Interleukin-1 production in acute viral hepatitis

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SUMMARY The in vitro production of interleukin-1 in 15 children with acute hepatitis A and five children with acute hepatitis B was determined by measuring lymphocyte activating factor secreted by peripheral blood monocytes in a thymocyte proliferation assay. Aluminium hydroxide induced production of lymphocyte activating factor was significantly lower in patients with acute hepatitis A as well as patients with hepatitis B as compared with healthy control subjects. In both forms of acute viral hepatitis production of lymphocyte activating factor was severely depressed during the first week, increased gradually during the further course of the illness, but did not reach normal concentrations within the first three weeks after onset of the acute symptoms of the disease. No correlation could be found between in vitro production of lymphocyte activating factor and the severity of liver disease as estimated by the rise of serum concentrations of transaminases, bilirubin, or several parameters of acute phase reaction (α_1 antitrypsin, C reactive protein, erythrocyte sedimentation rate). The reduced production of interleukin-1, as assessed by determination of lymphocyte activating factor, could explain the only moderate acute phase reaction seen during acute viral hepatitis.

Many inflammatory processes, tissue injuries, microbial invasions, and immunologic reactions induce a generalised host reaction known as acute phase response. It is indicated by several clinical symptoms and laboratory findings, including fever, leucocytosis, depressed serum iron and zinc concentrations, and a dramatic increase in the synthesis of hepatic acute phase proteins.^{1,2} In recent years much evidence has been accumulated that indicates that a central part is played by interleukin-1, produced primarily by phagocytic cells,³ as a mediator of the whole range of acute phase response. Released into the circulation, the pleiotropic nature of this cytokine leads to induction of fever by acting on the hypothalamus,⁴ leucocytosis by increasing bone marrow output,⁵ activation of T⁶ and B⁷ cells, and an increase in the synthesis of acute phase proteins by the liver.^{8,9}

In contrast with this general picture, it is a well described fact that acute viral hepatitis is characterised by a lack or only a moderate degree of acute phase reaction.¹⁰ In many patients, especially in children, the disease takes an asymptomatic course,^{11–13} and the development of specific antibodies only indicates viral infection. Even in patients with an icteric course of the disease acute phase symptoms such as fever or myalgia are

minimal,^{11,14} and laboratory acute phase parameters are only moderately raised.^{14–16}

In order to clarify whether a diminished interleukin-1 activity could be responsible for the low or absent acute phase response in acute viral hepatitis we determined the in vitro production of this cytokine by measuring its proliferation-inducing effect (lymphocyte activating factor) on mouse thymocytes.

Patients and methods

Two groups of children who had been admitted to hospital with acute viral hepatitis were studied: 15 patients (eight boys, seven girls; mean (SD) age: 7.6 (3.8) years, range 2–14 years) had hepatitis A and five patients (three boys, two girls; mean (SD) age: 6.7 (2.3) years, range 4–12 years) suffered from hepatitis B (table 1). The diagnosis was based on characteristic clinical, laboratory, and serological features. The clinical course of acute disease was mild to moderately severe; two children with hepatitis A suffered from a more prolonged disease with raised aspartate aminotransferase and alanine aminotransferase for eight and 10 weeks, respectively. No supportive treatment with substitution of electrolytes and fluid was necessary and no other

Table 1 Patient characteristics and peak laboratory measurements during acute viral hepatitis. Figures are given as mean (SD)

