Measles virus and subacute neurological disease: an unusual presentation of measles inclusion body encephalitis

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SUMMARY A 20-year-old girl developed a subacute neurological illness characterised by seizures and epilepsy partialis continua, which resulted in her death within 10 weeks of her first symptom. Although she had a history of unusual reactions to viral infections, there was no evidence of any underlying disorder resulting in immunosuppression. Histopathology demonstrated the presence of dense infection with measles virus. The unusual clinical features of this cases suggest that measles virus may be responsible for a wide spectrum of neurological disease ranging from measles inclusion body encephalitis on the one hand to subacute sclerosing panencephalitis on the other.

Measles virus may cause both an acute post-infectious meningo-encephalitis, and persisting central nervous system infection resulting in the clinical syndrome of subacute sclerosing panencephalitis.1 The role of altered immunity in subacute sclerosing panencephalitis has been much debated, but the strongest evidence now indicates that measles virus may persist in the central nervous system because in certain cells of the brain the "M" protein is not synthesised.2 Altered immunity may, however, modify the clinical consequences of measles infection, and it is well-recognised that immuno-suppressed patients may develop a rapidly progressive illness, characterised by focal seizures and coma following measles infection.3-5 Such cases are likely to increase our understanding of host-virus interaction in measles-induced neurological disease.

We now report a case in which there was a subacute progressive illness characterised by focal seizures, epilepsy partialis continua and decline in consciousness, leading to death within ten weeks. The patient had a history of unusual reactions to viral infection, but there was no history of a recent acute measles infection. Necropsy demonstrated the presence of eosinophilic inclusion bodies which fixed measles antibody.

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Received 11 March 1982
Accepted 9 April 1982

Case report

A 20-year-old female university student, successfully studying modern languages, developed a repetitive, persisting jerking of the left calf muscles. This continued for three to four days before she developed some occasional twitching of the muscles on the right side of her face. A week after the first symptom she had a more extensive right sided focal motor seizure involving the arm, which culminated in a generalised tonic-clonic seizure precipitating her admission to hospital.

She recovered consciousness and was lucid, although jerking of the right facial muscles continued. Over the next day, during which she was noted to be pyrexial (37.5°C), the rhythmic jerking of the right face spread to involve the right hand, and she began to exhibit confusion. In spite of anticonvulsant therapy she had further tonic-clonic seizures and her conscious level deteriorated. She showed no evidence of neck stiffness but mild pyrexia continued. Other than a tachycardia there were no other abnormal findings, and no exanthematous rash was noted. Two weeks into her illness she was unconscious with occasional spontaneous eye-opening and grimacing to painful stimuli. No spontaneous movements occurred on the left, and upper limb tendon reflexes were absent. Over the subsequent two weeks the continuous jerking affecting the right face and arm subsided but she developed similar continuous repetitive jerking affecting the left arm and face. For a period of a few days this jerking was present both on the right and the left but at differing rates on the two sides. Her condition deteriorated whilst on treatment with dexamethasone and anticonvulsant drugs, and she died ten weeks after the onset of her illness.

There was no history of preceding rash or upper
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respiratory tract infection, and the only prior medical history of note was that at the age of two she had developed a localised herpetic eruption in a thoracic distribution, and at the age of six had had a further episode of right ophthalmic herpes zoster. She had clinical rubeola between these dates.

On admission to hospital, haemoglobin was 12.9 g/dl, and peripheral white cell count 9.1 × 10⁹/l with a normal differential count. ESR was 46 mm/hr and plasma, urea and electrolytes and liver function tests were normal. Radiographs of skull and chest were normal. CSF examinations were performed on several occasions during her illness. CSF total protein varied between 0.2 and 0.4 g/l. CSF glucose was normal and, apart from two initial specimens in which there were lymphocytes 7/cmm, there was no increased cellularity. CSF IgG was 0.036 g/l (normal range 0.013-0.14) and CSF IgG/albumin ratio was not disturbed. Serum and CSF viral antibodies did not show any change in titres at 6, 13 and 27 days into the illness. In particular, measles, and herpes simplex virus antibodies were present in the serum at a titre of 1:160. Whilst herpes simplex antibodies were not detectable in CSF at any time, the measles antibody titre in CSF was 1:4 on day 13 of the illness, and 1:2 on day 27. EEGs were performed throughout the illness. These initially showed a generalised diffuse slow wave disturbance. However there was a progressive change with the development of high voltage periodic spike-slow wave complexes. CT scanning 10 days into the illness was entirely normal, but at six weeks a low density lesion in the right temporo-parietal region was evident,
which did not show contrast enhancement. Six weeks into
the illness a right frontal cortical biopsy was performed.
This showed gross loss and degeneration of cortical
neurones with moderate glial infiltration. Blood vessels
appeared normal and there was no evidence of perivascu-
lar cuffing. A deeper needle biopsy showed a patchy loss
of myelin and areas of spongiose change. Inclusion bodies
were not identified.

