

Correlation of Serum IgD Level With Clinical and Histologic Parameters in Hodgkin Disease

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The concentration of serum IgD was measured in 100 patients with Hodgkin disease; 65 had 3–50-fold increases in IgD levels. Several parameters were found to influence serum IgD concentration: IgD level in older patients (>50 yr) was significantly lower than in the younger patients (<18 yr). IgD concentration was significantly higher in splenectomized than in nonsplenectomized patients ($p < 0.005$). Therapy was found to depress IgD concentration, which fell to a value significantly lower than in untreated

patients ($p < 0.05$). An interesting correlation was found between IgD levels and histologic type of the disease, lower levels being preferentially associated with the lymphocyte predominance type and higher with the lymphocyte depletion type. The logarithms of the means of these two groups were significantly different from the overall mean of the disease ($p < 0.05$ and $p < 0.0005$, respectively). Mixed cellularity and nodular sclerosing showed intermediate values.

IMMUNOGLOBULIN D is a major Ig class on the surface of human, mouse, and monkey lymphocytes¹⁻⁵ and therefore it is thought to serve a function as a lymphocyte receptor.^{3,4} However, its precise role in the immune system is still unknown. Since IgD is present as a minor component in human serum,⁶ it may reasonably be assumed that further information about its role may also be gained by studying serum IgD level in different pathologic conditions.

We recently reported that serum IgD is markedly increased in approximately two-thirds of Hodgkin disease (HD) patients.⁷ The limited number of subjects considered in that study did not allow a precise analysis of the relationship between IgD concentration and other important parameters such as sex, age, splenectomy, staging, histologic type, duration of disease, and clinical state. We have since then extended our study to a total of 100 HD patients, subdivided according to a number of parameters in an attempt to explain the variability in IgD concentration found in the group as a whole.

MATERIALS AND METHODS

The patients with confirmed diagnosis of Hodgkin disease were classified according to the scheme of Lukes et al.⁸ and staged following the recommendations of the 1971 Ann Arbor Conference. Of the 100 patients studied, 80 were seen at the Department of Haematological Medicine, University of Cambridge, U.K., and the other 20 were seen at the Department of Haematology, University of Genova Medical School, Italy. The 40 normal subjects used as controls were chosen to match the HD patients in age and sex distribution.

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IgD concentration was determined by the radial immunodiffusion method.⁹ When the IgD level was below the lower limit of detectability of this technique (10 $\mu\text{g/ml}$) a solid-phase radioimmunoassay was used.⁷

Determination of serum IgG, IgA, and IgM levels was also performed by radial immunodiffusion using commercial plates (Behringwerke, Germany), and reference sera were similarly purchased from Behringwerke. Since serum IgD (as well as other Ig classes) concentrations are not distributed in a Gaussian manner,^{19,26} geometric means instead of arithmetic means were calculated for the various groups of patients. Differences between the groups tested were determined by Student's *t* test using the logarithmically transformed values.^{13,27}

RESULTS

The rather wide range of IgD concentrations in the serum of normal individuals raises the problem of what concentration of IgD is to be considered abnormally high.

The upper limit of normal values was set at 32 $\mu\text{g/ml}$ because of the following considerations: The log mean (1.077) and its SD (0.274) (corresponding to 11.93 ± 10.5 $\mu\text{g/ml}$) calculated for IgD concentration in 40 healthy subjects showed that 97.5% of normal values are lower than 32.5 $\mu\text{g/ml}$. (Log mean had to be used instead of the arithmetic mean because IgD values do not show a normal distribution.) Of a total of 100 HD patients, 65 showed levels of serum IgD ranging from 32 to 640 $\mu\text{g/ml}$, confirming our previous observation on a limited number of cases (14 of 21 HD patients, corresponding to 66.7%).

Serum IgD concentrations detected in normal individuals and in HD patients are reported in Table 1. Log mean and range were in good agreement with the values found in our previous study. HD patients were then subdivided in order to find if the variability of IgD levels within the group as a whole correlated to any of the following parameters: duration of the disease, age, histologic type, clinical state, staging, splenectomy, therapy, or sex. The log means of the various groups were then compared using Student's *t* test.