	Patients with hepatitis A (n=15)	Patients with hepatitis B (n=5)	p Value
Boys	8	3	
Girls	7	2	
Age (years)	7.6 (3.8)	6.7 (2.3)	NS
α_1 antitrypsin (g/l) (normal: 0.7-3.5)	4.3 (0.50)	4.3 (0.51)	NS
C reactive protein (mg/l) (normal: <13)	23 (9.0)	<13	<0.025
White cell count ($\times 10^9/l$)	6.8 (1.589)	7.240 (1.415)	NS
Lymphocyte count ($\times 10^9/l$)	3.077 (1.169)	3.036 (.489)	NS
Erythrocyte sedimentation rate (mm in the first hour)	33 (17)	13 (6)	<0.025
α_2 globulin (as percentage of total protein)*	8.8 (2.4)	8.2 (0.6)	NS
Bilirubin ($\mu\text{mol/l}$)	79 (47)	111 (77)	NS
Aspartate aminotransferase (IU/l)	478 (462)	425 (477)	NS
Alanine aminotransferase (IU/l)	690 (508)	548 (500)	NS

*Measured on admission to hospital.

therapeutic measures were taken. After a variable clinical course all the children eventually recovered from hepatitis without complications; none of the cases with hepatitis B took a chronic course.

Twelve healthy young adults served as controls. Previous investigations on a small number of healthy children did not show any difference in production of lymphocyte activating factor by their monocytes as compared with young adults.

Blood for determination of lymphocyte activating factor production was drawn at variable intervals while the children were in hospital. Routine methods were used for determination of white cell counts and differential counts, serum bilirubin concentration, and aspartate aminotransferase and alanine aminotransferase activities; erythrocyte sedimentation rate was measured according to the method of Westergren and the value after the first hour was recorded. These parameters were assessed at least twice a week. C reactive protein and α_1 antitrypsin serum concentrations, determined by standard nephelometry, were assessed weekly. In addition, serum protein electrophoresis was performed at the beginning of the children's stay in hospital.

PRODUCTION OF LYMPHOCYTE ACTIVATING FACTOR

A total of 10 ml of heparinised (preservative free heparin, Immuno) peripheral venous blood was collected and processed within three hours. Mononuclear cells were isolated by buoyant density gradient centrifugation on Lymphoprep (Nyegaard),¹⁷ washed three times with 0.9% saline and resuspended to 1×10^6 mononuclear cells/ml in RPMI 1640 supplemented with 15% pooled, heat inactivated (30 minutes at 56°C) human AB serum, penicillin (100 U/ml), streptomycin (100 $\mu\text{g/ml}$), and L-glutamine (2 mM). Aliquots of 0.5 ml of this cell suspension were poured into wells of a 24 well plate (Falcon) and incubated for 90 minutes at 37°C in a humidified atmosphere containing 5% carbon dioxide. After this, non-adherent cells were aspirated and the plates washed twice with 0.9% saline. The adherent cell population contained a mean (SD) 87 (7)% monocytes as judged by morphology and non-specific esterase stain. Then 0.5 ml of aluminium hydroxide (0.8 mg/ml) dissolved in RPMI 1640 with 5% pooled human AB serum was added to each well as a stimulant,¹⁸ and the cells were further incubated for 40 hours. Wells without added aluminium hydroxide were included in each experiment as controls. After incubation the supernatant was harvested, centrifuged at 2500 rpm for five minutes, filtered through a 0.45 μm membrane filter (Gelman), and stored at -20°C.

ASSAY FOR LYMPHOCYTE ACTIVATING FACTOR ACTIVITY

Thymus glands of 4 week old male Balb c mice were removed aseptically, placed in Petri dishes filled with RPMI 1640 medium, teased apart with scissors, and gently pressed through a stainless steel sieve. The single cell suspension obtained was washed three times in RPMI 1640, checked for viability by trypan blue exclusion, and adjusted to 1.5×10^6 viable cells/ml in RPMI 1640 with 5% fetal calf serum (Flow Laboratories). At the next stage 100 μl of this cell suspension and 100 μl of the supernatant tested (final dilution: 1:10 and 1:20) were added in triplicate with 20 μl phytohaemagglutinin (PHA, HA 16, 0.2 $\mu\text{g/well}$, Wellcome) into wells of a microtiter plate (Greiner). Cultures were incubated for 72 hours at 37°C in a humidified atmosphere containing 5% carbon dioxide. Sixteen hours before termination of culture each well received 20 μl of tritiated thymidine (185 GBq/mmol, Amersham). The radioactivity incorporated into proliferating thymocytes was determined by liquid scintillation in a beta counter (Mark III Searle Analytic Inc). Results of lymphocyte activating factor activity in supernatants were expressed either as counts per minute (cpm) (mean value of triplicate wells in each experiment) or as percent of the mean cpm of

