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ANALYSIS OF THE CLASSIFICATION OF HERPES ZOSTER VIRUS AND PRINCIPLES FOR IMPROVING LABORATORY DIAGNOSTICS

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Abstract. A serious health concern that can impact people of any age is herpes zoster. People over 50, those with impaired immune systems, and those using immunosuppressive medications are more likely to experience it. The varicella zoster virus reactivation is the cause. This reactivation is influenced by cell-mediated immunity. Before a rash appears, frequent symptoms include fever, discomfort, and itching. The most frequent side effect of herpes zoster is post-herpetic neuralgia. Age, immunological state, and the timing of therapy initiation all affect risk factors and problems related to herpes zoster. Herpesvirus-induced infections of the central nervous system (CNS) have different epidemiologies depending on host characteristics and geographic distribution. Early diagnosis and treatment can save lives. This study assessed an internal laboratory methodology for cerebrospinal fluid (CSF) molecular testing criteria, examined the epidemiology of herpesvirus CNS infections in Western Greece, and compared clinical and laboratory results with global data. 940 out of 4300 CSF samples were eligible for RT-PCR detection of varicella zoster virus (VZV) and herpes simplex virus (HSV-1, HSV-2) during the research period. 53 (5.63%) of them tested positive: 7 HSV-2, 9 HSV-1, and 37 VZV. The greatest CSF white blood cell (WBC) counts (231/mm3) were seen in HSV-2 cases, which were found in younger patients (median age 41), followed by VZV (125/mm3) and HSV-1 (26/mm3). HSV-2 infections had greater levels of CSF protein. The most sensitive imaging technique for identifying CNS inflammation was magnetic resonance imaging (MRI). These findings show that VZV is the most common herpesvirus in this area, highlighting the importance of prompt molecular identification and high clinical suspicion in elderly patients.

Keywords. CNS, varicella zoster virus, herpes viruses, HSV-1, HSV-2, VZV, herpes zoster, post-herpetic neuralgia

Introduction. The varicella zoster virus reactivates to cause herpes zoster, also known as shingles. Herpes zoster can afflict people of any age, particularly those with a weakened cell-mediated immunity due to any disease or medication, but adults over 50 are more likely to have it due to the immunosenescence associated with aging. Herpes zoster has been linked to complications because it affects the ocular, splanchnic, cerebral, and motor nerves. However, post-herpetic neuralgia is the most frequent side effect. The cornerstone of preventing herpes zoster infection is vaccination against the herpes zoster virus. For both post-herpetic neuralgia and herpes

