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Complicated Varicella Zoster Infection in 8 Paediatric Patients and Review of Literature

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ABSTRACT

Background: This is a study of complicated varicella zoster infection in paediatric patients.

Aim: To find out the number of patients with such complications, the types of complications and their outcome.

Method: This involved a retrospective review of the case records of 8 patients who presented to our unit over a 12-month period (Jan – Dec 96). All patients were previously well without any underlying immunodeficiency. Varicella zoster (VZ) infection was confirmed by VZ immunofluorescence from vesicular fluid.

Results: CMS complications accounted for 6 of the 8 cases. Of these, 3 presented with encephalitis, 2 with cerebella ataxia and 1 with aseptic meningitis and cerebella ataxia. Of the non-CNS cases, 1 presented with glomerulonephritis with superimposed *staphylococcus* infection of skin ulcers; the other had disseminated VZ infection with haemorrhagic vesicles, hepatitis, ileus with mesenteric adenitis and disseminated intravascular coagulation.

Outcome: The patient with disseminated VZ infection and multiple organ involvement died 5 days after a stormy course. One patient with encephalitis who had status epilepticus for 2 hours had behavioural problems and poor memory. The remaining 6 patients had no sequelae.

Conclusion: VZ infection usually a minor illness, can result in serious life-threatening complications in previously healthy patients.

Keywords: varicella zoster, complications

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INTRODUCTION

Varicella infection has traditionally been regarded as a benign disease in healthy children. However, potentially life-threatening complications have been reported in immunocompetent hosts. Fleisher (1) reported 9 deaths in 80 immuno-competent children from Reye syndrome (7), varicella pneumonia (1), ruptured mycotic aneurysm secondary to septicaemia (1). One other death occurred in a neonate with congenital varicella. Of the 10 survivors with Reye syndrome, 4 showed evidence of neurologic deficit at the time of discharge. Pollard[2] noted that occult bacterial infections with Group A *Streptococcus* or *Staphylococcus aureus* might complicate chickenpox and cause potentially lethal disease. We reviewed retrospectively, the case records of 8 patients who presented to our unit over a 12-month period (January – December 1996), with complicated chickenpox infection, to highlight the complications commonly seen in our cohort of patients as well as their outcomes. All the patients were previously well. All cases had varicellar zoster (VZ) confirmed by VZ immunofluorescence from the vesicular fluid.

METHODS AND MATERIALS

Most cases of varicella infection in children are managed as outpatients. Cases that need close medical attention are admitted to the Communicable Disease Centre (CDC) at Tan Tock Seng Hospital (TTSH). The paediatric staff from the Department of Paediatrics, TTSH will be consulted if complications occurred. The cases will then be transferred to our department for further management.

Over the one year period from January – December 1996, a total of 8 cases of complicated VZ infection were admitted to our department at TTSH. The case records of the patients were reviewed retrospectively with regards to the type of complications and their outcomes. Immuno-deficiency work-up was done in two patients (patients 1 and 5). These included full blood count, immunoglobulin levels (A, G, M), T-and B-cell markers, complement level (C3, C4 and CH 50). All the other children were previously healthy with no history to suggest immunodeficiency.

PATIENTS' REPORTS

Patient 1, a 12-month-old girl, presented at day 4 of chickenpox illness with oliguria and progressive facial swelling over 1 day. She was the third person in the family to be affected with varicella infection. On admission, she was febrile (temperature 39°C), tachypnoeic and tachycardic. Generalised haemorrhagic vesicular rashes were present over the body. Her face was swollen with pitting oedema. Examination of the abdomen revealed gross hepatosplenomegaly. She was treated with intravenous acyclovir for severe varicella infection with possible visceral dissemination.

