Measles encephalitis during immunosuppressive treatment for acute lymphoblastic leukaemia

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Abstract
Between 1971 and 1989 measles encephalitis was identified in five children receiving chemotherapy for acute lymphoblastic leukaemia. Review of these and previously reported cases of measles encephalitis in immunosuppressed patients failed to identify any pathognomonic features in the history, the clinical presentation, or the results of electroencephalography or computed tomography. Detection of measles virus antigen in nasopharyngeal secretions or intrathecal synthesis of specific antibody was not possible in all instances. Early diagnosis by direct detection of viral antigen in the brain was confounded by difficulties in identifying areas of the brain suitable for biopsy. Increasing herd immunity to measles in the general population by vaccination is the only effective intervention against measles encephalitis in immunosuppressed children. Measles encephalitis must be remembered as a possible explanation of encephalopathy in the immunocompromised child: the benefits of early use of antiviral agents need to be evaluated.

The prognosis of childhood malignancies has improved dramatically in the past 20 years. Acute lymphoblastic leukaemia now has at least a 60% five year disease free survival, but curative chemotherapy and radiotherapy cause major immunosuppression. Infection was the cause of death in 8-3% of one cohort of children with acute lymphoblastic leukaemia, and measles accounted for between 20 and 40% of these deaths. In a more recent study of 51 deaths (29%) among children with acute lymphoblastic leukaemia in clinical remission were attributed to measles.

Encephalomyelitis occurs in one per thousand normal children who develop measles, and between five and 10 children per million contracting measles will develop subacute sclerosing panencephalitis. In immunosuppressed children the risk of developing encephalitis after measles is much greater. Kernaghan et al used a sensitive immunofluorescent antibody technique to detect measles virus antigen in children with malignant disease who developed a fever or respiratory illness. Seventeen cases of measles were identified of whom three developed encephalitis.

A review of patients attending the department of oncology at Royal Manchester Children's Hospital identified 10 cases of measles during the period 1971–89. Five of the children developed encephalitis. We present here the neurological, radiological, and virological findings as an aid to diagnosis and management.

Case reports
Case 1 developed acute lymphoblastic leukaemia at the age of 2-6 years. Her measles immunisation history was not recorded, but there was no history of measles. She was entered into the Medical Research Council UK Acute Lymphoblastic Leukaemia (MRC UKALL) IV trial. After three months' treatment, at which stage she was in clinical remission, she was in contact with measles. Two weeks later she developed coryza, a cough, conjunctivitis, and Koplik's spots followed two days later by a fleeting macular rash. She recovered from this illness without specific treatment. Ten months later she developed ataxia and continuous generalised seizures necessitating treatment with ventilation and anticonvulsants. She became deeply comatose and died 21 days after the onset of her neurological symptoms.

Case 2 developed acute lymphoblastic leukaemia at the age of 7-3 years. He had had neither measles immunisation nor measles. He was entered into the MRC UKALL VIII trial regimen A. Two months after commencing treatment he developed a pyrexial illness with cough and a maculopapular rash.

Three months after this illness, while in clinical remission, he developed left sided weakness. On admission to hospital he was emotionally labile, confused, hypertensive, and had a left hemiparesis. His level of consciousness subsequently declined to deep coma. Seizures also occurred: these were initially partial but became continuous and generalised. He was treated with anticonvulsants, antihypertensives, and intermittent positive pressure ventilation. There was no recovery of consciousness and he died four months after the onset of the neurological symptoms whilst still receiving intensive care.

Case 3 developed acute lymphoblastic leukaemia at the age of 2 years. She was entered into the MRC UKALL VIII trial regimen B. Before the onset of the leukaemia she had received measles immunisation with normal human immunoglobulin because of a previous febrile convulsion. After 22 months of treatment, while in clinical remission, she developed a cough and fever. Parainfluenza virus type 3 was isolated in tissue culture from nasopharyngeal secretions. Four weeks after her respiratory illness she became disinhibited and was noticed to fall to the left. On examination, she had a mild left hemiparesis and bilateral choroidoretinitis. Subsequently her level of consciousness declined and she developed partial seizures that became
generalised and continuous. She was treated with anticonvulsants and intermittent positive pressure ventilation. She became hypotensive with evidence of inappropriate secretion of anti-diuretic hormone. She died two and a half months after the onset of the neurological illness without regaining consciousness.

