Evaluation of varicella zoster virus IgM, IgG and avidity results used in the diagnosis of varicella zoster virus

Varisella zoster virüs tanısında kullanılan varisella zoster virüs IgM, IgG ve avidite sonuçlarının değerlendirilmesi

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Abstract

Aim: Varicella zoster virus (VZV) is a disease that is rapidly transmitted through the respiratory tract and has a high seroprevalence worldwide. This study aimed to evaluate the results of VZV IgM, VZV IgG and VZV avidity serological tests studied in our laboratory.

Methods: In this study, the VZV IgM, VZV IgG, and VZV avidity test results in serum samples sent to our laboratory for preliminary diagnosis or screening of chickenpox between November 2019 and December 2024 were retrospectively examined. Kruskal-Wallis and Chi-Square tests were used to evaluate the results according to mean age, gender, and years.

Results: In this study, VZV IgG positivity was found to be 88.5% (2721/3074) and VZV IgM positivity was found to be 5.2% (51/990). VZV IgG negativity was found to be 7.8% (122/1569) in females of childbearing age, and 7% (4/57) in elderly individuals over 65 years of age. In only three of the 29 samples in which both IgG and IgM were requested and both were found positive, the avidity test was performed and found to be high avidity. No low avidity result was detected. No statistical significant difference was detected between the patients whose VZV IgM and VZV IgG results were positive, negative or borderline values according to gender and age means. In addition, no statistical significant difference was detected between the years in terms of VZV IgM and VZV IgG results.

Conclusion: Despite the high positivity of VZV IgG, antibody screening with VZV IgG can be recommended for high-risk groups. In addition, it was considered appropriate to study the VZV avidity test as a reflex test in laboratories.

Keywords: Avidity; immunoglobulin M; varicella-zoster virus

Öz

Amaç: Varisella zoster virüs (VZV), solunum yoluyla hızlı şekilde bulaşan ve dünya genelinde seroprevalansı yüksek olan bir hastalıktır. Bu çalışmada laboratuvarımızda çalışılan VZV IgM, VZV IgG ve VZV avidite serolojik testlerinin sonuçlarının değerlendirilmesi amaçlanmıştır.

Yöntemler: Çalışmada, Kasım 2019-Aralık 2024 tarihleri arasında laboratuvarımıza suçiçeği ön tanısı ya da tarama amacıyla gönderilen serum örneklerinde çalışılan VZV IgM, VZV IgG ve VZV avidite test sonuçları retrospektif olarak incelendi. Sonuçların yaş ortalamalarına, cinsiyete ve yıllara göre değerlendirilmesinde Kruskal-Wallis ve Ki-Kare testleri kullanıldı.

Bulgular: Çalışmada, VZV IgG pozitifliği %88,5 (2721/3074), VZV IgM pozitifliği %5,2 (51/990) olarak saptanmıştır. Doğurganlık çağındaki kadınlarda VZV IgG negatifliği %7,8 (122/1569), 65 yaş üstü yaşlı bireylerde de bu oran %7 (4/57) olarak saptanmıştır. IgG ile IgM istemi birlikte yapılıp her ikisi de pozitif saptanan 29 örneğin sadece üçünde avidite testi çalışılmış ve yüksek avidite olarak bulunmuştur. Düşük avidite sonucu saptanmamıştır. VZV IgM ve VZV IgG sonucu pozitif, negatif ya da ara değer saptanan hastalar arasında cinsiyete ve yaş ortalamalarına göre istatistiksel olarak anlamlı fark saptanmamıştır. Ayrıca yıllar arasında da VZV IgM ve VZV IgG sonuçları açısından istatistiksel olarak anlamlı fark saptanmamıştır.

Sonuç: VZV IgG pozitifliği yüksek olmakla birlikte, riskli gruplarda VZV IgG ile antikor taramasının yapılması önerilebilmektedir. Ayrıca VZV avidite testinin laboratuvarlarda refleks test olarak çalışılmasının uygun olabileceği düşünülmüştür.