Over the next 2 days, her facial oedema progressed to involve mainly the upper half of her body, sparing the ankles. However, chest X-ray did not show any evidence of cardiomegaly or widening

of mediastinal shadow. Doppler ultrasound of the neck veins done to explore for possibility of superior vena cava obstruction was normal. 2-D echocardiography of the heart revealed no pericardial effusion or structural abnormalities. The contractility of the heart was normal. Subsequently, her oedema became generalised and she threw one episode of generalised tonic-clonic seizure secondary to hyponatremia (Na 118 mmol/L) from fluid retention. Her blood pressure was normal. Her initial investigations revealed a low serum albumin (29 g/L) and total protein (43 g/L) with normal liver transaminases and alkaline phosphatase level. Her 24-hour urinary protein was 18 mg/m^2/hr (elevated). Her urea/creatinine, complement assay (C3, C4), triglyceride/cholesterol levels were normal. Full blood count revealed leucocytosis (20,000/mm^3), haemoglobin 10.3 g/dL and thrombocytopaenia (43,000/mm^3) on admission. Repeat full blood count done later showed normalisation of platelet count of 289,000/mm^3. Peripheral blood film showed no abnormalities. Blood culture and work-up for immunodeficiency were normal. Her clinical picture was suggestive of acute glomerulonephritis.

Her oedema improved after being given 3 lots of intravenous albumin infusion (1 g/kg each). She developed several large and deep-seated necrotic skin ulcers measuring 5-8 cm with superimposed *staphylococcus aureus* infection and was treated with intravenous cloxacillin. Desloughing of the necrotic ulcers were done. She was finally discharged home on the 14th day of admission. On follow-up in the outpatient clinic, she was well apart for the multiple healed scars at the old wound sites. Renal biopsy was not done.

Patient 2, a 5-year-old previously healthy boy, was admitted at day 2 of illness with a 1 day history of abdominal pain. On admission, he had low grade fever (37.7°C); he had vesicles over the face, neck and upper trunk. He was orientated, his neck was supple and his vital signs were stable. However, his abdomen was distended, tender and guarded. His bowel sound was sluggish. The provisional diagnosis of probable varicella pancreatitis was made and he was put on nil-by-mouth and given intravenous hydration. Serum amylase was normal but urine amylase was elevated (669 U/L). Liver function test showed raised transaminases (ALT 462 U/L, AST 466 U/L) with normal serum total protein, serum albumin, bilirubin and alkaline phosphatase. Abdominal X-ray revealed dilated loops of bowel. He was stable on day 2 of admission apart for bouts of abdominal pain. However, on day 3 of admission, his abdomen became more distended and tense. An emergency laparotomy done showed mesenteric adenitis with clear peritoneal fluid. The mesentery was haemorrhagic. The distal ileum and jejunum were noted to be distended. The rest of the bowel was normal. Post-operatively, he was started on intravenous acyclovir, ceftriaxone and metronidazole.

On the first post-operative day, he had a right lower lobe pneumonia and developed bilateral conjunctivitis. His vesicular rashes became haemorrhagic in nature. He was progressively drowsy, disorientated and went into shock, with disseminated intravascular coagulation. Despite aggressive fluid resuscitation, fresh frozen plasma, platelet and inotropic support, he died on the second post-operative day from disseminated varicella infection. Blood culture and culture from the peritoneal fluid were negative. No immuno-deficient work-out was done in view of the rapid progression of the illness.

Patient 3, a $4^1/_2$-year-old boy, presented at day 3 of illness with encephalopathy. On admission, he was drowsy but arousable. Deep tendon reflexes were brisk with positive Babinski sign and bilateral ankle clonus. Fundoscopy revealed no papilloedema. He had sparse vesicular rashes over the body. His condition deteriorated overnight with evolution of signs suggestive of raised intracranial pressure (ie. progressive drowsiness, right lateral rectus palsy, unequal pupil sizes which reacted sluggishly to light and decorticate posturing). He threw multiple episodes of generalised tonic-clonic fits which were controlled after administration of intravenous phenytoin and mannitol. He was also started on intravenous acyclovir. CT scan of the brain revealed cerebral oedema with no midline shift. Full blood count, urea/electrolyte/creatinine, liver function test and blood culture were normal. Lumbar puncture was not done.