zoster infection, numerous therapeutic approaches have been established. Alpha-herpesviruses are double-stranded DNA viruses with significant neurotropism, including Varicella Zoster virus (VZV) and herpes simplex viruses 1 and 2 (HSV-1, HSV-2). With the exception of central nervous system (CNS) infections, whose results rely on the etiologic agent and host immunological state, they generate recurrent infections with minimal mortality. Meningitis and encephalitis are two CNS illnesses that are on the rise as more aged and vulnerable individuals are admitted to hospitals. Alpha-herpesvirus-associated central nervous system infections, especially those brought on by VZV, have significantly decreased since focused vaccination programs were implemented [1-6]. By reducing primary disease and related neurological sequelae, widespread immunization against bacterial infections during infancy has changed the epidemiology of CNS infections. However, since changes in viral reactivation patterns and population immunity may affect the residual burden of CNS illness, ongoing surveillance is still necessary. Over 80% of viral meningitis cases are caused by enteroviruses, which account for the majority of contemporary occurrences of aseptic meningitis or encephalitis. With the exception of herpesvirus infections, which call for specialized antiviral treatment, viral meningitis often has a good prognosis and is treated supportively. Since early diagnosis and treatment are crucial to lowering morbidity and mortality, bacterial meningitis must always be taken into consideration because clinical symptoms are similar across etiologies. Depending on age, period, and location, the annual incidence of meningitis in the UK is roughly 13.5 per 100,000, with viral meningitis accounting for about 2.75 per 100,000. Localized epidemics and emerging diseases are influenced by environmental and geographic factors, such as population movement and climate change [7-12]. Together with meningitis, encephalitis is the second most serious CNS illness and a neurological emergency. Seizures, altered awareness, behavioral abnormalities, or specific neurological deficits, including cranial nerve involvement, may manifest depending on the location of the lesion. Although viruses are the most common cause, the etiology is still unknown in the majority of cases. The most common causes are herpesviruses, especially HSV-1, which causes severe, potentially deadly encephalitis if left untreated. VZV is the next most common cause. Depending on age, the annual incidence of sporadic infectious encephalitis varies from 1.5 to 7 cases per 100,000 people. The detection of viral CNS infections has been significantly improved by the use of polymerase chain reaction (PCR) in diagnostic procedures. This has made it possible to quickly identify pathogens in cerebrospinal fluid with excellent sensitivity and specificity (96–98% and 95–99%, respectively). Even with these developments, a significant percentage of cases still have an unknown cause. Alpha-herpesvirus-associated CNS infections are becoming more common, as evidenced by the wider use of PCR, which calls for their regular evaluation in all suspected cases [13-18]. The purpose of this study was to examine the prevalence of CNS illnesses linked to alpha-herpesvirus in Western Greece and compare the results with information from other areas. To evaluate regional differences, laboratory, imaging, and demographic features were examined by virus subtype. The effectiveness of an internal algorithm incorporated into the molecular diagnostic workflow for herpesvirus detection was also assessed. Our study's primary goals are to ascertain the prevalence, risk, and sequelae of herpes zoster in both healthy and immunocompromised individuals as well as to enhance patient care through precise diagnosis, prompt treatment, and strategies to avoid herpes zoster and its recurrence [19-23].

The main purpose of the presented manuscript is to provide a brief analysis of the classification of herpes zoster virus and the analysis of principles for improving laboratory diagnostics based on the results of authoritative scientific works.

Etiopathogenesis. One of the eight herpes viruses that are only harmful to humans is the varicella zoster virus. It causes a very contagious primary infection known as varicella/chicken pox,

which primarily affects youngsters. It is most frequently spread by direct contact with the lesion or by airborne transmission from person to person. The varicella rash is caused by the virus spreading from the bloodstream to the skin, oral mucosa, and lymph nodes during the initial infection. The varicella zoster virus lies latent in the sensory dorsal root ganglion cells following an initial infection or immunization. The varicella zoster virus-specific memory T cells are produced when the initial infection resolves. A higher risk of contracting herpes zoster is correlated with the decrease below a hypothetical "zoster threshold." Exogenous boosting (varicella exposure) or endogenous boosting (subclinical reactivation from latency) can both improve memory immunity to the varicella zoster virus. After an infection, immunity against varicella typically lasts for 20 years. Virus reactivation is known to be influenced by age, stress, immunocompromised condition, and immunosuppressive medications [5-12]. When someone gets herpes zoster, it is advised to find out if they have HIV. After the virus is reactivated, it moves along the afflicted sensory nerve, damages neurons, reaches the appropriate dermatomes, and produces the herpes zoster vesicular rash. Direct contact with lesions is more prevalent than airborne transmission of the varicella zoster virus from herpes zoster cases. It has been demonstrated that immunizing youngsters against the varicella zoster virus lowers their long-term chance of contracting herpes zoster. However, a study by Brisson et al. revealed that a widespread childhood vaccination against the varicella zoster virus increased the incidence of herpes zoster in the first 30 to 50 years of life. It is uncertain what pathophysiology causes the varicella zoster virus to reactivate. However, the varicella zoster virus may reactivate due to any cause influencing cell-mediated immunity [14-21].

