Acute encephalitis complicating rubella

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During an epidemic of rubella in Hong Kong between October 1996 and June 1997, four male patients presented with rubella complicated by encephalitis, the symptoms of which started 1 to 5 days after the appearance of the rash characteristic of rubella. Two patients recovered completely within 1 week and one complained of a slight impairment of short-term memory. Severe cerebral oedema, and herniation across the brainstem and cerebellum developed in the fourth patient, who died 15 days later. The presence of serum immunoglobulin M antibody against rubella virus was demonstrated in all four patients; one patient also had immunoglobulin M antibody against rubella virus in his cerebrospinal fluid. No virus could be isolated during post-mortem examination of the fourth patient.

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Introduction

The incidence of acute viral infection affecting the central nervous system is unknown. For all viruses, the incidences have been estimated to be less than 0.003% for all age-groups, and less than 0.020% for children aged less than 16 years.[1] The specific virus can be determined in 20% to 40% of patients.[2-4] In a local survey of children aged less than 14 years who had viral encephalitis, the viral aetiology could be determined in 26% of patients.[5]

The incidence of encephalitis complicating rubella has been estimated to be 1 per 3000 to 1 per 24 000 rubella patients, and the case fatality rate has been found to vary from 0% to 30%.[6-9] Among the survivors, there are very few irreversible deleterious changes in intellectual function[8]; most patients with non-fatal rubella encephalitis recover quickly with minimal or no sequelae.[7,8]

There was an epidemic of rubella in Hong Kong between October 1996 and June 1997. Four male patients presented with rubella complicated by encephalitis to the Princess Margaret Hospital, which has an Infectious Disease Team and which receives referrals from the special administrative region's population of approximately 6.7 million. The high incidence of rubella encephalitis is one of the features of an epidemic of rubella.

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Case report

The four patients had a similar clinical presentation (Table 1). Patient 2 had a complicated clinical course which is presented here. Patient 2 was a 16-year-old boy who had a history of good health. On presentation, the patient was febrile and a maculopapular rash developed over his chest the following day. Six days later, he became less responsive to those around him and was subsequently admitted to the Princess Margaret Hospital. There was neck stiffness and the suboccipital lymph nodes were enlarged. The patient had visited a private practitioner who performed a fundal examination, followed by a lumbar puncture (the pressure was not measured). Results from cerebrospinal fluid (CSF) investigations were as follows: red blood cells $55x10^6$ /L (normal, 0 /L), white blood cells $182x10^6$/L (normal range, 0-$5x10^6$ /L), lymphocytes 95%, protein 1.2 g/L (normal, <0.4 g/L), glucose 4.0 mmol/L (normal range, 2.8-4.4 mmol/L); the serum glucose level was 7.5 mmol/L (normal range [fasting], 3.9-6.1 mmol/L). Further tests on the CSF—Gram staining, bacterial culture, acid-fast bacilli, and cryptococcal smears—gave negative results.

After admission to the Princess Margaret Hospital, the patient's score on the Glasgow coma scale was found to be 8/15. The neck was stiff, and computed

Table 1. Clinical courses of patients with rubella encephalitis

Patient details	Patient 1	Patient 2	Patient 3	Patient 4
Age (y)	17	16	19	30
Sex	Male	Male	Male	Male
Clinical features	Fever, rash, enlarged suboccipital lymph nodes, decreased memory	Fever, rash, enlarged suboccipital lymph nodes, neck stiffness	Fever, rash, enlarged postauricular lymph nodes, rotatory nystamus	Fever, rash, reduced alertness
GCS* score	15/15	8/15	15/15	9/15
CT†, brain	Normal	Cerebral oedema	—	Normal
MRI‡, brain	—	Herniation	Normal	—
CSF§ findings				
CSF pressure (cm H_2O)	28	—	10	—
white blood cells (x10^6 /L)	363	182	2	6
neutrophils (%)	20	5	—	—
lymphocytes (%)	80	95	—	—
protein (g/L)	2.6	1.2	1.2	1.1
glucose (mmol/L)	3.7	4.0	3.7	3.7
Serum glucose (mmol/L)	4.2	7.5	5.7	6.2
Serum anti–rubella virus IgM	Positive	Positive	Positive	Positive
CSF anti–rubella virus IgM	—	—	—	Positive
Outcome	Slightly impaired short-term mermory, slightly poorer academic results	Died on day 15	Complete recovery after 5 days	Complete recovery after 7 days

*GCS Glasgow coma scale
† CT computed tomography
‡ MRI magnetic resonance imaging
§ CSF cerebrospinal fluid

tomography of the brain showed cerebral oedema; the fundi were normal. Penicillin G and acyclovir were given by intravenous infusion. One day later, the patient had generalised tonic-clonic convulsions and required mechanical ventilation. Electroencephalography (EEG) showed slow wave activity but no epileptogenic activity. The intracranial pressure was monitored and mechanical hyperventilation was administered. Mannitol was given intravenously to lower the intracranial pressure and phenytoin was given to treat the convulsions. The patient's condition continued to deteriorate. Magnetic resonance imaging of the brain showed downward brainstem and cerebellar herniation.

