Increasing age—an important adverse prognostic factor in hepatitis A virus infection

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Acute hepatitis A virus infection is usually regarded as a relatively benign disease of children and young adults, and fulminating hepatic failure is a rare complication [1]. In the Liver Failure Unit at King’s College Hospital only 15 such cases have been proven in British residents during a three-and-a-half-year period. The median age of these patients was 40 years (range 13-58 years; 25-75 per cent interquartile 27-46 years). This raised the possibility that increasing age might be related to a more severe and/or fulminant course after exposure to this virus, and prompted an analysis of deaths from acute hepatitis A in relation to age.

Prior to 1987, the Office of Population Censuses and Surveys (OPCS) for England and Wales did not maintain separate records for the frequency of notifications of hepatitis A, but it is likely that the great majority of notified episodes of infective jaundice will have been due to this virus [1] and that collected data will reflect the true incidence of hepatitis A.

Since 1979, the OPCS has however recorded mortality statistics specific to hepatitis A. Although the IgM antibody test, by which diagnosis of acute infection is confirmed [2], was not widely available in the earlier of these years, it is unlikely that a positive diagnosis of mortality from hepatitis A will have been recorded on death certificates without strong circumstantial evidence. Since the option for certifying death from unspecified viral hepatitis has remained, it is likely that national figures for hepatitis A deaths underestimate the true frequency, but there is no reason to infer a systematic bias.

We report here the mortality from hepatitis A in relation to age in patients referred to the Liver Failure Unit and as recorded in national statistics.

Materials and methods

Fifteen consecutive patients normally resident in Britain presented to the Liver Failure Unit over a 42 month period with fulminant hepatic failure (as defined by Trey and Davidson [3]) secondary to hepatitis A. The 15 patients (six male) had a median age of 40 years (range 13-58 years) and had been ill for a median of eight days prior to referral (range 4-42 days) (Table 1). All patients had IgM antibody to the hepatitis A virus (Abbott Labs: HAVAB-M) confirming acute infection with this agent [2]. All but two patients had recently eaten shellfish or travelled abroad. Marked hepatic encephalopathy and severe abnormalities of liver function occurred in all 15 patients (Table 1). Clinical management was not influenced in any way by the patient’s age and all were treated with full supportive measures, including invasive haemodynamic monitoring. Seven patients had oliguric renal failure, requiring haemodialysis in five, and nine patients suffered cerebral oedema which was treated [4] by hyperventilation and mannitol (with ultrafiltration in the five on haemodialysis) (Table 1). No patient had severe acidosis (pH < 7.3).

Table 1. Clinical characteristics of patients admitted to the Liver Failure Unit with fulminant hepatitis A.

| Case | Age (years) | Duration of symptoms (days) | INR | ARF | HD | Cerebral Edema Survived |
|------|-------------|-----------------------------|-----|-----|----|------------------------|
| 1 M  | 18          | 8                           | 1.4 | -   | -  | +                      |
| 2 F  | 22          | 27                          | 13.3| -   | -  | +                      |
| 3 F  | 42          | 4                           | 3.1 | -   | -  | +                      |
| 4 F  | 13          | 9                           | 5.4 | -   | -  | +                      |
| 5 M  | 40          | 8                           | 4.7 | +   | +  | +                      |
| 6 F  | 50          | 42                          | 2.6 | +   | +  | -                      |
| 7 F  | 58          | 7                           | 4.4 | -   | -  | -                      |
| 8 F  | 37          | 6                           | 6.1 | +   | +  | -                      |
| 9 M  | 43          | 10                          | 5.4 | +   | +  | -                      |
| 10 M | 40          | 20                          | 6.4 | +   | +  | +                      |
| 11 F | 46          | 5                           | 2.6 | -   | -  | -                      |
| 12 M | 51          | 7                           | 4.5 | -   | -  | -                      |
| 13 F | 47          | 7                           | 13.8| +   | -  | -                      |
| 14 F | 23          | 7                           | 3.7 | -   | -  | +                      |
| 15 M | 27          | 11                          | 3.2 | +   | -  | +                      |

INR: international normalised (prothrombin) ratio; ARF: acute oliguric renal failure; HD: haemodialysis required.

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The incidence of infective hepatitis and the mortality from hepatitis A in England and Wales during the years 1979-85 were collated from OPCS documentation [5,6], and cumulative deaths from the entire seven year period were summated for individuals belonging to each of the age bands for which equivalent incidence data can be retrieved.

Statistical analysis was by the Mann–Whitney ‘U’ test.

