fall was due to a reduction in stillbirths. Further analyses indicated that only a third of this reduction could be attributed to the changes in parity, age, and social class of the mothers.⁵ Thus it seems reasonable to conclude that the remainder of the reduction was a function of either improved health and diet in the general population or changes in obstetric and paediatric practice. Further analysis of all births in which the infant weighed more than 2000 g (table VI) showed that whereas the neonatal death rate fell proportionally at the same rate whether the labour was induced or of spontaneous onset, the stillbirth rate fell most among the induced cases.

Discussion

Obviously interpreting data on induction is difficult because the populations of women who undergo induction and those who do not are not strictly comparable. The former group contains more women with abnormalities such as diabetes, pre-eclampsia, heart disease, and poor obstetric history, whereas the non-induced group will include infants born at very early gestation.

As the prevalence of induction increased over the period, the group of women being induced would probably have been, on average, slightly less at risk. The non-induced group would probably also have become gradually more and more "fit." Thus merely by increasing the chance of induction one would

expect the perinatal mortality rate to fall in both non-induced and induced groups, though not overall.

That there has been an overall fall in perinatal mortality can be explained partly by a reduction in the proportion of high-risk elderly women and those of high parity and low social class, but changes in obstetric practice may also have caused an overall reduction, especially in stillbirths.

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References

- ¹ Fedrick, J, in press.
- ² Acheson, E D, *Medical Record Linkage*. London, Oxford University Press, 1969.
- ³ Baldwin, J A, *Proceedings of the Royal Society of Medicine*, 1972, **65**, 237.
- ⁴ Chalmers, I, *et al*, *British Medical Journal*, 1976, **1**, 735.
- ⁵ Fedrick, J, and Yudkin, P, in preparation.

e Antigen in acute hepatitis B

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Summary

To examine the association between e antigen and hepatitis-B surface antigen (HBs Ag) we studied 90 inpatients with acute viral hepatitis type B. e Antigen was present in 24 of the patients; these patients had detectable levels of HBs Ag for significantly longer than the 66 with no e antigen in their serum. The HBs Ag subtypes D (adw) and Y (ayw) were similarly distributed among patients with e antigen and among those without, and no differences in the results of biochemical liver function tests were observed between the two groups during the acute phase of illness. Three of the five patients who developed clinical and histological signs of chronic liver disease were positive for e antigen, a finding which supports the hypothesis that e antigen has a prognostic value in hepatitis B.

Introduction

In 1972 new immunological specificities closely related to the synthesis of hepatitis B surface antigen (HBs Ag) were identified.¹ One of the specificities in this new antigen-antibody system

was designated e. Unlike the determinants of HBs Ag described by Le Bouvier,² e was not a surface component of HBs Ag but represented another distinct antigen carried on free particles physicochemically different from HBs Ag. Further characterisation of e antigen indicated that it had a considerably lower molecular weight than HBs Ag, and, in contrast to HBs Ag, the e antigen was not a lipoprotein, as judged from its buoyant density and non-staining with lipid stains.³ Clinical studies showed that the e antigen was commonly associated with HBs Ag-positive chronic liver disease after hepatitis B.⁴⁻⁶

We report here the results of studies designed to assess the significance of the e antigen in inpatients with acute hepatitis-B infection.

Patients and methods

We studied 90 patients with HBs Ag-positive acute hepatitis who were admitted to the clinic for infectious diseases, East Hospital, Göteborg, from July 1972 to July 1973. Viral hepatitis was diagnosed on the basis of raised aminotransferase levels (at least 10 times the upper limit of normal). Only patients admitted within 10 days after the onset of illness (first appearance of dark urine) were included.

In most cases liver biopsy was not performed, but the diagnosis was histologically confirmed in 30 patients.

All patients received the same treatment, which included a stay in hospital during the period of overt jaundice. Follow-up with repeated biochemical tests of liver function about every two weeks was continued until the values became normal. Corticosteroids were given to 14 patients because of prolonged nausea and vomiting. They initially received 30 mg of prednisolone daily, but this was gradually reduced by about 5 mg a week.

