Assessment of Pediatric Cases with Chickenpox and Zona Hospitalised at Our Inpatient Clinics

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Abstract

Objective: Chickenpox and zona are benign virus infections caused by varicella zoster virus (VZV). However, in immunocompromised individuals, including patients with malignancy, the infection may cause severe complications and mortality. The complications of VZV are one of the arguments in favor of universal vaccination programs in children.

Material and Methods: In this study, patients between ages 15 days and 18 years (median: 5.7±3.8 years), hospitalized in our inpatient clinics from January 1986 to December 2013, were retrospectively evaluated. A z

Results: Of all patients, 159 (83%) had varicella zoster infection and 33 (17%) had zona; 67 (42%) of 159 patients with varicella zoster infection and 32 (97%) of 33 patients with zona were immunocompromised. Complications occurred in 123 (64%) cases; 84 (68.3%) of these 123 patients were immunocompetent, and 39 (31.7%) patients were immunocompromised. The major complications were as follows: cerebellitis and/or encephalitis [n=37 (30%)], pneumonia [n=32 (26%)], secondary bacterial skin/soft tissue infections [n=20 (16.2%)], varicella gangrenosum or purpura fulminans (n=7 (5.7%)], disseminated intravascular coagulopathy [n=3 (2.4%)], aseptic meningitis [n=2 (1.6%)], septic shock [n=2 (1.6%)], myocarditis [n=2 (1.6%)], hemophagocytic syndrome [n=1 (0.8%)], transverse myelitis [n=1 (0.8%)], meningoencephalitis [n=1 (0.8%)], purulent meningitis [n=1 (0.8%)], facial palsy [n=1 (0.8%)], septic arthritis [n=1 (0.8%)], and immune thrombocytopenic purpura (ITP) [n=1 (0.8%)]. In one of the cases listed above (which had autoimmune lymphoproliferative disease), severe hemolytic anemia also developed. Concomitant pneumonia and skin infections [n=4 (3.2%)] and concomitant encephalitis and pneumonia [n=4 (3.2%)] were among the complications defined. In 2 other patients (1.6%), concomitant encephalitis and skin infections were also noted. In a single immunocompetent patient who was hospitalized recently, septic shock, adult respiratory distress syndrome (ARDS), purpura fulminans, osteomyelitis, and septic arthritis were observed. Parenteral acyclovir treatment was administered to immunocompromised patients (e.g., patients with malignancy or under steroid treatment for any kind of reason), as well as immunocompetent patients with central nervous system (CNS) complications. During the follow-up period, 3 patients (1.6%, n=192) died; 3 others who developed encephalitis survived with neurological sequela.

Conclusion: Varicella zoster infection, which is known as a benign disease, may cause severe complications and mortality in immunocompetent pediatric patients, as well as immunocompromised ones. These data are consistent with the previous and are relevant in the decision-making process regarding the benefits of routine varicella vaccination.

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Introduction

Chickenpox and zona are viral diseases with a benign course caused by varicella zoster virus (VZV). Even though the ultimate aim is to minimize the complications through vaccination and antiviral prophylaxis, the virus causes serious mortality and morbidity in immunosuppressed people due to congenital or acquired reasons (1). It is commonly known that the antiviral therapy initiated without delay at the onset of the infection reduces mortality and morbidity (2).

After replicating in the respiratory tract mucosa, VZV, the causative agent of chickenpox and zona, travels to reticuloendothelial system through blood and lymphatic circulation, and then vesicular rashes occur on the skin. Although it frequently has benign course, complications may develop in 5.5% of the people with normal immune system (3). Cellular immunity has a big role in constraining the VZV infection. Infants, the elderly and those with immune system disorder constitute the risky group in terms of viremia and life-threatening viral dissemination. The most common complications after VZV infections such as bacterial superinfection of skin lesions, central nervous system pathologies (the most commoncerebellitis and cerebellar ataxia) and secondary pneumonia are significantly the common causes of mortality and morbidity. Hemorrhagic chickenpox than can lead all the way to disseminated intravascular coagulation, and mono or polyarticular arthritis infection are among the other complications (4).

