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Complications of varicella in children: emphasis on skin and central nervous system disorders

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A review of medical records at a tertiary hospital in southern Taiwan from June 1988 through May 1998 identified 136 children who had been hospitalized for varicella-related complications. Of the children, 83% (113/136) were healthy before the onset of varicella and 17% (23/136) had underlying illnesses. The mean age was 4.7 years (ranged from 1 day to 18 years) with a male predominance (1.7:1). The mean hospital stay was 5.5 days (ranged from 1 to 22 days). Secondary bacterial skin or soft tissue infections were the most common complications (44%), followed by central nervous system (CNS) involvement (23%), pneumonia (18%), thrombocytopenia (12%), and liver function impairment (10%). Among the 60 patients with secondary bacterial cutaneous infection, 16 (27%) had positive isolates, including 12 isolates of *Staphylococcus aureus* and four *Streptococcus pyogenes*. Age above 8 years was significantly associated with the development of varicella-associated CNS complications (p = 0.019). Of the 23 immunocompromised hosts, the most common underlying conditions were hematological diseases (11 patients, 48%), followed by neonatal varicella (7 patients, 30%) and chronic illness with steroid treatment (5 patients, 22%). All of the subjects in this study had a favorable outcome except for three lethal cases, resulting in a case-fatality rate of 2.2%. The cause of death was *S. aureus* septicemia in one patient, streptococcal toxic shock syndrome in one patient, and encephalitis with brain herniation in one patient. Our results demonstrate that varicella continues to be a serious disease that occasionally results in life-threatening complications in healthy and immunocompromised children. Routine immunization of all healthy children against varicella is recommended.

Key words: Children, complication, encephalitis, skin infection, varicella

Varicella is a common contagious disease, which is caused by primary varicella-zoster virus (VZV). Exposure is thought to occur by direct contact or airborne droplets. The incubation period is usually from 14 to 16 days with outside limits of 10 to 21 days [1]. Varicella has traditionally been regarded as a benign, inevitable disease of childhood, however, varicella-related deaths can occur in otherwise healthy children [1]. Adults, pregnant women, newborns and immunocompromised hosts are at greater risk for developing serious complications from varicella [2-6].

The aim of this hospital-based study was to report the clinical spectrum, severity of complications, and the morbidity and mortality in children during the last decade at a tertiary care hospital in southern Taiwan.

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Patients and Methods

All medical records of children hospitalized at the National Cheng Kung University Hospital from June 1988 through May 1998 due to varicella-related complications were reviewed. The demographic data, clinical features, laboratory findings, neuroimaging manifestations and outcome were recorded. Children were categorized as immunocompromised if they had received cytotoxic chemotherapy or long-term (> 2 weeks) corticosteroid therapy, or had neonatal chickenpox infection [7].

Definitions

Diagnosis of varicella was made based mainly on clinical findings, and viral cultures were done infrequently. The presence of skin and soft tissue bacterial infection was established by clinical findings, and 16 were confirmed by bacterial cultures. We defined central nervous system (CNS) dysfunction as documentation of any abnormal neurological

examination results. Cerebellar involvement was defined as the presence of ataxia, nystagmus, headache, nausea, and vomiting or nuchal rigidity in various combinations. Meningoencephalitis was defined as the presence of CNS dysfunction, sterile cerebrospinal fluid (CSF) and pleocytosis (white blood cell, WBC, > 5/ mm^3). Encephalopathy was defined as an altered mental status with normal CSF analysis. Pneumonia was diagnosed when interstitial infiltration or nodular lesion was found on chest roentgenography, with or without clinical evidence of respiratory distress. Thrombocytopenia was defined as a platelet count below 100, 000/mm^3. Hepatic involvement was defined as elevation of alanine aminotransferase (ALT). Reye syndrome was defined as an elevated serum ammonia level, CNS dysfunction, and compatible histopathological findings of liver biopsy.

The JMP soft work program (SAS Institute Inc., SAS Campus Drive, Cary, NC 27513, USA) was used for statistical analysis. The complications in different age groups were analyzed using chi-square analysis or Student's t test. A p value less than 0.05 was considered statistically significant.

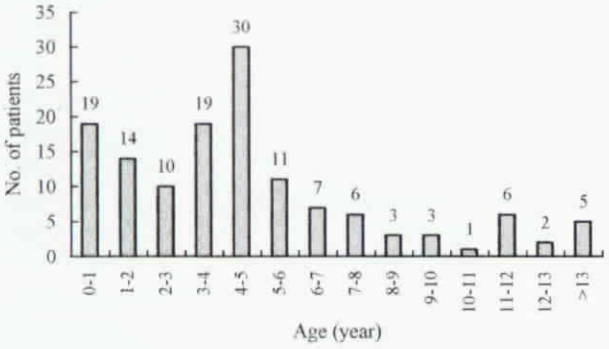

Fig. 1. Age distribution of the 136 hospitalized children with complications of varicella.