HBs Ag was determined by immunodiffusion and immunoelectrophoresis (IEOP) in parallel, as described.⁷ HBs Ag was subtyped as described elsewhere.⁸ e Antigen and e antibodies were determined by immunodiffusion as described by Magnius and Espmark.¹ The e reagents used have been described in another report.³

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To assess liver function serum concentrations of the following substances were measured: bilirubin, alkaline phosphatase, alanine aminotransferase (SGPT), and aspartate aminotransferase (SGOT); thymol turbidity and galactose tolerance were also assessed. The methods and normal values have been described elsewhere.⁷

Results

The e antigen was shown during the acute phase of illness in 24 patients (27%). Precipitating antibodies against the e antigen (anti-e) were not found in any patient. Seven (29%) of the patients with demonstrable e antigen in serum had subtype D (adw) of HBs Ag and the rest had subtype Y (ayw). A similar distribution of HBs Ag subtypes D and Y was found in patients without demonstrable e antigen (table I).

TABLE I—Persistence of HBs Ag in serum and distribution of HBs Ag subtypes (D and Y) in patients with hepatitis B positive and negative for e antigen. Results are numbers (percentages) of patients

Patients	No studied	Subtype of HBsAg		Persistence of serum HBs Ag		
		D (adw)	Y (ayw)	<6 weeks	>6 months	Not followed
e positive	24	7 (29%)	17 (71%)	10 (42%)	3 (13%)	3 (13%)
e negative	66	18 (27%)	48 (73%)	54 (82%)	2 (3%)	4 (6%)
Total	90	25 (28%)	65 (72%)	64 (71%)	5 (6%)	7 (8%)

In 83 patients regular analyses for HBs Ag were performed every two to three weeks until the antigen was no longer demonstrable or for at least 15 weeks. Four weeks after onset of illness HBs Ag was still demonstrable in the serum in 62% of patients positive for e antigen but only 23% of those negative for e antigen ($P < 0.05$) (see fig). HBs Ag persisted for more than 6 months in the serum of three e-positive and two e-negative patients (table I). The remaining 78 patients all became HBs Ag-negative and had normal liver function within four months of the onset of illness.

Persistence of HBs Ag after onset of illness in 83 patients with acute viral hepatitis (21 e positive and 62 e negative). Percentage of patients still HBs Ag-positive at each week is shown.

Serial liver biopsies in the five patients in whom serum HBs Ag persisted for over six months showed histological findings consistent with chronic persistent hepatitis⁸ in four cases (two e positive) and chronic aggressive hepatitis⁹ in one patient, who was also positive for e antigen.

Four patients positive for e-antigen (17%) received corticosteroids during the acute stage of their illness. The corresponding number of corticosteroid-treated patients among those who were negative for e antigen was 10 (15%). One of the five patients who showed persisting serum HBs Ag had received initial corticosteroid treatment.

The maximal levels of serum bilirubin and SGPT during the acute phase of illness were similar in both groups of patients (table II).

TABLE II—Maximal levels of serum bilirubin and SGPT and period of raised SGPT levels in 24 patients positive for and 66 patients negative for e antigen

Patients	Mean maximal level (range) of:		No (%) with abnormal SGPT levels for:		
	Serum bilirubin ($\mu\text{mol/l}$)	SGPT	≤ 3 months	> 3 months	Not followed-up
e positive	174 (33-640)	1260 (640-2010)	8 (33%)	3 (13%)	3 (13%)
e negative	161 (31-436)	1220 (350-2800)	34 (52%)	5 (8%)	4 (6%)

Conversion: SI to traditional units—Bilirubin: $1 \mu\text{mol/l} \approx 0.058 \text{ mg/100 ml}$.

Discussion

Serum e antigen is highly prevalent among patients who develop HBs Ag-positive chronic liver disease after an acute attack of hepatitis B.⁴ Our results indicate that serum e antigen is also found during the acute phase of hepatitis B in some patients who later develop chronic liver disease. This finding supports the suggestion that the presence of e antigen has a prognostic value in assessing the clinical course of hepatitis B.^{5,6} Nielsen *et al*⁵ found clinical and biochemical differences between e-positive and e-negative patients with hepatitis B. Those positive for e antigen had lower levels of serum bilirubin and aminotransferases than the others. But among our patients, all of whom had hyperbilirubinaemia, there were no differences in the maximal levels of serum bilirubin or aminotransferases between the two groups. The assay for demonstrating e antigen (immunodiffusion) has a rather low sensitivity. Consequently the demonstration of e antigen depends on relatively high serum levels. With a more sensitive technique it might have been possible to show serum e antigen during the acute phase of the illness in most of the patients in these two series.