His mental status improved 3 days later and was discharged after completing 10 days of intravenous acyclovir therapy. On follow-up, he was well with no recurrence of fits.

Anticonvulsant therapy had since been taken off.

Patient 4, a 5-year-old boy, presented at day 8 of varicella infection with fever, headache, neck stiffness, drowsiness and disorientation. Clinically, he had generalised scabbing over the body. A few vesicles were seen at the left foot. Fundoscopy revealed no papilloedema. CT scan of the brain was normal. Lumbar puncture revealed opening pressure of 32 cmH_20, pleocytosis of 75 cells (polymorphs and few lymphocytes), total protein of 31 mg/dL (10-40). Culture of the cerebrospinal fluid (CSF) for pyogenic bacteria was negative. He was treated for varicella meningoencephalitis with 14 days of intravenous acyclovir. Two days later, his mental status returned to normal and neck stiffness resolved. On follow-up, he was doing well.

Patient 5, a $5^1/_2$-year-old girl, presented at day 6 of chickenpox with headache for one day and convulsive generalised status epilepticus lasting 2 hours. On admission, she had bilateral papilloedema and threw focal seizures involving her left upper limb. Her neck was supple. A diagnosis of varicella encephalitis with raised intracranial pressure was made. Her fits were controlled after she was given intravenous phenytoin and

intravenous mannitol. Investigations revealed her full blood count, urea/electrolyte/creatinine, and glucose levels to be normal. Lumbar puncture was not performed.

Electroencephalography done after she was loaded with anticonvulsant showed excessive slowing of background with no epileptiform activity. MRI scan of the brain was normal. Investigation for immunodeficiency was normal. She was given 2 weeks of intravenous acyclovir. The anticonvulsant therapy was stopped before she was discharged from the hospital. On review at the outpatient clinic, she had behavioural changes with temper tantrums and mood changes as well as poor memory.

Patients 6, 7 and 8, aged 6 – 12 years, presented with acute cerebellar ataxia at days 5 – 8 of varicella infection. Signs and symptoms included vomiting, headache, vertigo, dysmetria, truncal ataxia and unsteady gait. Nystagmus was not present.

Patient 8 had neck stiffness with photophobia. Lumbar puncture revealed CSF white cell counts of 18/mm^3 and total protein of 138 mg/dL. No pyogenic organism or virus was isolated from CSF. This patient was given 10 days of intravenous acyclovir for possible meningeal involvement, whereas patients 6 and 7 were treated symptomatically without acyclovir. All of them recovered 4 weeks after onset of illness.

DISCUSSION

This article, as in other published articles[1-4], dispels the myth that varicella infection is benign in otherwise healthy children. One must be alert to potential complications of the disease. We highlighted 8 cases of varicella infection with complications in our series ie. encephalitis (3); acute cerebellar ataxia (2); acute cerebellar ataxia with aseptic meningitis (1); infected vesicles with glomerulonephritis (1), and disseminated varicella infection (1).

The VZ virus is highly contagious and is transmitted via the respiratory route from varicella or herpes zoster-infested patients. In an otherwise healthy child, varicella is usually characterised by a generalised vesicular rash with relatively insignificant systemic manifestations. An elevated body temperature (38.3°C – 38.9°C) may occur in the first 2 – 3 days of the illness. Otherwise healthy children may develop general malaise, headache, anorexia and sorethroat. Secondary family cases tend to have more severe disease as determined by a longer clinical course and approximately 50% more skin lesions, but the magnitude of fever and the complication rate are not greater. Asymptomatic primary infection develops in less than 5% of children. In otherwise healthy children, the mortality rate is estimated to be 1 – 4 deaths per 100,000 cases of varicella[5].

