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## IMMUNOGLOBULINS AND INTERFERON RESPONSES IN INFECTIOUS AND TRANSFUSION ASSOCIATED HEPATITIS

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### INTRODUCTION

Adults with infectious hepatitis (IH) and transfusion associated hepatitis (SH) show similar degrees and variations of immunoglobulin (Ig) responses for IgM\* (19S-beta<sub>2</sub>macroglobulin), IgG\* (7S, gamma-G) and IgA\* (7S, beta<sub>2</sub>A). In general, there was a significant rise in all three immunoglobulin values in both groups. Immunoglobulin responses in children during an institutional outbreak of infectious hepatitis has been previously reported.<sup>(1,2)</sup> In the adult group, the IgM and IgG responses were similar to those found in the children. However, there was a marked rise in IgA values in adults which was not seen among the children.

In addition to the immunoglobulin studies, interferon (virus inhibitory substance) response in peripheral blood leucocytes was studied in the adult group, providing another parameter with which to compare and evaluate the immunologic status of patients with both infectious and transfusion associated hepatitis.

### METHODS AND STUDY

*Patient Source and Studies* — A total of twenty-one patients were studied; 12 with infectious hepatitis and 9 with blood transfusion associated hepatitis. These represent only those hepatitis patients who were seen in consultation with members of the Pediatric and Medical Services regarding the immunologic status of the patient. Only the laboratory findings are summarized without detailed clinical aspects as these will be reported elsewhere.

Serum immunoglobulin (IgG, IgA and IgM) levels and leucocyte interferon responses were tabulated with related hepatitis studies. These related studies were: (1) total serum proteins; (2) percent protein distribution zones from electrophoretic mobili-

\*World Health Organization, report on nomenclature for human immunoglobulins, Prague, May 29-30, 1964.

ty patterns; (3) serum bilirubin levels (total and direct) and (4) serum transaminase (SGOT) determinations. The studies were made during the acute icteric stage of the disease and convalescent non-icteric stage, whenever sera became available. The primary purpose of the study is to correlate these determinations with the degree and variations in immunoglobulin responses during the acute stage of the disease in adults and to compare these with the findings reported in children.<sup>(1,2)</sup>

*Electrophoretic Mobility of Serum Proteins* — The standard biuret procedure was used for determining total proteins. Standard methods for serum electrophoresis on cellulose acetate strips were used to determine percent distribution of serum proteins.

*Quantitative Determination of Serum Immunoglobulins (Ig)* — Serum immunoglobulins (IgA, IgM and IgG) were determined by a micro-double diffusion in agar technic developed and standardized in this laboratory. Details of the immuno-chemical methods of analysis have been published elsewhere.<sup>3</sup> *Normal adult serum immunoglobulin levels* have been found to range (mean  $\pm 2$  standard deviations) as follows: 600-1400 mg/100 ml for IgG; 30-135 mg/100 ml for IgA and 30-110 mg/100 ml for IgM. Serum immunoglobulin levels in *normal infants and pre-school children* have been established and are being reported elsewhere.<sup>(4)</sup> The values in children differ considerably for the respective immunoglobulins on a monthly basis for the first year of life, not reaching the lower adult ranges until one to three years, with the exception of IgM which reaches adult values within the first month of life. These standard values are necessary in order to discuss the degrees of immunoglobulin responses in varying clinical entities. This is illustrated in hepatitis where the IgA responses in children<sup>(1,2)</sup> differ from those in adults.

*In Vitro Interferon Response of Peripheral Blood Leukocytes* — The individual's cytological immune status in regard to viruses (i.e., his ability to respond with interferon production) was made by an *in vitro* method of assay. A comparative study between humoral immune status and interferon response in health and disease has been reported from this laboratory.<sup>(5)</sup> In healthy individuals 91.3% produced interferon titers from 1:32 to 1:512 or greater and 8.7% produced titers of 1:16. An interferon titer of 1:8 or less was not found among healthy individuals fulfilling our criteria.<sup>(5)</sup> Therefore, titers of 1:32 or greater are considered "*good responses*" in this test system; a titer of 1:16 is a "*borderline response*" and a titer of 1:8 or less, a "*poor response*."