Material and Methods

In this study, patients aged 15 days and 18 years (median:5.8+/-3.8 year old) hospitalized and monitored in all the pediatric wards of our clinic between January 1986 and December 2013 were investigated and the distribution of the disease in immunosuppressed and immunocompetent individuals, cause of hospitalization, the implemented therapy, complications and prognosis were retrospectively evaluated. The diagnoses of chickenpox and zona were made based on the characteristics of rashes and typical course of the disease. Clinical status such as cerebellitist, encephalitis, meningoencephalitis, transvers myelitis, aseptic meningitis,pneumonia, skin-soft tissue infections, varicellagangrenosum, purpurafulminans, septic shock, disseminated intravascular coagulation, myocardia, septicarthritis, haemophagocytic syndrome, immune thrombocytopenic purpura were defined as VZV infection complications.

Statistical analysis

Statistical analysis was made using Chi-square test and Student t-test in SPSS 13.0 program. A p value of <0.05 was defined as statistically significant.

Results

Complications developed in 123 cases (%64). 39 (32%) of these cases were immunosuppressive and 84 (68%) were immunocompetent patients. While the average age of children with complication was 5.2+/-3.5 year, the average of those without a developing complication turned out to be 6.5+/-4.1. Statistically the average age of children with a developing complication was significantly low (p=0.02). Nearly all of the 69 (36%) patients without a complication were hospitalized due to underlying immunodeficiency (presence of hematologic malignity, being under steroid therapy due to various diseases or under immunosuppressive therapy due to organ transplantation, HIV infection etc.), young age or prevalent and serious chickenpox lesions to be given acyclovir therapy. The cases with or without developing complications were compared in an attempt to clearly indicate the effect of the factors such as immunity, age and the presence of an underlying disease to the course of the chickenpox infection.

Thirty-three (17%) of the total of 192 of the patients of whom 93 (48.5%) were females and 99 (51.5%) male constituted the zona cases. Thirty-two (97%) of these 33 zona cases and 67 (42%) of the 159 (%83, n=192) chickenpox cases were composed of patients with immune deficiency (Table 1). A case whose natural immune barrier was deteriorated and a case with a lack of protein S were also present in this study. While most of the zona patients were immunosuppressed cases, the rate was in favor of immunocompetent patients in the chickenpox cases. Given the seasonal distribution of the disease, the most cases were seen in winter and early spring, primarily in March.

The average hospital-stay duration of the cases turned out to be 9.4+/-8.0 days. Among the 93 immunocompetent patients (48.4%, n=192), apart from an operation-scheduled fallot case, a case with dental abscess, another patient with a lack of protein S, 4 cases two of who were neonatal and two under 2 years of age and two cases with many lesions hospitalized due to bad oral intake, only cases developing complications were hospitalized and monitored; and all the patients with immune deficiency were hospitalized and monitored

regardless of whether they developed any complications.

One hundred and twenty-three (64%; n=192) cases had complications. 39 (31.7%) of these cases were immunosuppressive (9 zona, 30 CP) and 84 (68.3%) were immunocompetent patients (1 zona, 83 CP) (Table 2, 3). In other words, while there were complications in 39 (39%) of the total of 99 immunosuppressed patients, 84 (90%) of 93 immunocompetent patients had complications. The complications that developed in the patients were recorded as; cerebellitis and/or encephalitis in 37 cases (30%), pneumonia in 32 cases (26%), secondary bacterial skin/soft tissue infections (cellulite, necrotizing fasciitis, abscess etc.) in 20 cases (16.2%), varicella gangrenous or purpurafulminans in 7 cases (5.7%), disseminated intravascular coagulation in 3 cases (2.4%), aseptic meningitis in 2 cases (1.6%), septic shock in 2 cases (1.6%), myocardia in 1 case (0.8%), septic arthritis and myocardia in 1 case (0.8%), haemophagocytic syndrome in 1 case (0.8%), transvers myelitis in 1 case (0.8%), meningoencephalitis in 1 case (0.8%), purulent meningitis in 1 case (0.8%), facial paralysis in 1 case (0.8%), septic arthritis in 1 another case (0.8%) andimmune thrombocytopenic purpura in 1 other case (ITP) (0.8%). The following cases had combined infections; 4 cases encephalitis and pneumonia (3.2%), 4 other casespneumonia and skin infection (3.2%), 2 cases encephalitis and skin infection (1.6%) (Table 4). In one case monitored with the diagnosis of lymphoproliferative syndrome, severe hemorrhagic shock status developed. Septic shock, ARDS, purpurafulminans and then osteomyelitis and septic arthritis was observed in 1 other case. It was reported that 1 AML and 1 neuroblastoma cases had CP infection. An immunocompetent patient was interned due to secondary bone marrow suppression.