The most common complication in children less than 5 years of age is usually secondary bacterial skin infections from *staphylococcus* or *streptococcus* infection[6]. Other cutaneous complications include haemorrhagic vesicles, bullous varicella, necrotising fasciitis especially due to group A *streptococcus* infection, purpura fulminants[7], and localised gangrene. Pollard[2] reported the presence of potentially lethal bacterial infection associated with varicella infection in 13 children. Eight of them had toxic shock syndrome and another one had status epilepticus. One died from group A *streptococcus* septicaemia. He cautioned that occult bacteraemia may be difficult to diagnose especially in the first 3 days of infection and a high index of suspicion is needed. In our series, patient 1 had deep-seated ulcers with superimposed *staphylococcus aureus* infection which healed with scar formation. Patient 4 showed rapid deterioration in the first post-operative day with evidence of multi-organ dysfunction. Though skin swab was not sent for culture, the absence of organism being isolated from blood culture and peritoneal fluid made the possibility of toxic shock syndrome from superimposed bacterial infection less likely.

Varicella complications involving the central nervous system have been documented in various articles[1,8-11], occurring in about 1% of cases. Aseptic meningitis, Guillain-Barre syndrome and transverse myelitis have been reported. Three major syndromes described are encephalitis, cerebella ataxia and Reye syndrome. Cerebellar ataxia and Reye syndrome occur during acute varicella infection. Reye syndrome carries a high mortality rate. Cerebellar ataxia which occurs primarily in children, is a relatively mild disease. It usually presents at the same time as the varicella rash with a range of 4 days before to 14 days after eruption. Three of our patients with acute cerebellar ataxia presented at days 5 – 8 of illness, with vomiting, headache and ataxia. Nystagmus and slurred speech were not found in our patients. The neck stiffness that was present in patient 7 was probably due to concomitant aseptic meningitis. Seizures are uncommon in patients with acute cerebellar ataxia.

Cerebrospinal fluid is usually normal or shows mild lymphocytic pleocytosis. The ataxia usually resolves completely over days or weeks. Our patients were well within one month of illness.

Encephalitis which may be due to acute viral replication in the central nervous system or a post-infectious immune-mediated process, is often quite severe. Incidence is estimated at 4 /10,000 cases of chickenpox. Majority of cases occur in the first week following the exanthem. However, it can manifest from 11 days before to several weeks following the rash. Our patients presented during the acute infective period (days 3 – 8). Symptoms include headache, vomiting, meningism and altered sensorium. In contrast to cerebella ataxia, convulsions are relatively common. Two out of 3 patients with encephalitis had convulsion during the acute phase. Sensory changes, visual impairment and urinary retention have been reported. It is less common than cerebellar ataxia and adults are more

frequently affected. CSF shows normal cell count or lymphocytic pleocytosis, protein is normal or slightly raised and pressure may be elevated. Electroencephalography in the acute phase shows diffuse slow wave activity. About a third have persistently abnormal EEG and these usually have residual symptoms and epilepsy (10% – 15%). CAT scan may also be abnormal, showing cerebral or cerebellar oedema and areas of low attenuation consistent with demyelination. Mortality rates vary from 5% – 35%. We did not have any death from encephalitis. However, one patient with encephalitis had poor memory with behavioural problems while on follow-up.

Varicella infection with CNS vasculopathy and ischaemic infarcts have been reported, the complications occurring weeks to months after the infection[13-17]. Tsolia et al[18] reported a paediatric patient who had cerebrovascular infarcts before varicella became clinically apparent a day later. CAT scan or MRI can be utilised to demonstrate the presence of infarcts. Detection of antibodies, virus isolation in tissue culture or VZV DNA in CSF by PCR lend support for a causal relationship. Definite proof would lie in the histologic demonstration of the virus in affected blood vessels.