*Serum Transaminase and Bilirubin* — Serum glutamic-oxaloacetic transaminase (SGOT, normal values 0-40 units/ml) and serum bilirubin (total/direct, normal values 0.02-1.0/0.05-0.3 mg%) were performed on fresh serum by the clinical biochemistry laboratory.

## RESULTS

Of twenty-one hepatitis patients, twenty were studied during the acute stage when all demonstrated clinical jaundice. One patient was studied one year after the acute onset of hepatitis with jaundice. Of the twelve patients with *infectious hepatitis (Table-I)*,

## IMMUNOGLOBULINS AND INTERFERON RESPONSES

seven were studied only during the acute stage of the disease, three were followed from 5 to 8 weeks after the acute stage and two were followed for 19 and 30 months respectively. All were adults varying from 20 to 63 years of age with the exception of one child who was 7 years old.

Eleven of these twelve patients (Table-I) were evaluated for immunoglobulin responses during the acute stage of illness as determined by the degree of serum bilirubin and transaminase values shown. All twelve patients showed *IgM values* of at least 2 standard deviations (SD) above the normal mean value for adults. The twelfth patient (H-171) was evaluated 1 year after the acute episode when bilirubin and transaminase values were normal but high *IgM* values were found and persisted, indicating continued antigenic stimulation to the immune mechanism. A rise in immunoglobulin-M is the primary response to infectious hepatitis and *IgM* is most consistently elevated above the normal range of serum levels during the icteric stage. The *IgG responses* given in Table-I, reflect the stage and duration of the infection. *IgG* values usually increase above the normal range of serum levels as the infection subsides while the *IgM* values return to normal during this period. The responses seen in adults during the acute stage, show the same degree and variations described and tabulated for the children with infectious hepatitis.<sup>(1,2)</sup> In contrast, the increase in *IgA responses* shown in five of the twelve patients with infectious hepatitis (Table-I), was not found in any of the 64 hepatitis children studied.<sup>(2)</sup> The significance of the rise in *IgA* is not known at the present time.

In comparing *electrophoretic mobility values* for the five zones reported, the gamma region is no index to the immunoglobulin classes involved. Immunoglobulins (*IgG*, *IgA* and *IgM*) may all contribute to the gamma or beta zones of electrophoresis. *IgA* and *IgM* values cannot be determined by electrophoresis and the *IgG* value may or may not be comparable to the value given for the gamma zone. This is illustrated by the two patients, H-163 and H-171 who were followed for 18 and 30 months respectively. Elevated *IgM* in serum may persist for months or years, long after the clinical signs and symptoms disappear and serum transaminase levels return to normal.

*Interferon studies* were made in seven of the twelve infectious hepatitis patients. The interferon yields in the peripheral blood leucocytes were good and within normal values obtained for this test.

The nine patients with *transfusion associated hepatitis* showed the same degree and variations of immunoglobulin responses as found in the infectious hepatitis group. These are shown in Table-II. Seven of these patients were studied only during the acute stage and two were followed for 3 to 18 months respectively. All were adults varying from 44 to 73 years of age with the exception of one child who was 9 years old.

All nine of these patients demonstrated elevated *IgM* values above 2SD during the acute stage. Six patients showed elevated *IgG* and seven elevated *IgA* values. In