The distribution of developing major complications was evaluated in accordance with immunity and age status. Accordingly; while all the central nervous system (CNS) complications were observed in 47% of the patients, they were available in only 3.0% of the patients with immune deficiency. There was a statistically significant difference between them ($p<0.001$). It was also concluded that there were significantly more skin and tissue infections in immunocompetent patients (in 19% of them) in comparison to the patient with immune deficiency ($p<0.04$). While they were observed respectively 19.7% and 19.7% in patients with pneumonia, immunocompetent and immune deficiency ($p=0.69$), the rates for the patients groups of varicella gangrenous and purpura-

Table 1. Underlying diseases causing immune deficiency

Zona cases (n=32)
Hematologicmalignity (24)
Solid organ tm (3)
Steroid orimmunesuppressivesecondary to the use of other drugs (FSGS*, Transplanted Kidney, Autoimmune Lymphoproliferative Syndrome) (3)
Hyper IgM Syndrome (1)
Undefined cellular immune deficiency (1)
Chickenpox cases (n=67)
Hematologic malignities (43)
Solid organ tm (8)
CombinedImmune Deficiency (1)
Wiscott Aldrich (1)
Lack of IgA (1)
HIV** infection (2)
Chronic renal failure (2)
Steroid or immunosuppressive secondary to the use of other drugs (Nephritic Syndrome, Asthma Bronchial, West Syndrome, Autoimmune Hemolytic Anemia, Chronic ITP***) (7)
Langerhans Cell Histiocytosis (1)
Ichthyosis Disease (1)
*Fokal Segmental Glomeruloskleroz **Human Immunodeficiency Virus ***İmmün Trombositopenik Purpura ITP: Immune thrombocytopenic

Table 2. The rates of complication development in patients (n=159) with CP infection

	With immune deficiency	**Immunocompetent**	**Total**
Complication present	30 (%18.8)	83 (%52.2)	113 (%71)
Complication not present	37 (%23.3)	9 (%5.7)	46 (%29)
Toplam	67 (%42.1)	92 (%57.9)	159 (%100)
CP: Chickenpox			

Table 3. The rates of complication development in patients (n=33) with Zona infection

	With immune deficiency	**Immunocompetent**	**Total**
Complication present	9 (27%)	1 (3%)	10 (30%)
Complication not present	23 (70%)	-	23 (70%)
Toplam	32 (97%)	1 (3%)	33 (100%)
CP: Chickenpox			

fulminans were respectively 6.4% and 2.1% (p=0.28), and no significant difference was found between these groups with regards to these complications. Given the distribution of complications by age, it was revealed that-there were significantly greater incidences of skin and soft tissue infections in infants (aver. 3.8+/-3.2 years) in comparison to older children (aver. 6.1+/-3.8 years) (p=0.003). Regarding the prevalence of complications such as pneumonia, CNS complications, varicellagangrenous/purpurafulminans, no variability was observed (respectively p was 0.261, 0.683, 0.929). It was found that the frequency of complication development was independent of gender.

All the patients with primer or secondary immune deficiencies regardless of their immunity status or with CNS complications were given parenteral acyclovir therapy.

While 3 cases (1.6%, n=192) with immune deficiency in this study dies, 3 other cases with encephalitis complications, on the other hand, improved with neurological sequela.