Anahtar Sözcükler: Avidite; immünglobulin M; varisella-zoster virüsü

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INTRODUCTION

Varicella-zoster virus (VZV), an alphaherpesvirus of the Orthoherpesviridae family, is the causative agent of chickenpox in humans and is common worldwide (1). It can be transmitted rapidly through the respiratory tract (2). VZV infections usually occur in early childhood and can remain dormant in the anglionic sensory neurons for many years. It can then be reactivated and cause shingles (herpes virus) (3).

In our country, VZV vaccine was included in the national vaccination program in 2013, as a single dose for 12-month-old infants. Since then, it has been reported that the incidence of chickenpox, especially in children under 5 years of age, has decreased significantly (4). Although the incidence of primary infection has decreased, herpes virus activation can still be observed in individuals with immune system defects due to factors such as human immunodeficiency virus (HIV) infection, advanced age, and diabetes mellitus (5-7). Determining previous VZV infection in patient groups receiving immunosuppressive therapy is important to rapidly detect reactivation.

Additionally, VZV, which is usually a mild infection in childhood, can also cause serious complications in pregnant women, older adults, and immunocompromised individuals who have undergone organ transplantation or have hematological malignancies (8).

Since antiviral agents such as acyclovir and valacyclovir can be used in treatment, it is important to make the diagnosis correctly (3). Although diagnosis is made with clinical findings such as disease history and skin lesions in typical cases, laboratory tests with different sensitivities should be used in the diagnosis of atypical cases and at-risk patients (9). Among the variable diagnostic tools used to detect VZV infection include, fluorescent-antibody-to-membrane-antigen (FAMA) test, the enzyme-linked immunosorbent assay (ELISA), as well as PCR (10).

The aim of this study was to contribute to epidemiological data and to evaluate the ELISA tests used in the diagnosis of VZV infection from a laboratory perspective. In addition, the age and gender status of patients with positive and negative VZV antibodies were examined, and the vaccination requirements of females of childbearing age and the elderly were investigated.

MATERIAL AND METHODS

All VZV IgM, VZV IgG and VZV avidity results studied in patient serum samples sent to our laboratory from various clinics between November 2019 and December 2024 for the purpose of chickenpox preliminary diagnosis or antibody screening were retrospectively examined. If more than one serum sample was sent from the same patient, one result from that patient was included in the study. Age and gender of the patients were recorded from the hospital documentation system.

Serum samples were studied with the microelisa method using the Anti-VZV Glycoprotein ELISA IgM and Anti-VZV ELISA IgG, Avidity determination of IgG antibodies against VZV (Euroimmun, Germany) kit. In accordance with the manufacturer's recommendations: In the semiquantitative evaluation for VZV IgG and VZV IgM; <0.8 IU/l = negative, ≥0.8 to <1.1 = borderline, ≥1.1 = positive. For VZV avidity, relative avidity index percentage; <40% = low avidity, ≥40% to <60% = borderline, ≥60% = high avidity.

This study was approved by the Düzce University Faculty of Medicine Non-invasive Health Practices Ethics Committee (date: 16.12.2024, decision no: 2024/259).

Statistical analysis

Statistical Package for the Social Sciences software for Windows, version 22.0, was used for the statistical analysis (SPSS, Chicago, IL, USA). Chi-square test was used to determine the relationship between test positivity and gender and years; Kruskal-Wallis test was used to examine the relationship between test positivity and mean age. $p<0.05$ was considered significant.

RESULTS

The study included 3074 VZV IgG, 990 VZV IgM, and 62 VZV avidity test results. Among the 3074 patients considered for VZV IgG testing, 1956 (64%) were female and 1118 (36%) were male, and no statistical difference was found between patients who were found to be positive, borderline, or negative in terms of gender and mean age ($p=0.146$, $p=0.488$, respectively). Among the 990 patients considered for VZV IgM

Table 1. Distribution of VZV IgM, VZV IgG and VZV avidity test results according to age and gender