Age was found to influence IgD level. Patients aged 0–18 yr had levels higher than the general mean of the group, while patients over 50 yr old showed a lower IgD level. However, age-related changes in IgD levels, including decreased values in older patients, have also been reported for normal individuals.¹⁰ Splenectomy was found to affect the level of serum IgD, causing a definite increase of IgD concentration in splenectomized patients ($p < 0.0005$). It is interesting that splenectomy also affects the levels of other immunoglobulin classes. While the concentrations of IgG, IgA, and IgM in HD patients were somewhat lowered but within the normal range (Table 2) (previously reported also by others¹¹), the group of splenectomized patients had higher levels of IgG

Table 1. Serum IgD Concentrations in Normal Individuals and in HD Patients

	<i>n</i>	Range ($\mu\text{g/ml}$)	Log Mean \pm 2 SEM	<i>p</i> Value*
Normal	40	2–37	1.077 \pm 0.068 (11.93 \pm 1.17)†	
HD	100	5–640	1.649 \pm 0.243 (44.60 \pm 1.75)†	<0.0001

Only log mean was determined because IgD concentrations are not distributed in a normal manner.

*Differences between groups were determined by Student's *t* test using logarithmic values.

†Values in $\mu\text{g/ml}$.

Table 2. Effect of Splenectomy on IgG, IgA, IgM, and IgD Serum Concentrations

	<i>n</i>	IgG (mg/dl)*	IgA (mg/dl)	IgM (mg/dl)	IgD (μ g/ml)
Splenectomy	56	3.028 \pm 1.071 (1069 \pm 11.8)	2.209 \pm 0.662 (162 \pm 4.6)	1.778 \pm 0.450 (60 \pm 2.82)	1.774 \pm 0.352 (59.49 \pm 2.25)
No splenectomy	44	2.983 \pm 1.103 (967 \pm 12.7)	2.113 \pm 0.662 (130 \pm 4.6)	1.832 \pm 0.531 (68 \pm 3.40)	1.486 \pm 0.439 (30.68 \pm 2.75)
<i>p</i> value		<0.005	<0.0005	NS	<0.0005

NS, not significant.

*Applies to values in parentheses.

($p < 0.005$) and IgA ($p < 0.0005$) and somewhat lower levels of IgM ($p < 0.1$) when compared with the group of nonsplenectomized patients.

The effect of splenectomy on IgD level was neither immediate nor transient. Individual IgD values plotted versus time after splenectomy showed a lag phase of several months before a twofold increase of IgD concentrations. IgD remained at that level for about 1 yr and subsequently began to decline, falling to a concentration similar to that of nonsplenectomized patients within approximately 6 yr after splenectomy.

A very interesting correlation was found between IgD levels and histologic type. The IgD levels were the lowest in the lymphocyte-predominant (LP) type (Table 3) followed by the mixed cellularity (MC) type ($p < 0.05$), still below the general mean value, and the nodular sclerosis (NS) type, the log mean of which was very close to the overall value ($p < 0.25$). All patients in the lymphocyte-depleted group had extremely high levels of IgD (log mean 284.97), which despite the low number of cases was highly significant ($p < 0.0005$). Furthermore, the patients with low or close to normal levels of IgD (one-third of the cases) were unevenly distributed throughout the four groups. LP had the highest percentage (39%) followed by MC (37%) and NS (19%). No patients with low levels of IgD were present in the LD group. Patients with very high IgD values ($> 100 \mu\text{g/ml}$) were distributed in an inverse way, accounting for 80% of the LD group, 23% of the NS group, 18% of the MC group, and 11% of the LP type. The patients were then divided in two groups, one of which was receiving therapy or had received therapy in the 3 mo preceding the blood with-

Table 3. IgD Levels in Different Histologic Types

	<i>n</i> *	Log Mean \pm 2 SEM	<i>p</i> Value
LP	18	1.486 \pm 0.577 (30.64 \pm 3.78)†	<0.05
MC	27	1.592 \pm 0.523 (39.11 \pm 3.34)	<0.05
NS	43	1.654 \pm 0.447 (45.17 \pm 2.80)	N.S.
LD	5	2.454 \pm 1.540 (284.97 \pm 34.75)	<0.0005
Total	100	1.649 \pm 0.243 (44.60 \pm 1.75)	

*Histologic type of seven patients was not classified.

†Values in parentheses, $\mu\text{g/ml}$.

Table 4. Effect of Treatment on IgD Levels

	n	Log Mean \pm 2 SEM	p Value
Therapy	33	1.559 \pm 0.457 (36.25 \pm 2.87)*	<0.05
No therapy	67	1.691 \pm 0.356 (49.10 \pm 2.27)	

*Values in parentheses, $\mu\text{g/ml}$.

drawal for IgD determination, while the other group of patients had not been treated in the previous 3 mo. Only two patients had received no therapy and therefore were not classified in a separate group. As shown in Table 4, IgD levels of patients receiving treatment were significantly lower than those of patients without treatment ($p < 0.05$). However, if the therapy group included all of the patients who had been treated in the previous year, then no difference between the two groups was found, indicating a relatively short-term effect of therapy on IgD levels.