thymocytes cultured with phytohaemagglutinin and aluminium hydroxide stimulated monocyte supernatants of healthy control individuals.

Data are given as mean (SD) or mean (SEM). The statistical evaluation was performed by Student's *t* test for unpaired and (when applicable) for paired data.

Results

SPONTANEOUS PRODUCTION OF LYMPHOCYTE ACTIVATING FACTOR BY CULTURED MACROPHAGES

Phytohaemagglutinin comitogenic activity on mouse thymocytes, exerted by culture supernatants derived from unstimulated macrophages of children with acute hepatitis A or B and healthy control individuals, is shown in table 2. Neither healthy controls nor patients with acute hepatitis A or B produced substantial amounts of lymphocyte activating factor activity.

ALUMINIUM HYDROXIDE INDUCED PRODUCTION OF LYMPHOCYTE ACTIVATING FACTOR BY CULTURED MACROPHAGES

As shown in fig 1, phytohaemagglutinin comitogenic lymphocyte activating factor activity in culture supernatants (assayed at a final dilution of 1:10) of aluminium hydroxide stimulated macrophages derived from patients with acute hepatitis A was significantly reduced as compared with the activity found in culture supernatants from healthy controls ($p<0.0005$). Similarly, culture supernatants of aluminium hydroxide stimulated macrophages from patients suffering from acute hepatitis B also showed a diminished phytohaemagglutinin comitogenic lymphocyte activating factor activity when compared with that of healthy control subjects ($p<0.05$). Phytohaemagglutinin comitogenic lymphocyte activating factor activity, derived from cultured aluminium hydroxide stimulated macrophages of patients with hepatitis A, was found to be significantly lower than that observed in patients with hepatitis B ($p<0.05$). The same general pattern of phytohaemagglutinin comitogenic lymphocyte activating factor activity was seen when supernatants were tested at a final dilution of 1:20 (data not shown).

Table 2 Unstimulated production of lymphocyte activating factor by monocytes after incubation for 40 hours. Figures are expressed as mean (SD) counts/minute of tritiated thymidine uptake of mouse thymocytes after cultivation with monocyte culture supernatants for 72 hours

	Phytohaemagglutinin comitogenic activity
Tritiated thymidine incorporation in mouse thymocytes without culture supernatant (n=12)	1048 (536)
Healthy control subjects (n=12)	821 (203)
Patients with hepatitis A (n=15)	1127 (479)*
Patients with hepatitis B (n=5)	1005 (385)*

*NS.

Fig 1 Production of lymphocyte activating factor during acute viral hepatitis. Mean (SEM) of the maximal suppression of production of lymphocyte activating factor of patients during the acute phase of the disease is shown. Supernatants of aluminium hydroxide stimulated cultured monocytes were tested for phytohaemagglutinin comitogenic activity on mouse thymocytes. Tritiated thymidine incorporation (cpm) is given. Hepatitis A (n=15), hepatitis B (n=5, nine determinations), control subjects (n=12).

TIME COURSE OF LYMPHOCYTE ACTIVATING FACTOR PRODUCTION DURING ACUTE VIRAL HEPATITIS

Production of lymphocyte activating factor during the first week of symptomatic hepatitis A was severely depressed and increased gradually during the further course of the disease (fig 2). In symptomatic acute hepatitis B lymphocyte activating factor production was also diminished during the first week, but was found to be substantially higher than that seen in hepatitis A ($p<0.0005$). In both forms of acute viral hepatitis, lymphocyte activating factor production increased gradually as time went on but did not reach normal concentrations within the first three weeks after onset of the disease.