Serum immunoglobulin (Ig) M antibodies against rubella virus were present but there were no antibodies against the following viruses: measles, herpes simplex, influenza A and B, mumps, varicella-zoster, and Japanese encephalitis. There were also no antibodies against enterovirus, dengue viruses 1, 2, 3, and 4, or *Mycoplasma pneumoniae*. There was no virus isolated from the CSF. The patient died 15 days after admission to hospital. Brain biopsy showed a mild to moderate degree of perivascular and interstitial mononuclear cell infiltration. The neurons showed increased cytoplasmic eosinophilia but no intranuclear or intracytoplasmic inclusions. Immunohistochemical studies to detect the presence of viruses gave negative results and electron microscopy did not detect any virus. The biopsy showed encephalitis but could not confirm the presence of any virus.

Discussion

Three of the four patients with rubella complicated by encephalitis survived, and their condition improved quickly within 7 days of the initial symptoms. Acyclovir was given intravenously to all four patients soon after the clinical diagnosis of encephalitis, mainly because of the possibility of the development of herpes simplex encephalitis. While the efficacy of acyclovir to treat rubella encephalitis has not been proven, there is currently no specific and well-proven effective treatment for the disease. Giving corticosteroid has been reported to have a beneficial effect on rubella encephalopathy,[10] but its clinical effect (apart from controlling intracranial hypertension) is unclear. For patient 2, the intracranial pressure was monitored, hyperventilation was provided

mechanically, and mannitol was given to lower the intracranial pressure. Despite these treatments, the patient's condition continued to deteriorate, and he died on day 15.

The average onset of encephalitis is 4 days after the appearance of a rubella rash; however, the neurological signs can sometimes occur before the rash.[11] In fatal cases, death usually ensues within 3 days.[11] Coma and convulsion are unfavourable signs, but changes in the biochemistry of the CSF carry no prognostic value and EEG in the acute phase usually shows slow wave activity with no specific features. Unusual results from EEG such as repetitive triphasic complexes have been reported[12]; however, this feature was not apparent in this series of patients.

It had been suggested that encephalitis associated with rubella is a hypersensitivity reaction and that the pathology simulates experimental allergic encephalitis.[13] This concept changed when rubella virus was isolated from the CSF of a 14-year-old boy who had rubella encephalitis, thus directly confirming infection by the virus.[14] The difficulty of isolating rubella virus from the CSF is due to the small amount of virus in postnatally acquired rubella, the presence of antibody, and the requirement for special media for virus culture.[14]

Rubella encephalitis in Hong Kong has been reported once previously.[15] The four patients with rubella encephalitis in this report came from different regions of Hong Kong. They were all male and the vaccination programme during their childhood did not include the prevention of rubella. Medical practitioners have been required by law to notify the Department of Health of the incidence of rubella infection since 1994. The number of reported rubella infections increased from eight in 1994 to 606 in 1996.[16,17] This figure has risen further, to 4495, in the period between January 1997 and June 1997 (Table 2).[18-20] The true number of rubella infections was probably higher, because the infection can be subtle and pass unnoticed—diagnosis thus depends on clinical alertness. In addition, the true figure depends on the accurate reporting of rubella cases to the Hong Kong Department of Health. The increase in the number of cases of rubella encephalitis is not surprising, given the fact that the rubella epidemic of October 1996 to June 1997 was the first documented rubella outbreak that occurred in the local community. The notion that there may be different strains of rubella has been raised[21] but remains unsubstantiated, and we could not isolate any virus in this study.

Before the era of routine vaccination to protect against rubella, infection by rubella virus was common among young people, and preschool children and young schoolchildren were the main reservoirs for transmission of the virus.[22] Serological surveys of adolescents and young adults have indicated that 15% to 20% remain susceptible to infection by rubella virus—the majority of this age-group have already developed antibodies to rubella virus through natural infection and vaccination programmes.[22] In the late 1960s, vaccination strategies were employed in the United States and the United Kingdom for adolescent females, to protect them from rubella during pregnancy.[23] In Hong Kong, primary six level schoolgirls have been given rubella vaccine since 1978 for a similar reason. Because more females in the local community will have antibodies against rubella virus, the proportion of males with rubella increases. The vaccination programme was subsequently revised in 1990, and the measles-mumps-rubella (MMR) vaccine was given to all children aged 1 year, with a MMR booster dose given at the primary six level. From 1998, the booster dose will be given to all children at the primary one level. In countries where children are vaccinated against rubella virus earlier, the incidence of rubella has been shown to decrease after a few years.[24] A nationwide vaccination programme in Finland that included prevention of rubella has been shown to eradicate encephalitis associated with the rubella virus.[25] In the local community, the incidences of rubella and rubella encephalitis are likely to decrease when the majority of the population have acquired antibodies against rubella virus.

Table 2. Number of reported cases of rubella in Hong Kong

Year	No. of reported cases
Before 1994*	Data not available
1994	8
1995	19
1996	606
1997 (Jan-June)	4495

* Rubella was added to the list of notifiable diseases in 1994, following the revision of the Quarantine and Prevention of Disease Ordinance

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Addendum

Subsequent to the submission of this report, the new rubella vaccination programme that includes a booster

dose at the school primary one level started before the end of 1997.

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