Case 4 developed acute lymphoblastic leukaemia at the age of 3.3 years. Her measles immunisation and measles history were not recorded. She received treatment according to the MRC UKALL X trial regimen A. Treatment was uncomplicated until, after 23 months of clinical remission, she developed a pyrexial illness with cough and a rash described as being 'raised and pimply'. She had not been known to have any contact with measles. The cause of this illness was not defined, but she did not need any specific treatment or admission to hospital. One month later she developed a mild left hemiparesis and left sided focal seizures. She was treated with anticonvulsants. Subsequently her level of consciousness declined and she required intermittent positive pressure ventilation. She also had evidence of inappropriate secretion of anti-diuretic hormone. Twenty one days after onset of the neurological symptoms there was a deterioration in her respiratory status resulting in difficulty in maintaining oxygenation. She died three days later.

Case 5 developed acute lymphoblastic leukaemia at the age of 3.6 years. He had not received measles immunisation and there was no history of clinical measles. He was treated according to the MRC UKALL X trial regimen B. Five months later his sibling developed measles. The patient was given normal human immunoglobulin but after two weeks developed coryza, a cough, a rash which was described as 'generalised eczematous', and radiological evidence of pneumonitis. During this illness measles virus antigen was detected in nasopharyngeal secretions by immunofluorescence. He was treated with intravenous and aerosolised ribavirin and recovered from the pneumonitis within three weeks. Seven months after the onset of the measles he presented with an unsteady gait and dysphasia. He showed a right hemiparesis and involuntary movements affecting the left arm and leg. He had periods of reduced awareness and seizures with secondary generalisation. Anticonvulsant treatment produced a reduction in seizure frequency and over the subsequent four months there was slow improvement in his mobility, though with retention of language difficulties. He received no further chemotherapy and died of haematological relapse five months after the onset of his neurological signs.

**Results**

**NEUROLOGICAL INVESTIGATIONS**

Computed tomography of the brain was performed on three of the children. The first two scans in case 2 (three and seven days after the onset of the neurological illness) were normal. A repeat scan at 34 days showed cerebral oedema. Scans in cases 3 and 5 (days 17 and seven, respectively, after onset) showed areas of reduced density either in the right basal ganglia or the left parietal area.

Electroencephalography was done on four of the patients (cases 1, 2, 4, and 5) but only non-specific changes were observed. Electroencephalogram (EEG) activity was diffusely slow, often with spikes. In case 2, the EEG was repeated later in the course of the illness when it was flat and featureless.

**VIROLOGICAL INVESTIGATIONS**

Two patients, cases 3 and 4, did not have raised titres of measles antibodies in the last serum available before death (table). The other three patients seroconverted to measles within 10 weeks of the onset of the encephalitis. In cases 1, 2, and 5 measles antibody was detected in the cerebrospinal fluid (CSF). Furthermore, in cases 2 and 5 available data allowed the calculation of an IgG index (CSF:serum ratio of total IgG divided by CSF:serum ratio of albumin) and a specific IgG ratio (CSF:serum ratio of measles specific IgG divided by CSF:serum ratio of total IgG) in an attempt to prove intrahepal synthesis of the antibody rather than its leakage across a damaged blood-CSF barrier.

**POSTMORTEM EXAMINATION**

Permission for necropsy was granted by the parents of two of the children. Case 2 had testicular, bone marrow, and central nervous system relapse of his leukaemia, and both case 2 and case 3 had a subacute encephalitis with measles virus antigen detected in the brain by immunocytochemistry.

**Virological findings**

<table>
<thead>
<tr>
<th>Measles virus antibody*</th>
<th>Serum titre (at onset)</th>
<th>Serum titre (later)</th>
<th>Time elapsed (weeks)</th>
<th>CFS titre</th>
<th>CSF:serum ratio</th>
<th>IgG titre</th>
<th>Specific IgG ratio</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>&lt;10</td>
<td>320</td>
<td>3</td>
<td>4</td>
<td>1:80</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Case 2</td>
<td>&lt;10</td>
<td>320</td>
<td>10</td>
<td>32</td>
<td>1:10</td>
<td>1:6</td>
<td>5:1</td>
<td>–</td>
</tr>
<tr>
<td>Case 3</td>
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<td>&lt;10</td>
<td>8</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Case 4</td>
<td>&lt;10</td>
<td>&lt;10</td>
<td>3</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Case 5</td>
<td>&lt;10</td>
<td>80</td>
<td>6</td>
<td>8</td>
<td>1:10</td>
<td>2:3</td>
<td>5:2</td>
<td>–</td>
</tr>
</tbody>
</table>

*Not done.