Fig 2 Production of lymphocyte activating factor of aluminium hydroxide stimulated monocytes during the first three weeks after onset of symptoms of acute viral hepatitis and assayed for phytohaemagglutinin comitogenic activity. Lymphocyte activating factor production is expressed as mean (SD) percent of the mean lymphocyte activating factor production (mean cpm in phytohaemagglutinin comitogenic assay) of healthy controls. Hepatitis A ($n=15$) compared with hepatitis B ($n=5$, nine determinations): week 1, $p<0.0005$; week 2 and 3, not significant.

CORRELATION OF PRODUCTION OF LYMPHOCYTE ACTIVATING FACTOR WITH ACUTE PHASE REACTANTS AND OTHER LABORATORY PARAMETERS

The absent or only mild changes in acute phase reactants, as documented by their peak values during the course of the disease, are shown in table 1. Serum concentrations of α_1 antitrypsin, an acute phase reactant known to be moderately raised during acute hepatitis A and B,^{15 19} and of C reactive protein, found to be increased to a low degree in most cases of acute hepatitis A,¹⁴ but infrequently in the course of acute hepatitis B, varied independently of lymphocyte activating factor production. Similarly, other parameters of acute phase response were either not raised, such as leucocyte and lymphocyte counts and α_2 globulin fraction, or only moderately increased (erythrocyte sedimentation rate) (table 1) and did not correlate with lymphocyte activating factor production. In addition, serum concentrations of bilirubin and aspartate aminotransferase and alanine aminotransferase activities varied independently of lymphocyte activating factor production.

Discussion

We have shown a reduced in vitro production of

lymphocyte activating factor of peripheral blood monocytes derived from children with acute viral hepatitis. In particular, lymphocyte activating factor activity, which could be taken as one of the several known biologic activities of interleukin-1, was severely depressed in acute hepatitis A and to a lesser extent in the small number of patients with hepatitis B investigated, as compared with healthy controls. In both forms of acute viral hepatitis production of lymphocyte activating factor was lowest during the first week of symptomatic illness while impairment was less pronounced during the further course of the disease, but did not reach normal concentrations within the observation period—that is, three weeks after onset of symptoms.

We used the immunoadjuvant aluminium hydroxide as a macrophage stimulant for interleukin-1 production because we have found it to be an inert and reliable interleukin-1 inducer.¹⁸ Furthermore, in using aluminium hydroxide, we circumvent the abnormal reactivity described for other interleukin-1 inducers—that is lipopolysaccharide in the setting of certain hepatic injuries.²⁰

The reduced activity of lymphocyte activating factor in supernatants of aluminium hydroxide stimulated peripheral blood monocytes derived from patients with acute hepatitis A or B may be the consequence of a number of different underlying mechanisms, one of them being direct viral infection of the cells involved in lymphocyte activating factor production. Recently, hepatitis B virus also has been shown to infect cells of bone marrow origin,^{21–23} and a decreased production of interleukin-1 by infected monocytes has been shown as a functional consequence in vitro.²⁴ While infection of peripheral blood mononuclear cells is possibly the reason for the diminished interleukin-1 production in hepatitis B, it is less likely to be the cause in hepatitis A. Although hepatitis A virus infection of white blood cells has not been shown yet, one report, however, describes hepatitis A antigen in abdominal lymph nodes, the spleen, and the kidney²⁵; this suggests that cells other than hepatocytes may be infected with hepatitis A virus. Infection of macrophages by viruses other than hepatitis has been shown to result in reduced macrophage function; this results in depressed phagocytosis and oxidative metabolism, phagosome-lysosome fusion, and killing.²⁶ There will also be impaired antigen handling and presentation in HIV infection^{27 28} or a depressed lymphocyte proliferative response to mitogens as a result of a primary alteration of monocyte accessory cell function after infection with influenza A virus.²⁹ Direct viral infection of monocytes, however, is not necessarily accompanied by reduced interleukin-1 production,

as monocytes infected with influenza A virus in vitro³⁰ and monocytes infected with HIV in vivo³¹ showed enhanced production of interleukin-1.