HBs Ag subtypes D (adw) and Y (ayw) were similarly distributed among patients with serum e antigen and those without. Thus no inherent biological differences could be attributed to the different subtypes D and Y, which, apart from their apparent values as epidemiological markers, seem to be of less clinical importance.

On average the patients with hepatitis B and serum e antigen were HBs Ag-positive (with the IEOP method) for longer than the patients without detectable e antigen. Even when those who became chronic carriers of HBs Ag were excluded the difference was statistically significant ($P < 0.05$). Thus, demonstrating e antigen in the serum of patients during the acute phase of their illness might indicate not only that they are at increased risk of developing chronic liver disease but probably also that they will face a longer period of contagiousness.

Little is known about the individual clearance of HBs Ag from the serum of e-positive and e-negative patients. The persistence of HBs Ag in patients positive for e antigen might be explained by the existence of a less efficient immune response compared with those who are negative for e antigen. Another possibility is that high initial titres of HBs Ag in patients with e antigen, possibly after a large infective dose of hepatitis B virus, may be associated with a longer period of HBs Ag-positivity in these patients.

Available data suggest a correlation between the e antigen and the Dane particle. Dane particles are present in many HBs Ag-positive people with immunological deficiencies, such as those on haemodialysis.¹⁰ The presence of Dane particles in patients with acute hepatitis B also seems to point towards a subsequent development of chronic liver disease in some cases.¹¹ This agrees with the finding of e antigen in patients on haemodialysis and those with chronic liver disease. This correlation may not be absolute, however, since Sheikh *et al*¹² recently found a limited number of Dane particles in sera containing anti-e.

It is tempting to relate the occurrence of anti-e in healthy persistent carriers of HBs Ag the observation that Dane particles are not found in such individuals.¹¹ The specific agglutination of

Dane particles and tubules by sera containing anti-e with immune electron microscopy¹³ might also be a significant finding in this respect. The determination of DNA polymerase as a marker for the Dane particle provides further support for the suggested association between the e antigen and the Dane particle. In a series of patients from an institution for the mentally retarded a close correlation was found between the presence of serum e antigen and the presence of the Dane particle associated DNA polymerase. Conversely, a correlation was found between lack of DNA polymerase and presence of anti-e.¹⁴

If the e antigen turns out to be a constituent of the Dane particle it would not represent the core antigen since patients with e antigen have high serum levels of core antibodies.¹⁵ Furthermore, free core antigens have not been found in the serum of patients with acute or chronic hepatitis-B infection. The e antigen, however, may represent the DNA polymerase protein for which so far no immunological specificity has been determined. Another possibility is that the e antigen represents a matrix protein that links the core antigen to the HBs Ag of the Dane particle. Nevertheless, as suggested previously,^{6 12} it is not

excluded that the e antigen is produced as a specific host response to the replication of the hepatitis B virus.