The clinical states of the patients seem to influence their IgD levels, lower levels being present in patients in active phase of disease. Patients considered to be in remission were those who remained in remission at least 3 mo after IgD determination. All other patients were considered to be in a phase of active disease; however, the difference between the two groups was small (40.12 and 46.47 $\mu\text{g/ml}$) and not statistically significant.

Sex, staging, and duration of the disease were found to have no relation to IgD level; therefore their respective values are not reported.

DISCUSSION

The results reported above confirm and extend our previous observation that two-thirds of HD patients have elevated serum IgD concentrations. The aim of this study was to examine in a larger number of patients the possibilities of a correlation between the level of IgD and various parameters by which the patients could be subdivided.

The analysis of the different subgroups failed to show the existence of a homogeneous group formed by individuals with only low or high IgD. Nevertheless, it showed a clear correlation between IgD concentration and several parameters.

Age distribution analysis did not show significant variations in IgD level, apart from a definite tendency to lower levels in older ages. This finding, however, does not seem to be confined to HD, since it has been reported also in normal individuals.¹⁰ A similar consideration may also apply to the finding of lower IgD levels in treated patients (with either chemotherapy or radiotherapy). It is well known that one of the probable sequelae of the therapy of lymphomas is the impairment of cellular and/or humoral immunity; lower IgD levels during or after treatment would simply reflect a generalized effect on the immune system, since other Ig levels are also affected.¹²⁻¹⁴

The uneven distribution of IgD levels among the four histologic types, with high values concentrated in the prognostically least favorable group, LD,¹⁵ and low levels preferentially found in the relatively favorable LP type, is very

interesting and suggests a relationship between IgD level and the severity of the disease judged by histologic criteria. Proof of this correlation will be attained only after a followup of the patients over many years, but it is worth mentioning that no correlation was found between IgD level and the different stages or duration of disease, a clear indication that a raised IgD level is present at an early phase and is not dependent on the dissemination of the lymphoma. In line with previous reports no significant correlation was found between histologic type and the level of the other Ig classes.¹⁶

The effect of splenectomy is rather complex. Splenectomized patients show, in addition to a marked increase in IgD, a slight rise in IgG and IgA and an intriguing although not significant decrease of IgM levels, which had been noted already by others.¹²⁻¹⁶ The contrasting behavior of IgG and IgA on one hand and IgM on the other may suggest that in man, as in the mouse, the spleen is a major site of IgM synthesis while lymph nodes are engaged mostly in IgG production.¹⁷

The reason for the selective increase in IgD in HD is not yet known. Genetic factors such as *Gm* genotype¹⁸ and HLA loci A2 and A13¹⁹ have been associated with serum IgD levels, while HD has been associated mainly, although not exclusively, with loci A1, A5, A8, and A18.²⁰ Moreover, the variation in IgD level related to splenectomy, therapy, histologic type, and state of disease can hardly be justified by a purely genetic background.

IgD may be raised in HD in response to a chronic stimulation of the immune system caused by specific tumor-associated²¹ or viral²² antigens.

Increased serum IgD levels have been reported during pregnancy, with higher levels being correlated with increasing gestational age and possibly mother-fetus ABO/Rh incompatibility and lower IgD levels being found in premature deliveries.¹⁹ Furthermore, high levels of IgD have been reported in a number of pathologic conditions such as TB, aspergillosis, sarcoidosis, and leprosy,^{23,26-28} which, while apparently unrelated to HD, have in common with this disease an often severely impaired cell-mediated immunity. IgD levels comparable to those seen in HD have also been detected in ataxia teleangiectasia, where a severe lymphocyte depletion is associated with the absence of cell-mediated immunity.²⁹ Recently, suppressor T cells were detected in unusually high number both in human fetuses²⁴ and in HD patients.²⁵ Taken together these data suggest that IgD levels are somehow correlated to a proper functioning of cell-mediated immunity in general and to the number or functioning of suppressor T cells. It is clear that this correlation, as well as the significance of high IgD concentrations, is still a matter of speculation. However, for the time being, monitoring of IgD level may prove useful as both a diagnostic and a prognostic aid in HD.

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