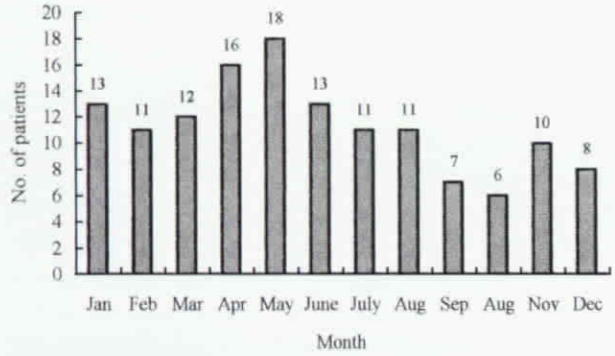

Fig. 2. Monthly distribution of the 136 hospitalized children with complications of varicella.

Results

Demographics

A total of 136 children treated for varicella infections were included in the study. The mean age was 4.7 years old (ranged from 1 day to 18 years) (Fig. 1) with a male predominance (1.7:1). Twenty children were older than 8 years of age. Varicella occurred year-round in with the greatest prevalence during the period from winter to early summer (Fig. 2). The average hospital stay was 5.5 days (ranged from 1 to 22 days). Fifty children (37%) had a household contact history.

Of the 23 immunocompromised patients, 11 (47.8%) had underlying hematological diseases (eight with leukemia, one lymphoma, one thalassemia who received splenectomy, and one histiocytosis who received azathioprine therapy), five (21.7%) were receiving steroid therapy concurrently with the development of varicella infection (including one chronic idiopathic thrombocytopenic purpura, two asthma, and two nephrotic syndrome), and seven (30.4%) were neonates. The seven neonates were exposed to maternal varicella within 1 week before and after delivery. These patients had skin lesions, which developed during the period from 7 to 12 days of life. Severe interstitial pneumonitis requiring mechanical ventilation developed in two neonates.

Clinical spectrum of complications

The most common complication was skin and/or soft tissue infection (60 cases, 44.1%), followed by CNS dysfunction (31 cases, 22.8%), pneumonia (25 cases, 18.4%), thrombocytopenia (16 cases, 11.8%), and hepatic dysfunction (14 cases, 10.3%).

Secondary bacterial cutaneous infection

The 60 skin and/or soft tissue bacterial superinfections of the patients are summarized in Table 1. Bacterial pathogens were isolated from 16 children, with *Staphylococcus aureus* in 12 (nine methicillin-sensitive, and three methicillin-resistant) and Group A beta-hemolytic *Streptococcus* (GABHS) in four. Two children died. One of them had thalassemia and had received splenectomy before development varicella and death due to *S. aureus* septicemia; the other one was previously healthy and developed GABHS pyomyositis infection with subsequent deterioration to streptococcal toxic shock syndrome [8].

CNS dysfunction

CNS dysfunction was the most common type of extracutaneous involvement. Cerebellar involvement

Table 1. Complications associated with varicella in 136 hospitalized children

Complication[a]	No. of patients (%)	
Skin and/or soft tissue bacterial infections	60	(44.1)
Superficial infection only	46	(33.8)
Superficial infection with conjunctivitis	14	(10.3)
Cellulitis	10	(7.4)
Pyomyositis	3	(2.2)
Superficial infection with blepharitis	2	(1.5)
Arthritis	1	(0.7)
CNS[b] dysfunctions	31	(22.8)
Cerebellar ataxia	13	(9.6)
Encephalopathy	10	(7.4)
Meningoencephalitis	6	(4.4)
Reye's syndrome	2	(1.5)
Pneumonia	25	(18.4)
Immunocompromised host infection	23	(16.9)
Thrombocytopenia	16	(11.8)
Hepatitis	14	(10.3)
Febrile convulsion	6	(4.4)

[a]Some children had more than one complication.
[b]CNS = central nervous system

was the most common neurological manifestation (41.9%, 13/31), occurring at a mean age of 8.2 days (ranged from 6 to 14 days) after the onset of the skin eruption. Meningoencephalitis was diagnosed in six children with a mean WBC in CSF of 22/mm^3 (ranged from 7 to 33/mm^3). Encephalopathy was noted in 10 children. Reye's syndrome occurred in two previously healthy children. Of the 31 children with CNS dysfunction, the patients whose ages older than 8 years old were more prone to have CNS involvement than those younger than 8 years (nine in 20 vs. 22 in 116, $p = 0.019$). One child died of meningoencephalitis complicated with brain herniation.

Pneumonia

Twenty-five patients developed pneumonia. Chest x-ray findings were bilateral interstitial or reticulonodular infiltrates in 23, lobar consolidation in one, and diffuse pneumonia patch associated with pleural effusion in one (*Pseudomonas aeruginosa* was isolated from pleural effusion).

Liver function impairment

Fourteen children (10.1%, 14/136) presented with hepatic dysfunction with a median level alanine amino transferase (ALT) of 162 U/L (ranged from 100 to 2068 U/L). All of these patients recovered completely.

Thrombocytopenia

Petechiae, ecchymosis and/or purpura developed in 16 healthy children. Thrombocytopenia developed 4.7 days after skin eruption (ranged from 4 to 7 days). All of them received supportive care only, and recovered completely within 2 weeks.