There are many other complications of varicella infection. Respiratory complications[19,20] include bacterial pneumonia, varicella pneumonitis and otitis media. Eye complications include keratitis, conjunctivitis, uveitis, and iritis. Infrequently, varicella may be complicated by arthritis, glomerulonephritis, myocarditis, orchitis, thrombocytopaenia, bleeding diasthesis, hepatitis and Henoch-Schonlein purpura. Patient 2 had haemorrhagic vesicles, pneumonia, conjunctivitis, hepatitis, mesenteric adenitis, ileus which eventually culminated into disseminated intravascular coagulation with shock and death. Interestingly, the multi-organ dysfunction was preceded by intense abdominal pain. Morgan[21] noted that in immunocompromised patients, intense abdominal pain was frequently the first sign of dissemination of varicella infection resulting in multi-organ dysfunction. Serum amylase was normal in all his patients. This predictable pattern of organ involvement enabled him to start anti-viral therapy early and resulted in the survival of 11 of 15 patients with life-threatening visceral involvement. Mild transient transaminase elevation can be found during uncomplicated chickenpox[22]. However, immunocompromised children with hepatitis often have associated manifestation of viral dissemination requiring prolonged hospitalisation[1].

Patient 1 had clinical features of glomerulonephritis. In view of the presence of *staphylococcus aureus* isolated from infected skin ulcers, it is difficult to pin-point whether *staphylococcus aureus* or varicella-zoster is the triggering factor. Varicella-related nephritis is very rare. In a large series of 2,534 patients, only 3 (0.12%) developed clinical nephritis[6]. However, the occurrence of renal lesion in fatal cases have been reported to be higher[23]. Histopathological features ranged from congested, haemorrhagic glomeruli, endothelial hyperplasia, varying degrees of tubular necrosis[24] to presence of cresenteric formation in the glomeruli[25]. During acute phase, peritoneal dialysis might be indicated. The overall outcome ranged from complete recovery, recovery with asymptomatic persistent microscopic haematuria/trace albuminuria to mild renal impairment[23-27].

Immunocompromised individuals with either primary varicella infection or recurrent infection (zoster) benefit from early therapy with intravenous acyclovir. Intravenous acyclovir therapy is recommended for any patient with severe varicella, including dissemination, irrespective of age, previous health or duration of symptoms[28]. If a decision was made to treat, intravenous acyclovir will be used in infants and toddlers, at least until the age of 2 years, as drug levels sufficient to inhibit the replication of varicella may not be achieved by the oral route. Oral acyclovir therapy is not recommended routinely for the treatment of uncomplicated varicella in otherwise healthy children in view of the marginal therapeutic effect of reduction in the number of skin lesions from 347 to 294 and the earlier defervescence of fever by 1 day[29, 30]; the cost of the drug, feasibility of drug delivery in the first 24 hours of illness, and the currently unknown and unforeseen possible dangers of treating otherwise well children. It is not recommended as a prophylaxis for immunocompetent household contacts of varicella because there is a possible attenuation of immune response which may not protect against reinfection or may predispose one to early zoster. In the absence of active skin lesions, acyclovir has no role in the treatment of the post-infectious varicella syndromes, such as cerebellitis, transverse myelitis, reactive arthritis or glomerulonephritis. However, oral acyclovir may be considered in those with cardiopulmonary disease (eg. infants with congenital heart disease or bronchopulmonary dysplasia, or adolescents with advanced cystic fibrosis) who may have an exacerbation of their underlying disorder and those with chronic skin disorders (eg. severe eczema, icthyosis or burns) who are at increased risk of bacterial superinfection and severe sepsis. When given, oral acyclovir should be administered for 5 days, starting within the first 24 hours of rash onset, at a dose of 20 mg/kg four times a day, with a maximum dose of 800 mg. The patient should be maintained in a well-hydrated state by encouraging adequate fluid intake. Data are lacking to determine whether children who receive non-immunosuppressive steroid treatments for asthma are at an increased risk of severe or fatal varicella infection. The Committee on Infectious Diseases, American Academy of Paediatrics recommend that children receiving short, intermittent or aerosolised courses of corticosteroids should be considered for therapy with oral acyclovir to minimise the likelihood of severe varicella infection. Australasian Society for Infectious Diseases[28]

advocate that children receiving < 1 mg/kg per day of prednisolone, or < 2 mg/kg on alternate days do not require acyclovir as they are not at an increased risk of severe varicella infection. However, both agreed that those who receive high dose steroids within 1 week of the onset of varicella should be treated as being at similar risk as other immunocompromised patients and intravenous acyclovir therapy is indicated.