At necropsy the brain showed flattening of the cortical
sulci and congestion of cortical veins. Venous sinuses were
patent and the arachnoid at the base of the brain slightly
thickened. The spinal cord appeared normal as did other
organs. Micropsy showed considerable neural destruction
which was most severe in the right temporal cortex and the
right central grey matter. Typical eosinophilic intranuclear
inclusions were seen in both neurones and glia (fig 1). Cor-
tical destruction was accompanied by considerable fibril-
lar glial increase (fig 2). Perivascular round cell cuffing
was seen in a few areas and occasional macrophages were
present. These appearances strongly suggested a viral
aetiology to the patient’s illness.

Immunofluorescent staining (carried out by AHT) failed
to detect antigen to herpes simplex virus, but staining with
rabbit anti-measles serum showed many infected neuronal
glial cells in the frontal and temporal lobes and central
grey matter of both hemispheres (fig 3). Human serum
from a case of subacute sclerosing panencephalitis gave the
same staining pattern and controls using rabbit and human
serum devoid of measles antibody were negative. The
findings all suggested a heavy infection with measles virus
despite the modest serum and CSF antibody titres. Further
studies with potent anti-measles serum (kindly donated by
Dr Margaret Haire) and PAP immuno-staining of the orig-
inal surgical cortical biopsy sections demonstrated occa-
sional infected neurons in this biopsy, and also in few
anterior horn cell neurones at different levels in the spinal
cord.

Discussion

This patient presented at the age of 20 years with a
rapidly progressive illness characterised by focal
epilepsy, epilepsy partialis continua and generalised
seizures which resulted in death within ten weeks of
the onset of the first symptom. The histopathology
and labelled antibody studies showed the presence of a dense and widespread infection with measles
virus. The clinical features of this patient’s illness are
similar to those previously described in a number of
patients under the titles of “immunosuppressive
measles encephalitis”, “subacute measles
encephalitis”, and “acute measles encephalitis of the
delayed type”. We prefer the term “measles
inclusion-body encephalitis” as this satisfactorily
differentiates this condition from post-infectious
measles encephalitis.

This condition was first described by Lyon in a
patient with nephrosis. Agamonolis et al. recently
reviewed the literature and clinical features of some
24 cases. The clinical features were in every way
similar to those of our patient. Focal seizures, and
epilepsia partialis continua were prominent, and
associated with a rapid decline into coma. Death
within a period of weeks was the rule, although
occasional prolonged survival has been recorded. A
more recently reported case showed a similar se-
quence of events.

However, the disorder is usually seen in children,
and only two previous cases have been reported in
patients over the age of twelve. The condition is
strongly associated with disorders in which there is
impaired immunity (most commonly acute lympho-
ctic leukaemia but also other lymphproliferative dis-
orders, nephrosis, neuroblastoma, and renal trans-
plantation). Many patients have also received
chemotherapy.

Our patient would seem to be unusual in not suf-
fering from any clearly recognisable underlying
immune disorder. She did however have a history of
two episodes of herpes zoster in early life. It may be
that this patient had a specific immune deficiency
in responding to viral infections capable of remain-
ing dormant within the central nervous system.
Whilst her immune system was not studied formally,
the minimal antibody response to measles in CSF and
serum would support this supposition. Only one
patient has previously been reported in whom there
was no preceding illness or therapy associated with
immunosuppression.

A further unusual feature of the present case is
that unlike the majority of cases of measles inclusion
body encephalitis there was no recent clinical
rubeola. A similar absence of such a history has
been reported in six patients. It is notable that in both the older patients thus far reported
there was a similar absence of recent rubeola infec-
tion. It thus appears that measles inclusion body
encephalitis may well arise because of activation of a
long-standing persistent measles infection, as well as
the more common situation in which it develops
within a period of months of rubeola infection.