Activity of lymphocyte activating factor in culture supernatants of monocytes may also be reduced because of an increased secretion of prostaglandin E₂, which in turn could inhibit interleukin-1 release. This mechanism seems to be the cause for the reported diminished interleukin-1 activity in monocyte culture supernatants of patients with liver cirrhosis and hepatocellular carcinoma.³² In these patients an increased prostaglandin E₂ secretion by monocytes was found, and indomethacin treatment of monocytes during culture restored interleukin-1 production.³³ Even though decreased interleukin-1 production in patients with chronic liver disease was related to the degree of liver cell function³⁴ this finding did not hold true for our patients with acute viral hepatitis: we did not observe any correlation with parameters of liver cell necrosis, impaired hepatic clearance, or protein synthesis by the liver.

In addition interleukin-1 inhibitor secretion, which has been described recently,³⁵ could also result in diminished interleukin-1 activity in monocyte supernatants. This inhibitor activity has been reported to be present in culture supernatants of monocytes infected with influenza A virus³⁰ and shown to be the cause of deficient interleukin-1 production in cytomegalovirus infected monocytes as well.³⁶

During the first week of symptomatic disease, children with acute hepatitis A showed a more severe depression of interleukin-1 production by their peripheral blood monocytes than children with acute hepatitis B. This finding could either be the result of a true difference in interleukin-1 production between these two forms of acute hepatitis or could mirror a different time kinetic inasmuch as the incubation time until the beginning of the symptomatic phase of the disease is shorter in hepatitis A than in hepatitis B¹⁰ and the time point of maximal depression of interleukin-1 production could be before the onset of symptomatic disease in hepatitis B. The gradual improvement of interleukin-1 production during the course of acute viral hepatitis points to a mechanism of interleukin-1 depression that is independent of liver cell function. This is illustrated by a slightly protracted course of hepatitis A in two children who nevertheless showed an increase in interleukin-1 production towards normal in the third week after onset of symptoms despite still raised serum aminotransferase activities.

Interleukin-1 has an important helper activity for lymphocyte activation.³⁷⁻³⁹ Reduced interleukin-1 production by peripheral blood mononuclear cells might explain, at least in part, some of the defective

immune functions seen during acute viral hepatitis, for example, a reduced lymphocyte transformation in response to phytohaemagglutinin and concanavalin A.⁴⁰⁻⁴²

In addition to its well known immunoregulatory function interleukin-1 is the principal mediator of the acute phase response in infectious diseases and inflammatory processes, inducing fever, leucocytosis, depressed serum iron and zinc concentrations, and a dramatic increase in the synthesis of hepatic acute phase proteins.² In contrast with most infectious diseases, acute viral hepatitis is characterised by a lack, or only a moderate degree of acute phase reaction,¹⁰ especially in children.^{11 12} This was documented also in our patients as a lack of increase of acute phase reactants in acute hepatitis B and as an only moderate increase in hepatitis A.¹⁶ A reduced interleukin-1 production by peripheral blood monocytes in acute viral hepatitis, as shown in our study, could well be one of the reasons for the modest acute phase response during the symptomatic phase of the disease. Other explanations for a blunted acute phase response could be a reduction in hepatic interleukin-1 receptors⁴³ during acute viral hepatitis or direct alteration of protein synthesis in infected hepatocytes, which in this way become unable to mount an acute phase response.

In summary, during the acute phase of viral hepatitis in children peripheral blood monocytes show a reduced ability to produce interleukin-1. This finding could explain the well known fact that the acute phase response is only moderate during these diseases.

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