Table I  
 SERUM IMMUNOGLOBULINS AND LEUCOCYTE INTERFERON IN INFECTIOUS HEPATITIS

PATIENT DATA			SERUM PROTEIN DISTRIBUTION (Acetate Electrophoresis)						IMMUNOGLOBULINS (Ig) (Immunochemical Analysis)			SERUM VALUES		INTERFERON RESPONSE (WBC)
Code	Age	Date of Serum	Total Proteins	Alb	Alpha-1	Alpha-2	Beta	Gamma	IgG	IgA	IgM	Trans. SGOT	Bilirubin Total/Direct	Titer (Response)
	Yrs.	(Standard Values)	(6.1-8.5) gm%	(4.0-5.7) gm%	(0.07-0.3) gm%	(0.4-0.8) gm%	(0.2-1.3) gm%	(0.42-1.4) gm%	(600-1400) mg%	(30-135) mg%	(30-110) mg%	(5-40 u/ml)	0.02-1.0/ 0.05-0.3 mg%	>1:32 (good)
H-160	45	6/11/64	6.2	2.79↓	0.34	0.89↑	0.75	1.43↑	1475↑*	162↑	283↑	260	12.8/8.0	—
H-174	25	8/29/66	7.9	4.3	0.3	0.43	0.85	1.54↑	1813↑	96	248↑	2200	2.5/0.96	1:64 (good)
H-182	20	12/13/65	8.6	4.16	0.25	0.49	1.02	2.68↑	1920↑	57	208↑	56	2.24/0.94	—
H-183	42	12/13/65	8.5	4.67	0.36	0.48	1.08	1.92↑	1547↑	207↑	121↑	1060	5.45/9.60	—
H-184	63	6/30/66	7.7	3.55↓	0.28	0.49	1.16	1.51↑	1877↑	260↑	320↑	90	3.8/2.0	—
H-185	63	10/28/66	8.5	3.33↓	0.17	0.22↓	0.33	4.22↑	5248↑	528↑	294↑	1300	7.7/4.1	—
PSH-90	31	2/1/65	8.3	4.08	0.25	0.77	0.63	1.08	1337	25↓	176↑	300	3.1/1.35	1:32 (good)
H-165	7	6/4/65	6.9	4.24	0.24	0.79	0.73	0.91	838	48	440↑	105	2.0/1.28	1:128 (good)
		7/19/65	7.6	4.57	0.24	0.79	0.82	0.93	992	25↓	158↑	—	—	1:32 (good)
H-167	25	7/28/65	7.5	4.11	0.36	0.58	0.81	1.25	1088	69	184↑	6000	11.5/5.4	1:32 (good)
		8/4/65	7.6	4.12	0.56↑	0.78	0.80	1.34	1339	64	238↑	76	4.8/1.92	—
		9/8/65	8.2	4.83	0.38	0.67	0.83	1.48	1150	75	101	—	—	—
H-177	52	11/16/66	7.8	5.02	.20	.46	0.79	.93	1451	218↑	228↑	1800	11.5/7.3	1:32 (good)
		12/2/66	7.5	4.47	.18	.49	1.04	.98	1092	212↑	134↑	280	0.9/0.3	—
		1/16/67	7.7	4.82	0.18	0.50	0.73	1.19	1355	212↑	96	—	—	1:64 (good)
H-163	49	5/1/65	7.8	4.25	0.35	0.58	0.75	1.51↑	1386	80	214↑	511	7.0/4.5	—
		6/1/65	7.7	3.98	0.40	0.66	0.99	1.66↑	1370	84	142↑	200	1.1/0.96	1:128 (good)
		10/8/65	7.6	4.57	0.23	0.46	0.65	1.66↑	1195	78	214↑	—	—	—
		3/29/66	7.1	4.76	0.19	0.35	0.53	1.27	981	77	160↑	—	—	—
		12/5/66	7.7	3.72	0.22	0.54	0.81	2.42↑	2165↑	102	185↑	—	—	>1:128 (good)
H-171	39	11/3/65	6.4	3.51↓	0.24	0.28	0.55	1.82↑	1589↑	96	288↑	21	0.1/0.32	—
		11/30/65	8.2	4.80	0.15	0.34	0.74	2.17↑	1931↑	77	243↑	11	0.16/0.64	—
		1/11/66	8.0	4.70	0.29	0.44	0.73	1.84↑	1352	69	184↑	14	—	1:256 (good)
		3/1/66	7.9	4.68	0.28	0.44	0.68	1.83↑	810	57	190↑	—	—	1:256 (good)
		7/7/66	7.0	4.17	0.32	0.45	0.61	1.46	1070	65	94	17	0.32/0.64	1:64 (good)
		11/18/66	8.8	5.13	.26	.60	0.90	1.92↑	1760↑	67	207↑	—	—	—