This present case is similar to the case reported by
Mandelbaum et al. as subacute sclerosing panence-
phalitis in an otherwise normal 14 year-old-boy, and
to that reported by Coulter et al. as a case of sub-
acute sclerosing panencephalitis after drug-induced
immunosuppression. The latter patient, suffering
from a neuroblastoma, had received radiotherapy
and chemotherapy ten years previously. She
developed an illness which over four months led to
deteriorating intellectual performance with subse-
fuent focal seizures, myoclonic jerks and epilepsy
partialis continua. This patient showed high com-
plement fixing titres to measles virus in both serum
and CSF and typical EEG changes of subacute
sclerosing panencephalitis. There was no clear-cut recent rubella infection. There seems no reason to differentiate these cases from others described as immunosuppressive measles encephalitis or measles inclusion body encephalitis. It does however raise the question of the adequacy of definition of two differing clinical entities.

The criteria for diagnosis of subacute sclerosing panencephalitis are dependant on the characteristic clinical picture, electroencephalographic appearances, the presence of measles antibody titres in serum and cerebrospinal fluid and typical histopathological changes. Both measles inclusion body encephalitis and subacute sclerosing panencephalitis may share similar EEG appearances, and histopathological changes including immunocytological demonstration of intraneuronal measles antigen. Whilst in some cases high measles antibody titres in serum and CSF may not be found in measles inclusion body encephalitis some cases show titres as high as those to be expected in subacute sclerosing panencephalitis. It therefore seems that the major criteria for differentiating between these two conditions is the clinical picture.

In subacute sclerosing panencephalitis the classical presentation and progress of the condition has been well-defined, with subdivision into four clinical stages. In stage I there is subtle intellectual and behavioural change, sometimes associated with convulsions, tremors, and chorioretinitis. In stage II ataxia develops along with generalised myoclonic jerks associated with periodic EEG complexes. Coma and decerebration develop in stage III. In stage IV myoclonus and spasticity diminish and death ensues. The characteristic focal seizures, epilepsy partialis continua, and generalised convulsion of measles inclusion body encephalitis are rarely seen in subacute sclerosing panencephalitis. The presence of epilepsy partialis continua, an unusual form of focal epilepsy, may be particularly helpful in making the diagnosis of measles inclusion body encephalitis. Measles inclusion body encephalitis was not included as a cause of epilepsy partialis continua in a recent comprehensive review of the subject. The frequency with which it occurs in measles inclusion body encephalitis needs to be emphasised.

Nevertheless, there are grounds for suggesting that the two entities form part of a spectrum of neurological disorder caused by measles virus. As well as similarities in the histopathology, and EEG changes, there may be a continuous clinical spectrum. Up to 10% of patients with subacute sclerosing panencephalitis have a rapidly progressive illness. Whilst the clinical features of these acute cases are poorly described, some may be atypical in the clinical course of the illness, and seizures may be a prominent presenting feature. Conversely some patients with measles inclusion body encephalitis may survive for prolonged periods. Whilst subacute sclerosing panencephalitis usually has a much longer incubation period than measles inclusion body encephalitis, in our patient and in others, a typical inclusion body encephalitis syndrome may develop many years after a clinical measles infection. The growth of measles virus in neurons and glial cells is similar in the two conditions in that infected cells fix antibody from both the serum of patients with subacute sclerosing panencephalitis and hyper-immunised rabbits, and the patient usually produces some antibody to measles virus. In neither condition is antibody to "M" antigen produced. It can be argued, therefore, that infection with measles virus can evoke a spectrum of neurological disease, and that it is the state of immune competence of the patient which may be important in determining the clinical manifestations in an individual case.

We are grateful to Dr E Sherwood-Jones for his kind permission to report this case, and to Dr M Haire for donating potent anti-measles serum.

References

1 Adams JM. Clinical pathology of measles encephalitis and sequelae. Neurology (Minneapolis) 1968;18:52-86.
11 Roos PR, Graves MC, Wollmann RL, Chilcote RR, Nixon J. Immunological and virologic studies of


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J Neurol Neurosurg Psychiatry 1982 45: 680-684
doi: 10.1136/jnnp.45.8.680

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