

## COMPARATIVE STUDY OF PATIENTS AND HEALTHY CARRIERS OF ANTIBODIES AGAINST VARICELLA-ZOSTER VIRUS

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*The degree of seropositiveness against Varicella-zoster virus (VZV) were established by examination of 737 single serum samples from clinically healthy donors aged 1-60 years by using CF-test. Comparatively, 91 of them were studied by ELISA (Behring-Germany, Ensygnost-Varicella-Zoster). Additionally, 37 single serum samples of patients with clinical symptoms of herpes zoster were examined by CF-test. The results of the healthy population showed a mean seroprevalence of 48,98 % by CF-test and of 60,44 % by ELISA. The difference of seroprevalence of healthy and ill individuals (with typical clinical signs) in matched age intervals was considerable only with patients suffering from herpes zoster.*

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**Key-words:** Varicella-zoster virus, Varicella, Herpes zoster, ELISA, CF-test

Varicella-zoster virus (VZV) is a member of the *Herpesviridae* family. The primary infection is manifested as varicella (leshtenka, Bulgarian folk name). According to bibliographic data available (10), somewhat about 3,5 million patients are registered annually in the USA, 95 % of them being children (1-14 years old) and only 2 % adults (over 20 years old). Bulgaria represents also a pediatric tendency in the disease (3). After primary infection the virus is latent in dorsal stem ganglia and

cranial nerve ones but its reactivation later on leads to herpes zoster. The same is with rest members of this family; one of the explanations of this phenomenon is a suggested incomplete immunity not being sufficient to eliminate the virus away from the patient's organism. The latter transfers into a latent status and its reactivation in later terms is associated with temporary dysbalance or total lack of cellular immunity (7,8).

The host immune response towards VZV-infection is not yet clear. Early humoral immune reaction in most patients is registered about 6 days after the beginning of the primary infection with formation of

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IgM and IgG anti-VZV-antibodies established by immunofluorescent or ELISA techniques. It persists for many years after the acute infection (5,11,15). The seroprevalence is of 96 % in North America (9,14), 90 % in South Africa but the age representation is increased gradually and about the age of 60 years it is practically 100 % (12).

The present study is our attempt to compare the level of VZV-seroprevalence in healthy individuals and the induction of humoral immune response in patients with varicella or herpes zoster.

## MATERIAL AND METHODS

A total of 737 single serum tests of clinically healthy subjects aged between 1 and 60 years divided into age groups were examined (Fig. 1). Some 37 single serum tests of patients with varicella examined 7 days to 1 month after the onset of characteristic rash on the skin were studied along with 33 single serum tests of patients with clinically manifested signs of herpes zoster examined after the manifestations of typical clinical symptoms.

The following methods were applied: CF-test was used to detect anti-VZV-antibodies the micro-method (2,6) being reported in our previous study (1). Values of titres of CF-antibodies under 1:4 were

considered negative, whereas values of those titres over or equal to 1:4 were considered positive for antiviral immune reaction. A soluble antigen (provided by NIIPD-Sofia and Behring-Germany) was used in our study. Other authors (13) accepted titres of 1:2 (over or equal) as a positive sign may be due to the weaker sensitiveness of test. ELISA-technique was applied for examination of 91 healthy donors with tests of Behring-Germany (Ensygnost-Varicella/Zoster). This method included a dilution of the serum sample 1:44 which, in turn, reacted with a standard antigen (preliminarily loaded) and control antigen (negative) both from human cell cultures and both inactivated in advance. The registration of the results was performed on Titertek Uniskan-Finland at 405 nm. The positive reaction of the serum test was a marker of previous VZV-infection.

## RESULTS AND DISCUSSION

CF-test with antigens from 2 different firms does not show considerably different results. Fig.1 presents the distribution of 737 clinically healthy individuals according to their age and percentage of seropositiveness (antibody titres over or equal to 1:4). A consequent increase of the level of seropositiveness associated with the

**Table 1***Patients' distribution according to titres of antibodies against VZV (by CF-test)*

Contingent	varicella patients		herpes zoster patients	
	n	%	n	%
Titre				
< 1:4	16	43,24	5	15,15
1:4	7	18,92	8	24,24
1:8	2	5,41	1	3,03
1:16	3	8,11	6	18,18
1:32	8	21,62	3	9,09
1:64	1	2,70	6	18,18
1:128			4	12,12
total	37	100	33	99,99

age is registered with a peak at 4-7 year age group. Therefore, this first result of sudden increase of the infection frequency is most probably due to the tradition that children are collected in kindergardens in this age. The literature data show that such a peak is established in the age group of 5-9 years (3,10). Further with age the level of seropositiveness is preserved with some slight ups and downs. Another peak, in the age group of 26-30 years, is registered and this result may be is due to the increased frequency or reactivation of the latent virus and its clinical manifestation in herpes zoster. The seropositiveness is of 66,66 % in the age group of 51-60 years, whereas the mean one for the whole examined population is of 48,98 %. Some 55 (60,44 %) of all 91 examined by ELISA clinically healthy donors are positive. The difference of seroprevalance could be explained

with higher sensitiveness of this test to compare to CF-test, confirmed by other authors, too (13).