\* Arrows (↑↓) indicate values above or below the normal range of serum levels (Ig being  $\pm 2SD$  from the mean)

Table II  
 SERUM IMMUNOGLOBULINS AND LEUCOCYTE INTERFERON IN TRANSFUSION ASSOCIATED HEPATITIS

PATIENT DATA			SERUM PROTEIN DISTRIBUTION (Acetate Electrophoresis)						IMMUNOGLOBULINS (Ig) (Immunochemical Analysis)			SERUM VALUES		INTERFERON RESPONSE (WBC)
Code	Age	Date of Serum	Total Proteins	Alb	Alpha-1	Alpha-2	Beta	Gamma	IgG	IgA	IgM	Trans. SGOT	Bilirubin Total/Direct	Titer (Response)
	Yrs.	(Standard Values)	(6.1-8.5) gm%	(4.0-5.7) gm%	(0.07-0.3) gm%	(0.4-0.8) gm%	(0.2-1.3) gm%	(0.42-1.4) gm%	(600-1400) mg%	(30-135) mg%	(30-110) mg%	(5-40) u/ml	0.02-1.0/ 0.05-0.3) mg%	≥1:32 (good)
H-161	44	1/25/65	8.4	4.08	0.32	0.40	0.52	3.08†	2829†*	192†	217†	2240	41/21	1:64 (good)
H-170	72	10/20/65	6.7	3.60	0.35	0.39	0.67	1.18	1038	101	152†	410	32/7	1:256 (good)
H-178	46	12/9/66	6.7	4.3	0.18	0.30	0.57	1.35	1248	130	176†	1100	10.5/5.4	1:32 (good)
H-179	57	8/2/65	8.0	4.70	0.32	0.54	0.76	1.35	1744†	156†	130†	580	6.8/3.2	—
H-180	73	5/20/66	6.7	2.93‡	0.25	0.65	0.89	1.99†	1408	240†	129†	1550	15.68/9.28	—
H-176	9	2/12/66 11/3/66	7.0 6.8	3.07‡ 2.96‡	0.25 0.16	0.37 0.13	0.66 0.45	2.65† 3.12†	1749† 3008†	121 330†	104 240†	(Cystic Fibrosis: Pre-Blood Transf. Values)		1:64 (good)
H-181	60	8/26/66 9/1/66	9.0† 8.1	4.48 4.07	0.39† 0.34	0.62 0.64	1.02 1.08	1.60† 1.98†	2219† 2219†	278† 270†	384† 688†	3100 1250	9.9/4.8 10.2/6.4	— —
H-173	55	1/11/65 4/7/65 4/20/65	7.0 8.6 8.4	3.12‡ 4.86 4.59	0.52† 0.26 0.39	1.32† 0.53 0.59	0.92 1.08 1.12	1.12 1.38 1.51†	1340 1555† 1586†	162† 126 153†	91 224† 137†	(Burn Pt. Pre-blood Transf. Value)		1:64 (good) —
H-162	48	12/17/64 12/29/64 1/18/65 4/9/65 11/1/65 5/17/66	7.3 7.0 8.1 8.1 6.8 7.6	2.6 ↓ 3.77‡ 5.39 4.52 4.04 4.05	0.4 0.46† 0.18 0.34 0.36 0.36	0.5 0.49 0.52 0.68 0.45 0.78	1.56 † 0.46 0.92 0.99 0.69 0.74	2.2 † 1.43† 1.10 1.55† 0.69 1.67†	— 1502† 1143 1168 1148 942	— 159† 141† 130 119 109	— 144† 252† 108 112 168†	4240 1840 — — — —	9.6/6.1 11.9/4.8 — — — —	— 1:8 (poor) — 1:64 (good) 1:8 (poor) 1:64 (good)

\*Arrows (†‡) indicate values above or below the normal range of serum levels (Ig being ±2SD from the mean)

two patients (H-176 and H-173) previous IgM values had been determined and were within the normal range, giving a baseline for comparison with the elevated IgM shown during transfusion associated hepatitis. For the most part, the immunoglobulin responses were the same for infectious hepatitis and transfusion associated hepatitis. The elevations of IgG and IgA are not consistent but the IgM elevation is consistent in these groups and is more consistently demonstrated in the acute stage of the disease.

