2	5·1

* Patients affected with severe *Streptococcus pneumoniae* and /or *Haemophilus influenzae* infections.

In Central African and Haitian patients (Tables 1 & 2), IgG-1 and IgG-3 levels were much higher than in Caucasian patients and IgG-2 levels were lower. Because of extremely high values in a few cases (Table 3), mean IgG-4 level was higher than in normal or diseased Caucasians. IgG subclass dysbalances were especially striking in patients with LIP (Table 3) with very high IgG-1 and IgG-3 levels. IgG-2 levels appeared to be relatively low in several cases (below 1 mg/ml in two patients). IgG-4 levels were extremely high in two cases and tended to be low in the others. Three of the LIP patients suffered severe streptococcus pneumoniae and/or *Haemophilus influenzae* respiratory infections, with no apparent correlation with subclass levels.

Acquired immune deficiency syndrome

In Caucasians, total IgG levels were increased in only 55% of cases. In contrast to LAS, IgA levels were often high (73% of cases) whereas IgM levels were increased in 27% patients (Table 1). The distribution of IgG subclasses (Table 2) was reminiscent of that found in patients with LAS, although IgG-1 levels were lower in AIDS than in LAS ($P < 0{\cdot}01$). The negative correlation between IgG-1 and IgG-2 levels was found again ($r = 0{\cdot}66$, $P < 0{\cdot}05$), but not the positive one between IgG-2 and IgG-4. IgG subclass levels were normal in 36% of patients who displayed no unusual clinical features. The observations made in Africans and Haitians confirm those made in Caucasians, with IgG-1 levels lower than in LAS (Table 2). In spite of the small number of patients in this group, it is clear that IgG-2 levels are low in African and Haitian AIDS patients.

DISCUSSION

The present study of 61 sera from LAS and AIDS patients confirms previous data on the levels of serum Ig classes. The elevation of IgG was more marked and more frequent in LAS than in AIDS. In Caucasians, IgA levels were higher in AIDS than in LAS. The new information in this study is provided by the measurement of IgG subclasses. In Caucasians, in spite of different IgG levels between LAS and AIDS, mostly due to a lower IgG-1 levels in AIDS, and in spite of variations from patient to patient, a general pattern was apparent: IgG-1 levels were commonly (close to 90% of LAS patients and 65% of AIDS patients) increased, together with a more moderate increase in IgG-3 levels. Although serum IgG-4 reached high levels in some cases, the mean level of this isotype was lower than in normal subjects. Similarly, in spite of moderately high levels in certain patients, mean IgG-2 levels tended to be slightly low. This is probably not meaningless since IgG-2 levels correlated positively with those of IgG-4 and negatively with those of IgG. As for Africans and Haitians, we lack normal values and therefore cannot draw any definite conclusion. However, by reference to data from the literature (Salimonu, Williams & Osunkoya, 1982; Kaschka *et al.*, 1984) which show higher levels than in normal Caucasians for every subclass, the abnormalities appear to be similar to those observed in Caucasian patients, with a more clear-cut decrease of IgG-2 levels. A search for

serum monoclonal Ig was performed by conventional methods and was negative. We do not know whether homogenous IgG which might be detectable by the immunofixation technique (Papadopoulos *et al.*, 1985) may participate in the increase of a given IgG subclass or not.

The most striking subclass dysbalances were observed in the six patients affected with LIP, all Africans or Haitians with LAS, who had very high IgG-1 and IgG-3 levels and variable (from very high to low) IgG-2 and IgG-4 levels. Three of the latter patients were affected with recurrent *Streptococcus pneumoniae* and/or *Haemophilus influenzae* infections. Antibodies against these pathogens are largely restricted to the IgG-2 subclass (Yount *et al.*, 1968; Siber *et al.*, 1980; Bird *et al.* 1984; Freijd *et al.*, 1984), and the occurrence of these infections in patients with primary IgG-2 deficiency is well known (Oxelius, 1984; Matter *et al.*, 1985). We found low IgG-2 levels in patient 1 on Table 3, as in a child with LIP and similar infections mentioned in a previous report (Church *et al.*, 1984). Similarly to a previously reported child (Rubinstein *et al.*, 1984), we also studied a Haitian girl with AIDS who suffered severe *Staphylococcus aureus* infections and found low IgG-2 levels. Since antiteichoic acid antibodies mostly belong to the IgG-2 subclass (Hammarström *et al.*, 1984), it is possible that an impaired production of IgG-2 antibodies might contribute to the occurrence of pyogenic infections. However our series includes patients with even lower IgG-2 levels and no pyogenic infections, as well as patients 3 and 5 on Table 3 (affected with such infections) who had IgG-2 levels that are probably in the normal range for Central Africans. Therefore, although the low—normal IgG-2 levels in these two patients are in contrast with the considerable IgG-1 IgG-2 increase, there is no clear evidence for a role of IgG-2 defects in the occurrence of bacterial infections in our patients.

In the mouse, the expression of IgG subclasses is more dependent on T cell help for those subclasses whose genes are located downstream (3′) to the C_H locus, as compared to the isotypes with upstream (5′) located genes (Martinez-Alonso, Coutinho & Andrei, 1980; Mongini, Paul & Metcalf, 1982). Although the data in man is not as clear cut, a similar conclusion is likely with a different regulation of upstream (IgG-3 & IgG-1) and downstream (IgG-2 & IgG-4) isotypes (Walker, Johnson & MacLennan, 1983; Mayumi *et al.*, 1983; Le Thi Bich-Thuy & Revillard, 1984; Scott & Nahm, 1984). Thus, our results are compatible with the hypothesis that polyclonal B cell activation in LAS and AIDS is largely T independent. Variations of IgG subclass levels in individual patients might reflect different combinations of defective T cell help, leading to reduced IgG-2 and IgG-4 responses, and of antigenic stimulation and polyclonal activation by microorganisms.

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