Table 4. Distribution of complications

Complications	**(n) %**	**ID***	**IC****
Cerebellitis and/or encephalitis	30% (37)	-	37
Pneumonia	26% (32)	17	15
Skin/soft tissue infection	16.2% (20)	7	13
Varicella gangrenous purpura fulminans	5.7% (7)	2	5
Disseminated intravascular coagulopathy	2.4% (3)	2	1
Aseptic meningitis	1.6% (2)	-	2
Septic shock	1.6% (2)	2	-
Myocarditis	0.8% (1)	1	-
Septicarthritis or myocarditis	0.8% (1)	-	1
Haemophagocytic syndrome	0.8% (1)	1	-
Transvers myelitis	0.8% (1)	-	1
Meningoencephalitis	0.8% (1)	-	1
Purulentmeningitis	0.8% (1)	-	1
Facial paralysis	0.8% (1)	1	-
Septicarthritis	0.8% (1)	-	1
Immune thrombocytopenic purpura (ITP)	0.8% (1)	-	1
Encephalitis and pneumonia	3.2% (4)	2	2
Pneumonia and skin infection	3.2% (4)	2	2
Encephalitis and skin infection	1.6% (2)	-	2

*With immune deficiency
**Immunocompetent

Discussion

It is commonly known that the virus-specific cellular immunity is crucially important in controlling viral activation and dissemination, and as a result, VZV infections in people with immune deficiency have more severe course of the disease. Immunity especially in patients with hematologic malignity is damaged in two ways due to both malignity itself and chemotherapeutic effects. Besides, it was reported that many more mucocutaneous lesions developed in immunosuppressive patients in comparison to normal patients and these patients had extended virus excretion and recovery period (1).

It is possible to come across many studies in the literature, mostly retrospective ones illuminating chickenpox infection epidemiology and complications. In a recent retrospective study in Poland in which 224 children under 18 with average age of 3.12 hospitalized due to CP infections, it was revealed that the most prevalent complications were respiratory tract infections (26%), respectively followed by skin infections (21%) and neurologic complications (18%); while it was also reported that complications regarding more than one system was found in 25 patients (11%), hospitalization rates declined by increasing age; the highest rate of hospitalization was in the first years of life; besides, 92% of the patients were completely healthy previously (5). In our study, on the other hand, the prevalent complications were cerebellitis and/or encephalitis with 30%, respectively followed by pneumonia (26%) and secondary bacterial skin/soft tissue infections (16.2%). Although the average age in our study was slightly higher (5.7 years), the complication rates in infants were higher, a result compatible with the study in question (p=0.02). The rate of previously healthy children in our study was 48.4%. The prevalence of complications regarding more than one system, on the other hand, was around 10%.

In a study done in Holland, a country known to have a lower rate of VZV infection in which the national medical records were investigated, patients diagnosed with chickenpox admitted and monitored on inpatient basis in 23 different hospitals were examined retrospectively (6). In this study in which 296 patients were included, it was reported that complications developed in 76% of the cases. The rate of complications monitored in our study was 64%. Majority of these complications were observed in immunocompetent patients. The

fact that immunosuppressive patients were to be hospitalized without any delay at the onset of the disease and their therapies started, and that immunocompetent patients, on the other hand, were to be monitored on inpatient basis without starting an antiviral therapy in the case of no presence of complications can explain this difference. Different from our study, secondary skin and soft tissue infections were reported to be the most prevalent complication in the Dutch study (28%cases). No chickenpox-related mortality occurred in this study. The rate of mortality in our study, on the other hand, was 1.6%.

In a multi-centered study done in Turkey between January 2008 and September 2008 (VARICOMP) (7), the researched aimed to investigate the rates of chickenpox-related hospitalizations, complications, mortality rates and the total costs (8). In this study where epidemiologic and economic data were highlighted, patient population aged between 0-15 were investigated, medical records from 27 medical institutions in 15 different cities were collected and50% of the child population in Turkey was reflected in the study. Throughout this period, 824 children 73% of whom were previously known to be healthy were hospitalized due to chickenpox and its complications. It was found that majority of the patients were children of 5 years old or younger and 30% of them were under 1 year of age. In our study, on the other hand, the rate of children aged 5 and under was 48%. The most prevalent complications in the VARICOMP study were; secondary bacterial infections (23%), neurologic system (19.1%) and respiratory system (17.5%) diseases. It was concluded that secondary bacterial infections and neurologic complications were more significantly prevalent in the previously healthy group ($p<0.001$). Similarly it was found in our study that neurologic system and secondary bacterial skin/soft tissue infections in previously children were significantly higher in comparison to the patients with immune deficiency ($p<0.01$ and $p<0.04$). According to the VARICOMP study, hematologic complications were more common in children with underlying diseases. Similar, in our study, it was found that all the patients with hematologic complications previously had immune deficiency. While average period of hospital-stay in the VARICOMP study was 6 days, the hospital-stay in our study was 9.4 days.

