Identifying a hepatitis B outbreak by molecular surveillance: a case study

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Infection outbreaks are usually recognised when an unexpectedly high number of cases of a clinical illness are observed. With hepatitis B infection, the incubation period is long and a substantial proportion of infected people—especially children and the immunocompromised host—may remain asymptomatic.^{1–3} These factors increase the risk of prolonged and unrecognised outbreaks. Denmark has not implemented universal childhood hepatitis B immunisation, and vaccination is not required for health workers performing invasive procedures.

Phylogenetic analysis of hepatitis B virus have been used to investigate recognised outbreaks,^{4 5} to reject or confirm suspected chains of transmission,⁶ and to prove unusual reservoirs or routes of infection.^{7 8} We present the unravelling of an outbreak of asymptomatic hepatitis B on a paediatric ward after the incidental identification of a single case of hepatitis B. The recognition and subsequent halting of the spread of this outbreak were possible owing to the availability of a DNA sequences library compiled from patients with hepatitis B in the locality.⁹

Case description

During preparation for bone marrow transplantation, a child was diagnosed with an acute asymptomatic hepatitis B infection at the paediatric haematology and oncology department at Odense University Hospital. Screening for hepatitis B had been negative two years previously, and serology testing and polymerase chain reaction in repository blood donation samples and follow-up samples from all involved blood donors were negative for the virus. The patient had had no contact with known hepatitis B cases during the suspected incubation period.

As part of a research programme, strains of the hepatitis B virus consecutively detected in the area had been partially sequenced. The patient's sequence (the hepatitis B epi strain) was identical to that of a known hepatitis B carrier who had been admitted to the ward 14 months earlier but to whom our case had no connection in time or place. It was suggested that more cases might therefore be involved in the transmission, and an outbreak investigation was launched.

Molecular epidemiology may identify hospital based outbreaks quickly by revealing unsuspected transmission routes

Ward description

The 10 bed ward served as the paediatric haematology and oncology centre of southern Denmark. Patients needing multiple infusions or intravenous chemotherapy had a central venous catheter inserted, and the catheters were used for blood sampling whenever possible. Handling of central venous catheters was described in written instructions that complied with universal precautionary measures. All intravenous injections and infusions were administered on the ward.

Cancer chemotherapy and blood components were delivered ready for infusion to the ward's drug preparation room, where all other intravenous medications were prepared. Saline and heparin aspirated from multidose phials in the preparation room were used when central venous catheters were flushed and sealed. Aspiration needles were not left in these phials.

Patients admitted with a malignant illness were screened for hepatitis B infection at first admission but with no routine follow-up.

Outbreak investigation

EDTA plasma was analysed for hepatitis B surface antigen and for antibodies to hepatitis B core antigen (AxSYM series assays, Abbott Diagnostic Division,

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Germany). DNA was isolated, and part of the hepatitis B virus S gene was amplified, sequenced, and subjected to phylogenetic analysis as described previously.⁹

The hospital's infection control team investigated ward facilities and procedures involving contact with blood, body fluids, and secretions. The investigations covered blood sampling; handling and maintenance of intravenous catheters; intravenous medications and transfusions; and disposal of material contaminated with blood, body fluids, or secretions.

Hepatitis B testing was offered to patients admitted in the period from the source patient's initial admission until procedures were corrected. In addition, members of the infected patients' households and staff were surveyed, and susceptible individuals were vaccinated.

We reviewed hospital records of infected patients. Data on age, sex, diagnosis, treatment (including insertion of central venous catheters), and dates of admissions and discharges were retrieved from the hospital database in all patients.

Results

We identified 175 patients, of whom we excluded the source and index patients, a patient who had already been infected with hepatitis B, 15 patients who died of their malignancy, and two patients lost to follow-up. Of the remaining 155 patients, 133 (86%) accepted screening. Unscreened patients had a single hospital stay of short duration and, except for one patient, had not had a central venous catheter inserted.

Apart from the index and source patients, seven patients and two relatives were HBsAg positive. One patient (receiving immunoglobulin substitution) and a sibling (without risk factors for hepatitis B) of another patient had antibodies to hepatitis B core antigen and to hepatitis B surface antigen. No staff member was infected. The hepatitis B epi strain was isolated from six of the patients; the other patient and the two relatives had unrelated strains and had (previously unknown) chronic hepatitis B infection—probably related to the fact that these three individuals had been born and raised in areas with a high prevalence of hepatitis B. Hence the outbreak consisted of the source patient and seven definite and two possible cases. All case patients remained positive for hepatitis B e antigen during follow-up, and none have had clinical disease.

Hepatitis B infection correlated significantly with the insertion of a central venous catheter (table). Disease category, time of initial admission, age, and sex were unrelated to hepatitis B transmission.

The only identifiable breaches in hygiene were associated with the ward's preparation room, which was used for collecting blood samples, drying bone

marrow smears, and (in periods of overcrowding) occasionally for blood sampling and transfusions, and multidose phials in use were placed next to the disposal pot for used infusion bags and lines, syringes, needles, and blood samples. As both sterile and non-sterile procedures were performed in the preparation room, the infection control team concluded that unintentional contamination of multidose phials and/or other intravenous preparations might have occurred.

Identified hazardous procedures were corrected immediately. The preparation room is now used for sterile procedures only; blood, body fluids, and used equipment are disposed of elsewhere; and single use phials have replaced multidose phials. Since these changes, no new cases of hepatitis B have been identified during active surveillance.