Results

Seven (two male) of the 15 patients referred to the Liver Failure Unit died (Table 1). Their median age was 47 years (range 22–58 years) compared to a median of 33.5 years (range 13–46 years) in the eight survivors; despite the small numbers, the difference in age is statistically significant ($p<0.03$). The surviving patients had slightly lower peak prothrombin ratios, had been ill for a shorter time before being referred to the liver unit, and had less renal impairment, but none of these differences neared statistical significance.

Table 2. Age and sex of recorded deaths from hepatitis A: 1979–1985 (OPCS data).

| Age (years) | Male | Female | Total |
|-------------|------|--------|-------|
| 0–4         | 4    | 6      | 10    |
| 5–9         | 2    | 2      | 4     |
| 10–14       | 2    | 2      | 4     |
| 15–19       | 1    | 3      | 4     |
| 20–24       | 1    | 0      | 1     |
| 25–29       | 3    | 1      | 4     |
| 30–34       | 2    | 0      | 2     |
| 35–39       | 2    | 1      | 3     |
| 40–44       | 2    | 3      | 5     |
| 45–49       | 2    | 1      | 3     |
| 50–54       | 5    | 2      | 7     |
| 55–59       | 3    | 5      | 8     |
| 60–64       | 13   | 3      | 16    |
| 65–69       | 10   | 6      | 16    |
| 70–74       | 7    | 5      | 12    |
| ≥75         | 12   | 17     | 39    |
| **Total**   | 71   | 67     | 138   |

The approximate annual frequency of notifications of infective jaundice was 6,500 (≈12 per 100,000 population) for each of the years 1979–85 and the median age of notification lay between 20 and 24 years (Fig. 1).

Cumulative mortality data for England and Wales for the years 1979–85 record 140 deaths from hepatitis A ($\approx 0.04$ per 100,000 per annum) with age at death recorded in 138 cases (Fig. 1 and Table 2). The male: female ratio was 1.06:1. In five of the seven years the median age of these individuals exceeded 60 years, and in 1984 five of the 11 deaths were in patients aged 70 years or more. The ratio of deaths from hepatitis A to the notifications of infective jaundice rose progressively, and approximately logarithmically, with increasing age (Fig. 2).

Data from national statistics and from a referral centre seeing a particular subgroup of affected patients indicate that clinically apparent hepatitis A is substantially more likely to prove fatal with increasing age.

Discussion

We have demonstrated an increased fatality from hepatitis A with increasing age in the general population and in a highly selected group of patients presenting with fulminant hepatic failure. This has not previously been brought to the attention of physicians, although hepatitis A is generally considered a more serious condition in adults than in children and geriatricians are beginning to recognise a graver prognosis in their patients [7,8,9]. Our conclusions must be treated with some caution, first because the notifications of infective hepatitis represent only a proportion of all cases of acute hepatitis A and include some with non-A infection, and second because our mortality analysis has included only deaths specifically attributed to hepatitis A. However, if mortality for all causes of non-B viral hepatitis (the only other available infective coding for hepatitis deaths) is considered in relation to reported ages at death, the major conclusion remains unaltered.
The frequency of notified infective jaundice in England and Wales is greater in men than women (male:female ratio 1.4:1), but the sex ratio was much nearer unity amongst nationally reported deaths from hepatitis A and skewed towards females in the non-survivors treated in the Liver Failure Unit (ratio 0.4:1). This may be a reflection only of the age/sex profile of infected individuals since the data suggest that, with increasing age, there will be proportionately fewer non-immune males, but it remains possible that the female sex is independently linked to a poorer outcome.

These findings are important because the proportion of healthy blood donors who are immune to hepatitis A (ie positive for IgG antibodies to the virus) is decreasing in London. In 1977, 47 per cent of 174 thirty- to fifty-year-olds were immune, while by 1985 only 32 per cent of 123 subjects of the same age had antibodies [10].

It has been shown [11,12] that antibody screening for hepatitis A in the UK is now more cost-effective than ‘blind’ use of gamma-globulin in prophylaxis, and the same will presumably obtain when the long-awaited hepatitis A vaccine [13,14] becomes generally available. This should not be allowed to draw attention away from our findings which indicate that the individuals most at risk of a serious outcome from hepatitis A infection are those aged over 30. Without an effective active immunisation programme specifically directed at this age group, it is essential that middle-aged and elderly travellers are screened for antibody (and given gamma-globulin as appropriate) if a major increase in the frequency of serious morbidity and mortality from hepatitis A is to be avoided.

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