References

- ¹ Magnius, L O, and Espmark, J Å, *Immunology*, 1972, **109**, 1017.
- ² Le Bouvier, G L J, *Infectious Diseases*, 1973, **123**, 671.
- ³ Magnius, L O, *Clinical and Experimental Immunology*, 1975, **20**, 209.
- ⁴ Magnius, L O, and Iwarson, S, at 13th Interscience Conference on Antimicrobial Agents and Chemotherapy, Washington DC, 19-21 September 1973, Abstract.
- ⁵ Nielsen, J O, Dietrichson, O, and Juhl, E, *Lancet*, 1974, **2**, 913.
- ⁶ Magnius, L O, et al, *Journal of the American Medical Association*, 1975, **231**, 356.
- ⁷ Iwarson, S, *Scandinavian Journal of Infectious Diseases*, 1973, **5**, suppl No 7.
- ⁸ Iwarson, S, et al, *British Medical Journal*, 1973, **1**, 84.
- ⁹ Bianchi, L, et al, *Lancet*, 1971, **1**, 333.
- ¹⁰ Couleru, O, et al, *Nouvelle Presse Médicale*, 1973, **2**, 1633.
- ¹¹ Nielsen, J O, Nielsen, M H, Elling, P, *New England Journal of Medicine*, 1973, **288**, 484.
- ¹² Sheikh, N E L, et al, *British Medical Journal*, 1975, **4**, 252.
- ¹³ Neurath, A R, et al, *Hepatitis-Scientific Memoranda*, H-946, 1975.
- ¹⁴ Nordenfelt, E, *Läkartidningen*, 1975, **72**, 3411.
- ¹⁵ Hoofnagle, J H, and Magnius, L O, 1974, unpublished data.

Neutrophil pyruvate kinase deficiency with recurrent staphylococcal infections: first reported case

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Summary

A woman with an intracellular killing defect in the neutrophils had neutrophil pyruvate kinase deficiency. She had had recurrent staphylococcal infections throughout her life. The enzyme present was unstable and its kinetics were abnormal.

Introduction

Defective bacterial killing by neutrophils is increasingly becoming recognised as a cause of recurrent bacterial infections. X-linked chronic granulomatous disease is the best known of these non-specific primary immunodeficiencies.^{1 2} Neutrophils from such patients do not increase their oxygen consumption or glucose metabolism after phagocytosis, do not produce hydrogen peroxide or superoxide, and fail to reduce nitroblue tetrazolium (NBT).³ Most patients with chronic granulomatous disease have recurrent abscesses affecting the skin, lymph nodes, lung, bone, and liver, and many die in childhood.^{1 2} Their infections are predominantly with coagulase-positive staphylococci and fungi. There are several variants of chronic granulomatous disease, some of which occur in female patients. They are summarised below.

Glucose-6-phosphate dehydrogenase (G6PD) deficiency	Male patients ⁴
G6PD instability	Female patients ⁵
	Male patients ⁶

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Reduced nicotinamide-adenine dinucleotide (NADH) oxidase deficiency	Male patients ⁷
Glutathione peroxidase deficiency	Female patients ⁷
Job's syndrome	Female patients ⁸
Lipochrome histiocytosis	Female patients ^{9 10}
	Female patients ¹¹

Patients with these disorders fail to reduce NBT normally; however, those with Job's syndrome (red-haired, fair-skinned girls with cold abscesses) are a mixed group, some having normal NBT reduction,¹² and some failure of reduction.¹⁰

One mechanism for the intracellular killing of bacteria seems to depend on the interaction of hydrogen peroxide with the enzyme myeloperoxidase and a halide.¹³ Myeloperoxidase deficiency has been described.¹⁴ These patients reduce NBT normally and only occasionally have a measurable defect in bacterial killing.

We report here a deficiency of neutrophil pyruvate kinase associated with an intracellular killing defect in the neutrophils. This has not been described before. The patient had recurrent staphylococcal infections throughout her 31 years of life and reduced NBT normally.

Case history

The patient, born in February 1944, was the first child of previously unrelated parents. She was of above average intelligence and worked as a needlework instructress. In her first week of life she had a septic finger. Infected eczema developed at 3 weeks and lasted until she was four years of age. She then had a series of staphylococcal boils and abscesses occurring about once a month; some episodes were severe, with infection in the right knee, left mastoid, and perineum. One abscess in the neck discharged for six months. She had staphylococcal pneumonia when 6, 8, and 12 years old. The last attack was followed by a staphylococcal empyema that required rib resection and discharged for about nine months. At the age of 13 she developed staphylococcal osteomyelitis of the lumbar spine with a paravertebral abscess. A sinus in her left loin subsequently discharged for three years. During childhood she had had measles, rubella, chickenpox, and whooping cough, and had recovered normally from each of these.

She continued to have staphylococcal abscesses about once a month until 29 years of age, when she started taking flucloxacillin 250 mg twice a day prophylactically. In the next 18 months she had only two further abscesses.