Discussion

To our knowledge, this is the first hepatitis B outbreak to be identified after the recognition of only one asymptomatic case. We began to investigate only because an otherwise unrecognised relation between the index case and a known carrier was established at the molecular level. If this molecular approach had not been available, this outbreak, already affecting 15% of surveyed ward patients with central venous catheters, would have probably propagated unnoticed for a long time. Any new bloodborne viral infection in a high risk setting should therefore raise the suspicion of hospital based transmission. Individual patients' dates of admissions and hepatitis B serology show that viral transmission probably occurred during at least three different time periods.

Although hepatitis B had not been isolated from the ward environment, the implicated route of transmission—on the basis of investigations by epidemiological and infection control teams—was probably central venous catheters and unintentionally contaminated multidose phials and/or other intravenous preparations. Similar transmission modes have been implicated in previous reports on both hepatitis B and less contagious bloodborne pathogens such as hepatitis C, HIV, and *Plasmodium falciparum*.^{4 10–14} Overcrowding and the use of the sterile preparation room as a multifunctional facility are believed to have increased the risk of such unintentional incidents. The implication of such breaches in hygiene is supported by the observed interruption of transmission after the hygiene procedures were improved. This outbreak of asymptomatic hepatitis B was identified by molecular epidemiology, and surveillance at the molecular level may be a valuable tool in reducing hospital based transmission.

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Contributors: All authors helped to collect and analyse the data and prepare the manuscript. LT-S and NF identified the index case as "suspicious," planned and conducted the initial blood donor investigation, and supplied serology results. NF supplied and analysed molecular data. NLTC and AH supplied clinical data retrieved from the hospital database. NLTC reviewed patient files and organised the seroepidemiological

Hepatitis B infection associated with central venous catheters among 131 children on an haematology and oncology ward. Values are numbers (percentages) of children, unless stated otherwise

	Positive for hepatitis B	Negative for hepatitis B	P value*
Central venous catheter			
Ever patients	7 (100)	41 (33)	0.0007
Never patients	0	83 (67)	

* Fisher's exact test.

investigations, which were planned by NF, NLTC, HJK, AH, PBC; HJK conducted hygiene investigations. NF computerised the data. Analysis and interpretation was conducted by NF and agreed on by all authors. NF wrote the initial draft; and NF and PBC revised it. All authors approved the final manuscript. NF is the guarantor.

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Lesson of the week

Opiate toxicity in patients with renal failure

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Opiates and their metabolites are known to accumulate in renal failure, with increased potential for toxicity, the most serious aspect of which is respiratory failure.¹ Despite this knowledge, we continue to see life threatening cases of opiate toxicity in patients with renal failure, two recent examples of which we present below.

Case reports

Case 1

A 68 year old woman with type 2 diabetes, angina, and obesity had an uncomplicated below knee amputation. Baseline creatinine was 133 $\mu\text{mol/l}$ (estimated glomerular filtration rate 36 ml/min).² In the first 36 hours after surgery she received 50 mg of morphine and 76 mg of codeine. On the second day she developed oliguria despite intravenous fluid resuscitation, and her serum creatinine rose to 213 $\mu\text{mol/l}$. She became increasingly drowsy and her respiratory rate fell to 8 breaths/min. Opiate toxicity was suspected after consultation with the on-call nephrologist. She did not respond to 400 μg intravenous naloxone, however, and therefore she was transferred to the regional renal unit.

On admission she was drowsy and uncommunicative. Observations showed oxygen saturation 91% on 28% inspired oxygen; respiratory rate 6 breaths/min; pulse 50 beats/min, and blood pressure 132/68 mm Hg. Pupils were pinpoint. Initial investigations detected sodium 130 mmol/l, potassium 7.6 mmol/l, urea 28.4 mmol/l, creatinine 320 $\mu\text{mol/l}$, pH 7.39, Po_2 7.9 kPa, and Pco_2 5.9 kPa. Electrocardiogram showed no hyperkalaemic changes. We noticed that the cannula previously used to administer naloxone had tissue.

We gave 400 μg of naloxone via a new cannula, and her Glasgow coma scale score improved to 14/15, and her respiratory rate rose to 14 breaths/min. We started a naloxone infusion, which was titrated to maintain her respiratory rate above 12 breaths/min. Her hyperkalaemia was managed conservatively. Within hours her urinary output increased, and in the following days her serum creatinine returned to baseline.

Case 2

A 63 year old woman with end stage renal failure, type 2 diabetes, and ischaemic heart disease was found semiconscious in bed. On the way to hospital she stopped breathing, and on arrival at the emergency department she was in cardiorespiratory arrest. We started cardiopulmonary resuscitation, and we intubated and ventilated her. After 90 seconds of pulseless electrical activity, we obtained cardiac output, and she became haemodynamically stable. Although she was obeying commands and resisting the endotracheal tube, she made no respiratory effort, therefore we sedated and paralysed her, and transferred her to the intensive care unit. Investigations found 17.4 mmol/l blood sugar, pH 7.02, Po_2 23.9 kPa, and Pco_2 9.5 kPa. An electrocardiogram showed a junctional rhythm, rate 50 beats/min, with no ischaemic changes. A chest radiograph was normal.

In the intensive care unit her pupils were noted to be small despite previous atropine and adrenaline administration. It was ascertained that she had been taking four tablets of Distalgesic (32.5 mg dextropropoxyphene hydrochloride and 325 mg paracetamol) a day for back pain for several days. We haemodialysed her for three hours, after which we extubated her. She

Unrecognised accumulation of opiates in patients with renal failure may be life threatening

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