*By complement fixation test.
†Normal ranges: IgG index <0.72, specific IgG ratio (see discussion).
Discussion

When a child undergoing treatment for acute lymphoblastic leukaemia develops neurological symptoms the differential diagnosis includes recurrence of the leukaemia, intracranial haemorrhage, infection, and drug toxicity. Measles encephalitis (variously known as 'immunosuppressive measles encephalitis', 'subacute measles encephalitis', 'measles inclusion body encephalitis', or 'acute measles encephalitis of the delayed type') has been reported in at least 34 immunocompromised patients.\(^4\) Our cases 1 and 2 have been reported in outline previously. Most patients were children receiving immunosuppressive treatment for malignant disease, though one child had intestinal lymphangiectasia\(^2\) and another was a renal transplant recipient.\(^3\) The condition has also been described in two adults: a patient with a renal allotransplant and another who was receiving treatment for Hodgkin's disease.\(^3\)

Though the clinical, virological, and necropsy features of measles encephalitis in immunocompromised patients have been fully described, no critical analysis of the methods available for diagnosis in life has been reported.

In our cases and in previous cases a history of contact with measles was sometimes absent.\(^4\) Measles encephalitis occurred in immunosuppressed patients despite a history of measles or measles vaccination. The measles rash was often mild or atypical with no Koplik's spots, and not all cases were preceded by clinical measles. Initial neurological illness and the encephalitis ranged from two weeks\(^5\) to 10 months (our case 5). Neurological symptoms and signs were variable. Alteration of consciousness, disturbance of pyramidal or extrapyramidal function, ataxia, and emotional lability have occurred. Most patients had focal or generalised convulsions, and continuous partial epilepsy was sometimes a prominent feature.\(^6\) Inappropriate secretion of antidiuretic hormone,\(^7\) hypertension,\(^8\) and retinopathy\(^9\) have all been reported. The EEG was non-specifically deranged. Computed tomography of the brain in two of our patients showed areas of reduced density and in a third was initially normal. Thus the medical and immunisation history, clinical presentation, and neuroradiological investigations are not diagnostic in measles encephalitis in immunosuppressed patients.

A virological diagnosis in this group of patients was also often elusive. Usually measles virus antigen could no longer be identified in nasopharyngeal swabs by immunofluorescence after the encephalitis had developed.\(^3\) Isolation of measles virus from CSF is rare.\(^7\) Detection of measles virus in the urine, throat secretions, and an open lung biopsy specimen of our case 4 perhaps reflected the relatively rare combination of measles giant cell pneumonia and encephalitis. Though never reported, brain biopsy with assay of measles virus antigen by immunofluorescence could perhaps have been justified early in the illness if specific treatment with tribavirin were contemplated (see below). However, our observations with computed tomography and electroencephalography suggested that identification of an area within the brain suitable for biopsy would be difficult. Also, a haemorrhagic diathesis secondary to chemotherapy or disease could preclude brain biopsy in a patient with acute lymphoblastic leukaemia. There was often a considerable delay before the appearance of measles antibodies in serum, and many patients died before the assay for them was done. Two of our own patients died before this occurred. None the less, if seroconversion occurs in serum, assay of measles antibody in CSF was valuable.

Detection of measles antibodies in CSF (our cases 1, 2, and 5) was not of itself diagnostic of measles encephalitis. The presence of such antibodies could have merely reflected damage to the blood-CSF barrier and consequential leakage of serum antibodies into the CSF. Demonstration of intrathecal synthesis of specific antibodies was the only non-invasive method of proving infection of the brain in life. We attempted to achieve this in cases 2 and 5 by calculating IgG indices and specific IgG ratios (also known as specific antibody indices).\(^2\) Raised IgG index values were obtained, indicating intrathecal synthesis of IgG antibody. None the less, use of the complement fixation test to quantitate measles IgG antibodies limited the discrimination of our specific IgG ratios as measures of intrathecal measles specific antibody synthesis.