Epidemiology. Frequency. According to a 2014 systematic review, the incidence of herpes zoster in North America, Europe, and Asia-Pacific is 3−5/1000-person years (PY), with an elevated incidence of 6–8/1000-person year at age 60 and 8–12/1000-person year at age 80. The occurrence of herpes zoster changes from year to year, as evidenced by three studies conducted in Italy in 1999, 2004, and 2010. The incidence rates were 4.14/1000-person year, 1.59/1000-person year, and 6.31/1000-person year, respectively. the annual fluctuations in the incidence of herpes zoster among multiple nations. Herpes zoster ophthalmicus affects 10–20% of patients, and there is a 1% lifetime risk. Distribution of ages. A population-based study carried out in Korea demonstrated that the incidence of herpes zoster rises with age, from 2.0/1000-person year in the childhood group to 21.8/1000-person year in those aged 70–79 years. The 60–69 age group has the highest documented incidence of herpes zoster, whereas those over 80 have the lowest incidence [6-14]. According to Legami et al., individuals over 72 years old had a higher incidence of hospitalization for herpes zoster (0.46/1000-person year) than patients between the ages of 15 and 44 (0.03/1000-person year), indicating that growing older is a risk factor for hospitalization due to herpes zoster. A US study using data from Medstat Marketscan found that older people had higher rates of hospital admissions, cost burden, problems, outpatient visits, and pain prescriptions than younger people. Disseminated herpes zoster, ophthalmic involvement, neurological involvement, bacterial infections, and post-herpetic neuralgia are known to be frequent consequences of herpes zoster that call for hospitalization. According to a study by Stein et al., patients 50 years of age and above who had a primary diagnosis of herpes zoster spent an average of 6.8 days in the hospital. However, those with a non-principal diagnosis of herpes zoster had an average hospital stay of 15.5 days, according to the same study. In a study that compared patients according to the age at which herpes zoster ophthalmicus first appeared (less than 60 years and more than 60 years). According to Ghaznawi et al., the prevalence of herpes zoster ophthalmicus peaked in people between the ages of 50 and 59. This could be due to the mandated childhood varicella vaccination, which increases the risk of herpes zoster infection in younger people. Many have advised immunization against herpes

zoster for people over 60, but some have argued that, given the severity and chronicity of the disease in young adults, it is preferable to vaccine immunocompetent patients under 60 as well [16-23].

Regional and seasonal distribution. According to certain research, there is a considerable risk of contracting herpes zoster during the start of summer. Other research, however, found no discernible seasonal fluctuation in post-herpetic neuralgia or herpes zoster. A Chinese study found that the incidence of herpes zoster was higher in urban areas (7.65/1000-person year) than in rural areas (2.06/1000-person year). In a similar vein, a Dutch study found a higher level of urbanization in comparison to municipalities. There are also other studies, nevertheless, that do not demonstrate any variation in incidence between rural and urban locations. This indicates that additional research is needed to validate the seasonal and regional differences in herpes zoster incidence [5-10]. Incidence among people with impaired immune systems. When compared to the healthy population, immunocompromised people have a higher incidence of herpes zoster, according to several prior research. According to a research by Chen et al., recipients of solid organ transplants had a lower incidence of herpes zoster (17.04/1000-person year) than recipients of bone marrow or stem cell transplants (43.03/1000-person year). Herpes zoster is more common in patients with HIV, multiple sclerosis, psoriasis, inflammatory bowel disease (IBD), rheumatoid arthritis (RA), malignancies, and systemic lupus erythematosus (SLE). A study by Megna et al. found that using biologics to treat psoriasis did not significantly raise the risk of contracting herpes zoster, despite the fact that people on immunosuppressive drugs are more susceptible to the disease. Patients with diabetes had a higher incidence of herpes zoster infection, according to two separate studies from Israel and Japan. Additionally, people with COPD, hypertension (HTN), Sjogren's syndrome, mental illnesses, osteoskeletal disorders, ophthalmic disorders, and renal failure are more likely to develop herpes zoster [13-21].