Again the serum protein distribution by electrophoresis is not a true index of the immunoglobulin responses, no correlation being possible between the two.

Interferon responses in this group were also good with the exception of one patient (H-162). This patient was interesting in that when she had a rise in all three immunoglobulins, her interferon response was poor, while when her immunoglobulins returned to normal the interferon response also returned to normal. This was clearly demonstrated twice within a period of 18 months, the patient having two apparent exacerbations, at least of the immunologic responses.

#### DISCUSSION

Immunoglobulin (Ig) determinations by immuno-chemical analysis is a helpful aid in studying virus hepatitis (IH and SH) patients. Serum IgM value is most consistently elevated and is the primary immunoglobulin response during the acute, icteric stage of the disease. IgG and IgA values may be elevated during jaundice but this is not a consistent finding. The degrees and variations of IgM and IgG responses in adult hepatitis are similar to those found in children studied during an acute outbreak of infectious hepatitis.<sup>(1,2)</sup> Serum immunoglobulin-A levels were elevated in 5 of the 12 adult patients with infectious hepatitis. This was not found in the 60 children with infectious hepatitis whose ages ranged from 1 to 15 years. Since the majority of the children (41 of the 60 studied) were 3 to 15 years of age, one cannot explain the lack of IgA response by the immaturity of the reticuloendothelial system. This would be a logical explanation for IgA values for children under three years of age but not for children over three years of age.<sup>(4)</sup> It is interesting to note the IgA response in patient H-165 (Table-I) who was a 7 year old child with infectious hepatitis. When hepatitis developed in this child, his IgM value became elevated but his IgA value decreased approximately 50 percent (from 48 mg to 25 mg per 100 ml of serum). This may be an individual variation but it may also suggest that lack of IgA responses in children with hepatitis could also be part of the immuno-depression described in 10% of the children studied with infectious hepatitis.<sup>(1,2)</sup>

Satisfactory explanations for the development of chronic liver conditions are still wanting. With new parameters to evaluate the immunologic status of individuals which can demonstrate immunologic disturbance in humoral or cytological aspects of immunity, we may have an opening for a better understanding of the chronic diseases in general.

## IMMUNOGLOBULINS AND INTERFERON RESPONSES

### SUMMARY

1. Twenty hepatitis patients (11 with infectious and 9 associated with blood transfusions) were studied during the acute, icteric stage of the disease. One patient was studied one year after the acute onset of hepatitis and followed for 18 months thereafter.
2. Serum immunoglobulin (Ig), (IgA, IgM and IgG) levels and leucocyte interferon responses were tabulated with: (1) total proteins; (2) electrophoretic mobility patterns of serum proteins; (3) serum transaminase (SGOT); and (4) bilirubin levels (total/direct).
3. There was no correlation between the values in the gamma zone from electrophoretic mobility patterns and IgG values by immuno-chemical analysis. Nor was there any indication in values from the beta zone electrophoretic patterns that IgA or IgM were abnormally high. The immunoglobulins must be studied by immuno-chemical quantitation rather than electrophoresis.
4. All the immunoglobulins were elevated during the icteric stage in both infectious and transfusion associated hepatitis. IgM levels were consistently elevated during this period while IgA and IgG values varied.
5. IgM values usually return to normal and IgG values increase above the normal range during recovery. However, this does not always occur as IgM values have been found elevated 18 and 30 months respectively in two patients.
6. Leucocyte interferon response was found to be "good" in all but one of the twenty-one hepatitis patients studied.

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