Treatment and outcome

The majority of children (95.6%, 130/136) recovered uneventfully. Three children with acute or chronic neurologic complications had prolonged convalescence. One of these patients had cerebellar involvement, and cerebellar signs and mood depression, which persisted for 1 month. The other two patients had meningoencephalitis and received anticonvulsants for seizure control.

Among the 16 immunocompromised hosts who had received cytotoxic chemotherapy or long-term steroid therapy, one with acute lymphocytic leukemia who was admitted 5 days after skin eruption developed varicella pneumonitis, pancreatitis, hepatitis, thrombocytopenia and secondary bacterial infection. He recovered completely after high dose intravenous acyclovir (50 mg/kg/day for 7 days), antibiotics and aggressive supportive care. One patient who had undergone splenectomy due to thalassemia major prior to the development of varicella, died of *S. aureus* septicemia complicated with varicella infection. The other 14 children received antiviral therapy within 48 h after skin eruption, and had a less complicated course. Of the seven newborns, six received acyclovir therapy (30 mg/kg/day for 5-7 days), while one received prophylactic intravenous immunoglobulin (IVIG, 1 gm/kg/day for 2 days) before skin eruption. All of them recovered completely without sequelae.

Three children died. One child with thalassemia disease, who had received splenectomy prior to the development of varicella, died of *S. aureus* septicemia. The other two children were previously healthy. One contracted GABHS pyomyositis with streptococcal toxic shock syndrome, and one developed encephalitis with brain herniation. The case-fatality rate was 2.2% (3/136).

Discussion

Secondary bacterial superinfection of the skin and soft tissue is the most common infectious complication of varicella in children [9], and *S. aureus* and GABHS are the most common offending organisms. In this series, *S. aureus* was the most common pathogen in cutaneous infections (75%, 12/16), followed by GABHS (25%, 4/16). The frequency and severity of GABHS infection has been reported to be on the rise and occurs predominantly in healthy adolescent or adult population

[8-11]. The yearly incidence of GABHS bacteremia rose by a factor of three in 1993 [12], and 50% new cases of invasive GABHS disease were associated with VZV infection. M types 1 and 3 of GABHS have been reported to be more frequently associated with invasive and fatal infections than other M types [13]. GABHS can cause severe invasive infections, including necrotizing soft tissue infections and toxic shock-like syndrome, as in the fatal case in one of the children in this series. Previously reported urgent warning signs of soft tissue infection in patients with varicella infection include a long febrile duration (more than 4 days after the onset of varicella); severe pain out of proportion to clinical findings, and elevated band count (> 5%) of WBC [14]. With prompt aggressive surgical intervention and medical treatment, a good outcome can be anticipated.

Neurologic involvement was the second most frequent complication in this series, as what has been noted in a previous study [15]. The incidence of neurologic involvement is about one in 4000 varicella cases among children younger than 15 years of age or less [16]. Cerebellar ataxia was the most common manifestation (39%) in this study, and although this complication was usually self-limiting, it was always very frightening for the parents. Encephalitis usually occurs 3 to 7 days after the onset of the skin lesions but at times may precede the exanthema [17]. The neurological signs occurring after the appearance of cutaneous lesions are most likely the results of a nonspecific, postinfectious autoimmune process, whereas, the neurological signs preceding or accompanying the exanthematous manifestation are likely to be directly related to viral invasion of the CNS [15]. In this series, children older than 8 years of age were more likely to develop CNS complications (p = 0.019).

In immunocompromised patients, varicella can lead to the development of more severe conditions. The development of more severe symptoms is correlated with the extent of immunosuppression and also depends on the type and timing of chemotherapy [18]. Early use of varicella-zoster immunoglobulin (or IVIG) for immunocompromised patients exposed to chickenpox and of acyclovir for patients with skin eruption [1], not only has a preventive effect, but also may shorten the duration of disease, decrease the number of skin lesions, and reduce discomfort [6,19]. It is worth noting that there is substantially increased risk of development of varicella in healthy children who are receiving systemic corticosteroids with a dosage of 0.5 to 1 mg/kg/day during the recent 3 months [20-22]. The majority (95.7%, 15/16) of patients who received chemotherapy or steroid therapy in this study were admitted after the development of skin eruptions. All of them received intravenous acyclovir (500 mg/m^2/dose, q8h) therapy.

Varicella is not as innocuous as it is often considered to be, and serious diseases and occasional life-threatening complications still occur in otherwise healthy children. The greatest progress in the prevention of VZV-associated disease is the use of a classical live-attenuated VZV vaccine. It had been shown to be immunogenic and clinically effective in both healthy and immunocompromised children by the Centers for Disease Control and Prevention [23]. Post-vaccination-illness is almost always mild [24]. It protects leukemic children against severe varicella with an efficacy approaching 100%, and significantly lowered the contraction rate of zoster from 15% to 3% [25]. VZV vaccine is available in Taiwan, and the appropriate inoculation age is between 12 and 24 months [26]. Wide-scale vaccine use (including incorporation of varicella vaccine into the infant immunization schedule) should reverse the trend and reduce the overall impact of varicella in both immunocompetent and immunocompromised children. Therefore, the administration of VZV vaccination to all healthy children is recommended.

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