A more sensitive test such as enzyme linked immunosorbent assay that gave continuous concentration values rather than titres would have been required to allow calculation of a specific IgG ratio corrected for local synthesis of polyclonal IgG and for IgG leakage through the blood-brain barrier. In the central nervous system and with an acceptably low interassay coefficient of variation. A measles specific antibody ratio should have a mean normal value of 1. The range could be up to 4 if the antibody titres derived from doubling dilutions were used as in our ratio,\(^2\) though a lower ratio might indicate intrathecal antibody synthesis. Thus, though we do not know the normal range for our specific IgG ratio, in both cases 2 and 5 the ratio was probably raised, suggesting intrathecal synthesis of measles specific antibody.

The nature of the immunological deficit that renders immunocompromised patients susceptible to measles encephalitis is poorly understood. In subacute sclerosing panencephalitis (a disease of the apparently immunocompetent) measles virus persistence in neurones and glial tissue is possible because of the incomplete expression of viral proteins. Incomplete virus expression together with high levels of specific antibody inhibit development of the complete cell mediated immune response necessary for virus elimination. Virus is rarely recovered from immunocompromised patients with encephalitis and thus it has not been possible to determine whether or not 'defective' measles virus is involved in causation. Nonetheless, the low levels of specific antibodies found in immunocompromised patients with measles encephalitis suggest that the pathogeneses of the two diseases are different. It is possible to speculate that the mechanism for disease emergence in the immunocompromised is the antithesis of the mechanism in subacute sclerosing panencephalitis. Both diseases result from a failure to eliminate measles virus through defective cell
mediated immunity. In subacute sclerosing panencephalitis a defective virus prevents the development of the immune response, whereas in the immunocompromised patient measles-specific cell mediated immune responses are suppressed as a consequence of cytotoxic chemotherapy or steroid treatment.2

Only one patient has been reported to have made a full recovery. The majority of patients died within three months of the onset of neurological symptoms. The four other reported survivors had severe neurological handicap.6-10 Interferon treatment has not been effective.11 Case 5 of our series survived for five months, having received tribuvirin for measles pneumonitis. He did sustain neurological handicap but eventually died of haematological relapse. Early empirical tribuvirin treatment may perhaps be warranted in immunosuppressed patients with measles. We have previously used tribuvirin with success for measles pneumonitis in a child with Hodgkin’s disease.12

Increased vaccine uptake in the UK to provide herd immunity would greatly reduce the risk of contact with measles and therefore of its serious complications in immunosuppressed children. After the recent introduction of measles-mumps-rubella vaccine in the second year of life, the average measles vaccine coverage is now 91%12 and measles encephalitis should become much rarer in the future. Prior measles vaccination does not protect an immunosuppressed child against measles encephalitis.4 Indeed the occurrence of measles encephalitis in immunocompromised adults8 raises the possibility that even pre-existing natural immunity may not be completely protective. Certainly, prophylactic normal human immunoglobulin after measles contact is at best only partly effective.14 Unfortunately, a trial of hyperimmune measles immunoglobulin after exposure has proved inconclusive.8

In conclusion, diagnosis of measles encephalitis during life in immunosuppressed patients by detection of viral antigen in brain biopsy material early in the illness may be precluded by the difficulty of localising disease within the brain. Alternatively the diagnosis could be made in some patients using a sensitive immunoassay to document a raised CSF:serum ratio of specific antibodies, ideally with confirmation of intrathecal antimeasles antibody synthesis by demonstrating a raised specific IgG ratio or confirmation of intrathecal immunoglobulin synthesis with a raised IgG index. In future cases, assay of measles virus RNA in CSF by reverse transcrip-
tion and the polymerase chain reaction8 might be attempted. Detection of herpes simplex virus DNA in CSF has already proved a valuable diagnostic test for herpes simplex encephalitis.21 Early empirical treatment with tribuvirin might be beneficial, but prevention by increasing vaccine uptake and hence herd immunity in the general population could be more realistic goal.

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