The comparative study of 37 patients with varicella establishes an age range between 1 and 22 as 9 of them (24,32 %) are 1-3 years old, 19 (51,35 %) are 4-7, 3 (8,11 %) are 8-10, 4 (10,82 %) are 11-14 years old, while in the age groups of 15-18 and 19-22 years there is one patient each (2,7 %). The seropositiveness (by CF-test) is of 56,76 % as compared to the mean one (40,4 5%) in healthy individuals from the same age group. Therefore, the seroprevalence of varicella patients does no differ considerably from that of the healthy population ( $p > 0,05$ ).

When analyzing the results it is essential to have in mind the time for serum sample collection. Patients examined by CF-test in the first 7-19 days after beginning of clinical

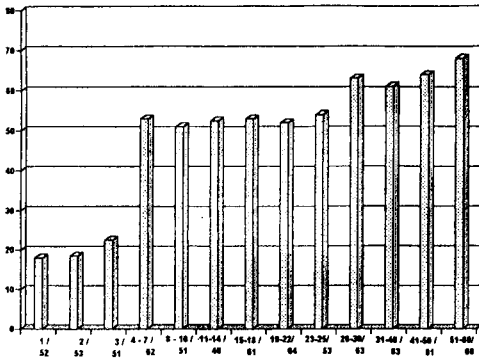


Fig. 1. Healthy donors' distribution according to age and percentage seropositivity against VZV studied by CF-test

symptoms have no antibodies. Titres of 1:4 - 1:16 are registered only 20 days after the onset of the disease. High titres (1:32 - 1:64) are established in reconvalescent patients, 1 or more months after the beginning of clinical symptoms. This means that in order to be precise in our etiologic diagnosis by CF-test we need a double serum sample in 1-month interval. A 4-time seroconversion of the reconvalescent serum test is an undoubtful indication of the disease.

Some 33 patients with herpes zoster are aged between 19 and 60 years: 7 from them (21,22 %) are 19-25 years old, 26 (78,78 %) are 26-60. The seroprevalence (CF-test) is of

84,84 % to compare to 55,89 % of mean seroprevalence in healthy individuals of the same age group,  $p < 0,001$ .

The considerable difference of seroprevalence between patients with varicella and herpes zoster ( $p < 0,01$ ) is another proof that herpes zoster is a manifestation of the reactivation of a latent VZV-infection and the formation of high titre antibodies for shorter period after the clinical symptoms is undoubtedly registered.

In conclusion, the seroprevalence towards VZV increases with the age of examined individuals reaching up to 66,66 % in the age group of 51-60 years, whereas the mean seroprevalence of the whole population under our study is of 48,98 %. The age-associated illness coincides with the registered peaks of healthy subjects in our study. Seroprevalence established by ELISA is higher than that by CF-test due to higher sensitivity of the former (13). The difference of seroprevalence of healthy subjects and patients with typical clinical symptoms in one and the same age range is considerable only with patients suffering from herpes zoster ( $p < 0,001$ ).

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## Сравнително проучване носителството на антитела срещу *Varicella-zoster virus* при здрави и болни индивиди

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**Резюме:** Степента на серопозитивност спрямо varicella-zoster virus (VZV) бе установена при изследване на 737 единични серумни проби от клинично здрави лица на възраст от 1 до 60 г. с комплемент-фиксиращ тест (CF-тест). В сравнителен аспект са изследвани 91 от здравите лица с ELISA-тест на фирмата Behring (ФПГ) (Ensygnost-Varicella/Zoster). Изследвани са 37 единични серумни проби от пациенти с клинични данни за варицела и 33 единични серумни проби от болни с клинични данни за херпес зостер с помощта на CF-тест. Резултатите от изследването на здравата популация показват средна серопревалентност от 48,98 % при CF-тест и 60,44 % - при ELISA-тест. Разликата в серопревалентността на здравите и болните с характерна клинична симптоматика индивиди в еднакъв възрастов диапазон е съществена само при болните с херпес зостер.