Zoster immunoglobulin (ZIG) should be given immediately to all asymptomatic neonates born 7 or fewer days after the onset of maternal varicella and to exposed preterm infants in the neonatal nursery born at less than 28 weeks gestation (or < 1000g) regardless of maternal history. ZIG modifies the severity of the illness, but may not prevent infection. Neonates with skin lesions at or shortly after birth do not require acyclovir as maternal antibodies would have crossed the placenta resulting in a mild illness. Similarly, those who develop varicella despite receiving ZIG usually have a mild infection. These neonates should be observed closely. Intravenous acyclovir can be given if there are signs of high fever, cough and respiratory distress or extensive cutaneous lesions suggesting potentially severe varicella infection. After 2 weeks of age, varicella is unlikely to be a severe infection in the normal host, even if the mother was zero-negative and generally did not require acyclovir. For a newborn infant younger than 7 days of age who has a sibling with varicella at the time of discharge from hospital, the risk to the neonate is negligible if the mother has had chickenpox. Otherwise, the baby may be given ZIG before going home.

There is little doubt that selected high risk groups viz children with malignancies and susceptible adults would benefit from VZ vaccine. In the case of normal children, they would benefit not by virtue of the severity of the disease but rather because of the inevitability of the disease and its associated expenses. Live attenuated VZ vaccine was developed in Japan in the 1970s[32]. Besides its use in preventing severe varicella in high risk children, a wider scope would be in incorporating it in the immunisation schedule. The seroconversion rate is 95% – 100%. The efficacy of the VZ vaccine lies between 75% – 85%; the remaining experiencing a modified form of the illness[33,34].

A recommended programme of immunisation would be to immunise all children and adults who are susceptible to varicella and then to institute routine immunisation at age 12 to 15 months or immunise all children who reach the age of 10 years and have not had varicella[35]. Side effects of VZ vaccine include rash localised to injection site or generalised rash occurring within a month of vaccination and persisting for a few days.

Although some degree of waning immunity has been observed in adults and leukaemic children who were immunised, follow-up studies in the United States and Japan over 7 and 10 years respectively have shown little evidence of waning immunity in healthy children vaccinated[34,36]. Of 343 healthy adults immunised, 9% developed breakthrough varicella[35]. The development of an MMRV vaccine and studies of the vaccine showing excellent response to all four antigens may result in its use in the future instead of the VZ vaccine[37].

In conclusion, it must be recognised that serious complications can occur in otherwise healthy children who have varicella infection. A high index of suspicion is needed to diagnose complications associated with varicella infection early.

Summary of 8 cases of varicella infection with complications and their outcome

Patients	Age	Day of illness*	Complications	Outcome
1	12-months old	4	Infected vesicles glomerulonephritis provoked seizure	Healed scars
2	5-years-old	2	Disseminated varicella infection	Died
3	4 1/2-years-old	3	Encephalitis	Well
4	5-years-old	8	Encephalitis	Well
5	5 1/2-years-old	6	Encephalitis	Poor memory and behavioural change
6	6 1/2-years-old	6	Acute cerebullar ataxia	Well after 4 weeks
7	12-years-old	8	Acute cerebullar ataxia	Well after 4 weeks
8	7 1/2-years-old	5	Acute cerebullar ataxia with aseptic meningitis	Well after 4 weeks

* Day of illness at presentation

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