				Median age, (IQR)	Mean age± SD	Gender [*n(%)*]	
		n	%			Female	Male
VZV IgG (n=3074)	Positive	2721	88,5	25 (11,00)	32,25±1,39	1728 (88)	993 (89)
	Borderline	131	4,3	24 (13,00)	30,77±1,13	93 (5)	38 (3)
	Negative	222	7,2	24 (4,00)	27,20±0,83	135 (7)	87 (8)
	p value			0,488		0,146	
VZV IgM (n=990)	Positive	51	5,2	35 (22,50)	39,06±2,37	28 (5)	23 (5)
	Borderline	26	2,6	36 (24,25)	41,57±3,20	13 (3)	13 (3)
	Negative	913	92,2	40 (24,00)	42,03±0,51	497 (92)	416 (92)
	p value			0,252		0,902	

n: Number, %: Percentage, IQR: Interquartile Range, SD: Standart deviation, VZV: Varicella zoster virus, Ig: Immunoglobulin

Table 2. Distribution of VZV IgM, VZV IgG and VZV avidity test results by year *

		2019		2020		2021		2022		2023		2024		
		n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*p value*
VZV IgG (n=3074)	Positive	143	92	335	86	585	91	539	86	619	86	491	91	
	Borderline	2	2	-	-	14	2	43	7	54	8	17	3	0,231
	Negative	10	6	53	14	41	7	41	7	45	6	32	6	
VZV IgM (n=990)	Positive	5	8	3	5	5	2	5	2	25	12	7	5	
	Borderline	-	-	-	-	9	4	9	3	7	3	1	1	0,125
	Negative	56	92	62	95	219	94	247	95	184	85	139	94	
VZV Avidity (n=62)	High avidite	34	100	7	100	1	100	8	100	3	75	7	88	
	Borderline	-	-	-	-	-	-	-	-	1	25	1	12	

*: Since the number of samples in 2018 was small, it was not included in the comparison.
n: Number, %: Percentage, VZV: Varicella zoster virus, Ig: Immunoglobulin

Table 3. Results of patients who had VZV IgG and VZV IgM testing requests made at the same time (n=524)

	IgM Positive	IgM Negative
IgG Positive	29	462
IgG Negative	3	30

testing, 538 (54%) were female and 452 (46%) were male, and no statistical difference was found between patients who were found to be positive, borderline, or negative in terms of gender and mean age (p=0.902, p=0.252, respectively). Among the 62 patients considered for VZV avidity testing, 60 (96.8%) were high and 2 (3.2%) were borderline. No low avidity results were detected. The distribution of VZV IgM and VZV IgG test results by age and gender is shown in Table 1.

VZV IgG negativity was found to be 7.8% (122/1569) in females of between 19-45 years of age, and 7% (4/57) in elderly individuals over 65 years of age.

When the distribution of VZV IgM and VZV IgG test results according to year was examined, no statistical difference was found between years in terms of positivity, borderline or negativity (Table 2).

A total of 524 patients were asked to have VZV IgG and VZV IgM tests, and three of these patients had IgM positivity alone (Table 3). Only one of these three patients had clinical findings and no immunosuppression was present. The ages and genders of these pa-

tients were 23, 24, 26 and female, female, male, respectively. Of the 29 patients who tested positive for both IgM and IgG, only three had VZV avidity testing, and all three had high avidity. VZV avidity test was studied in a total of 62 patients, and the clinics requested avidity testing alone in four patients, with IgG in nine patients, with IgM in 12 patients, and simultaneously with IgG and IgM in 37 patients.

DISCUSSION AND CONCLUSION

Chickenpox is a common infectious disease worldwide that usually causes a mild disease in childhood (11). With vaccination programs, VZV IgG positivity occurs from an early age, and possible complications of the disease are protected against (12). In a seroprevalence study conducted in Italy using the ELISA method, the VZV IgG positivity rate was 91.6%, and when compared with studies conducted before 2017, when vaccination was made mandatory for newborns, it was shown that antibody positivity increased significantly in children aged 6-9 (11). In a study conducted in pregnant women in India, where there is no national vaccination program, a seronegative rate of 22.2% was reported (13). In a study investigating antibody positivity in healthcare workers in our country, VZV IgG seropositivity was determined as 93.7%, while this rate was determined as 90.5% in a study conducted in students aged 14-18 (14,15). In a study conducted in Izmir between 2009-2010, the reported seropositivity rate was 94.3%, while in another study conducted in Izmir between 2011-2015, this rate was reported as 72.2% (16.9). In this study, the VZV IgG positivity rate was determined to be 88.5%, which is consistent with the literature. In addition, no statistical difference was detected between the antibody levels between 2019-2024.