In another retrospective study done in Italy involving 31 hospitals (8), the researchers reported the epidemiologic data regarding the hospital-stay periods of chickenpox cases. It was also reported that 47% of the 650 cases were composed of non-complicated and 52.9% complicated patients. In this study, it was pointed out that neurologic and respiratory system complications significantly increased in recent years, but no change was observed in the prevalence of other complications.

The results of a study (9) done at Ege University are in parallel with the current study and indicated that the complications of VZV infections in immunocompetent children were more prevalent than previously thought. Similarly, while CNS complications and prevalence of pneumonia in our study did not reveal clear differences, skin and soft tissue infections in infants were significantly more prevalent. Similar results came out of the study at Ege University as well. While CNS complications were on the top of the list, in parallel to the Ege study, cerebellitis was more prevalent than encephalitis. Again, similarly in two studies, given the seasonal distribution of the cases, the higher numbers emerged in winter primarily in March and early spring during which the disease reached its peak.

In a prospective study (10) involving previously immunologically healthy VZV-infected children under 16 that used the data of 458 pediatric hospitals in Germany, it was reported that most of the complications were seen in pre-school period (mostly frequently at the age of 4), that there was no gender-based variation and that neurologic complications were the most prevalent with 61.3%. The results of this study are mostly in parallel to the results of our study as well. The CNS complications in our study, too, are at the top of the list in our study. Similarly in the German study, it was reported that majority of the infectious complications were seen in children under 4 years of age, and neurological complication mostly in older children. In our study, on the other hand, the age factor had a specific role to play in only secondary skin/soft tissue infections, and the group of complications was more prevalent in younger ages (on average 3.8 years).

In a study done in Switzerland (11), CP complications requiring hospitalization and hospitalization rates were defined by being compared with the previous data in the literature. According to the results of this study involving the data of the last 10 years, it was found that average age was 5.6 years; and it was reported that CNS complications were the most prevalent complications in previously healthy children (23%, 26 patients). Similarly, most of the CNS complications in our study

were seen in children with normal immunity.

In the literature, it is possible to find many studies done in unvaccinated children and adolescent offering similar results as it is the case in our patient population. Our study has obtained similar results with the studies mentioned so far in many respects. While majority of the complications we came across had a mild or treatable status, some of them had serious complication which eventually led to mortality.

It is commonly known that nearly 882-1450 children in Turkey are hospitalized (466-768/100,000 cases) annually due to CP (7). It was revealed that the nationwide incidence of the disease was more prevalent in infants under 1 year old, a group unable to be vaccinated; and it was concluded once again that vaccination was the most effective and realistic solution in order to prevent complications and mortality in all age groups (7). Based on this conclusion, the addition of CP vaccine to the pediatric vaccine calendar and implementation strategies were evaluated at Advisory Committee meeting of the Ministry of Health, and it was decided with the official approval dated 25.01.2013 that the administration of the vaccine would be started as one dose after birth in the 12th month (12). As a result of studies and meta-analyses done in the United States, Canada and some European countries (13), second dose of CP vaccine is recommended in an attempt to complete the primer immunization in one-dose vaccinated individuals. It is emphasized that the first dose is administered between 12-18 months and the second dose 3 months later or longer after the first dose unless the person suffers from an illness. The future researches in Turkey should focus on studies that investigate disease incidence and complication development risks after one dose vaccination and under the light of the study results, the necessity of the second dose already in practice in developed countries should be established.

Conclusion

VZV can cause serious complications in children and adolescents that can eventually lead to mortality. Even though mortal complications are rare, they can reach some striking figures given the general incidence of CP infections in the whole population. It is commonly known that primer vaccination significantly reduces the prevalence incidence of the disease and its complications.

Ethics Committee Approval: Ethics committee approval was received for this study from the local ethics committee of İstanbul University, Medical Faculty of İstanbul University.

Informed Consent: Written informed consent was obtained from the patients who participated in this study.

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