Nowadays, there has been an increase in the number of conditions that result in immune suppression, including immunosuppressive treatments, organ transplants, malignant neoplasms, and HIV. Therefore, although the primary infection due to VZV, varicella, has decreased due to vaccination, shingles due to reactivation can be seen and can cause serious complications (17,18). Therefore, it is important to ensure correct diagnosis and treatment. In laboratory diagnosis of VZV infection, the most sensitive method is to detect viral DNA by PCR from skin vesicles, saliva, and cerebrospinal fluid if there are neurological symptoms. Although the detection of VZV antigens from vesicles by the direct immunofluorescent antibody (DFA) method is a rapid and specific method, its sensitivity is reported to be lower than PCR. ELISA or FAMA are the most commonly used tests as screening tests for seroepidemiological studies or for determining individuals susceptible to VZV (1). The sensitivity of the FAMA method, which can also determine antibody titer, is over 95%, while the sensitivity of the ELISA method is reported as 63-76% (10,19). While virus isolation from a sample taken from a lesion is the gold standard method and detection of VZV DNA by PCR is a highly sensitive diagnostic method, VZV IgM, which is also easy to apply, is often preferred for diagnosing acute infection. Additionally, VZV IgG can be used to determine past infection, and VZV avidity test can be used to decide on reactivation, although standardization of the avidity test has not been achieved (9). In the diagnosis of perinatal VZV infection in newborns, it is recommended to detect viral DNA by VZV PCR instead of serological tests due to low sensitivity (20). Kayın et al. determined the VZV avidity result of 15 cases who were not clinically considered to have chickenpox but were positive when the VZV IgM test was repeated, and two cases who had a chickenpox clinic and were found to have positive VZV IgM tests as high avidity, and concluded that the VZV IgM and IgG avidity EIA tests are of limited benefit in the diagnosis of acute infection (9). In this study, only one of the three patients who were IgM positive but IgG negative had clinical findings of acute VZV. This suggests that the IgM test may be false positive, consistent with the literature. In this study, it was observed that only three of the patients who were found to have positive IgM and IgG tests were tested for avidity. This situation shows the importance of clinic-laboratory collaboration. In addition, in order to ensure that physicians correctly request the VZV avidity test, it was considered appropriate to study the avidity test in the laboratory only on patients who are both VZV IgM and VZV IgG positive as a reflex test.

Since there is a risk of complications for both the mother and the fetus during pregnancy, it is important

for women of childbearing age to be vaccinated or to have had the disease before pregnancy to protect against the infection. Balbi et al. found VZV IgG positivity to be 93.33% in their VZV seroprevalence study among healthcare workers and medical students and found no statistically significant difference between male and female (21). Likewise, Bechini et al. found 84.5% VZV IgG positivity in their study and found no statistically significant difference between male and female (22). Similarly, in this study, VZV IgG negativity was found to be 7% in females (7.8% in females of between 19-45 years of age). Considering that exposure to VZV infection during pregnancy may cause fetal and maternal complications, it was considered important to investigate VZV IgG in women of childbearing age.

The limitations of our study are that the clinical conditions of the patients are unknown since the findings only include laboratory data, and that the tests were not performed using methods such as PCR or FAMA other than ELISA.

In conclusion, since the vaccine has been in our national vaccination program for 12 years, it is still important to screen for VZV IgG in susceptible individuals. In clinically at-risk cases, when it is necessary to confirm the diagnosis, it will be useful to apply the PCR method together with VZV IgM and avidity tests.

Conflict of interest and financial disclosure

The author declares that she has no conflict of interest to disclose. The author also declares that she did not receive any financial support for the study.

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