Summary. When they infect the central nervous system, members of the a-herpesvirus family can cause serious to fatal illnesses. Given the extended survival of immunocompromised and immunosuppressed people and the addition of molecular techniques to the diagnostic toolbox, epidemiology and laboratory diagnosis evolve throughout time. Regardless of the location of the disease, this retrospective investigation examined laboratory and demographic data from patients with CNS infections brought on by any of the three α-herpesviruses. Cases gathered during the course of a five-year study period provided the data. 5.63% of the 940 CSF samples tested positive for herpes virus CNS infections. While most research looks at meningitis and encephalitis cases individually, this study was unable to distinguish between the two [1-11]. By contrast, Lee et al. found that 15.2% of patients older than 16 had a positive result (80 of 525 samples: 59 meningitis, 21 encephalitis). Clinical indications for testing and diagnostic thresholds affect positivity rates. The main purpose of CT imaging in this study was to assure lumbar puncture safety by ruling out contraindications like mass effect or raised intracranial pressure, while it had minimal diagnostic utility. With HSV-1- and, to a lesser extent, VZV-producing distinctive inflammatory lesions with virus-specific anatomical patterns, MRI proved more sensitive, particularly in encephalitis. These results align with earlier publications. There are a number of limitations to this study. Because it was done at a single facility with few positive instances and is retroactive, it has gaps in data and incomplete records, which lowers statistical power. Information about the patients' complete immunological profile, VZV vaccination status, and eating habits was not available. The validity of the results is supported by the fact that, despite the small sample size, they are consistent with bigger research that use comparable diagnostic criteria. Furthermore, case classification is made

more difficult by the similar clinical characteristics of meningitis and encephalitis, making separate analysis for each illness impossible [14-22].

Discussion. A serious health risk that can impact people of any age is herpes zoster. People over 50, those with impaired immune systems, and those on immunosuppressive medications are more likely to experience it. Reactivation of a varicella zoster virus infection is the cause. This reactivation involves cell-mediated immunity. Before the rash appears, frequent symptoms include fever, discomfort, and itching. The most frequent consequence of herpes zoster is post-herpetic neuralgia. Age, immunological state, and the time of therapy initiation all influence risk factors and problems related to herpes zoster [2-9]. VZV continues to be a major contributor to dermatological morbidity, connecting basic immunology, virology, and clinical practice. Its two clinical manifestations—varicella as a primary infection and herpes zoster as reactivation—represent different biological manifestations of the same pathogen, both influenced by age-related vulnerability and host immunity. Knowing this continuum gives dermatologists a conceptual framework for precise diagnosis and evidence-based treatment. Clinical results have been improved by advances in molecular diagnostics and antiviral medication; however, underdiagnosis and delayed detection still occur, especially in unusual or immunocompromised presentations. Recombinant subunit vaccine represents a paradigm change away from reactive management and toward prevention through long-term immunologic control. As this preventative paradigm develops, the dermatologist's responsibilities go beyond therapy to include patient counseling, vaccine advocacy, and incorporating immunization techniques into routine practice. In the end, treating VZV infection is a wonderful example of how basic science and applied dermatology may work together [13-19]. The burden of VZV and its sequelae can be significantly decreased in the future with universal vaccination, prompt treatment intervention, and ongoing clinician knowledge. In terms of lowering the incidence of herpes zoster and post-herpetic neuralgia, routine vaccination for people over 60 has demonstrated a significant impact. It has been demonstrated that treating herpes zoster and post-herpetic neuralgia with antiviral medications and analgesics within 72 hours of the rash's beginning can lessen its severity and complications. Using reviews and publications from PubMed, Embase, the Cochrane Library, and a manual Google Scholar search, this study primarily focuses on herpes zoster. We discuss the prevalence of herpes zoster, its gender distribution, its seasonal and regional distribution, its incidence in immunocompromised people, the prevalence of post-herpetic neuralgia after a zoster infection, its complications, management, and prevention [20-23].

Conclusions. Geographical location, sample size, vaccine coverage, population genetics, and the timing of data collection as diagnostic procedures change all have an impact on regional epidemiological variations in herpesvirus CNS infections, as this retrospective analysis demonstrates. Due to increasing testing (even in the absence of rash or immunosuppression), improved sensitivity of molecular diagnostics (PCR, next-generation sequencing (NGS)), and higher clinical awareness of unusual VZV CNS presentations, VZV is frequently the most detected virus. Therefore, early detection with PCR testing is essential for prompt antiviral therapy when necessary, enhancing results, and lowering mortality.

Any age group can get herpes zoster, although older individuals and those with weaker immune systems are more likely to get it. Growing older increases the need for hospitalization and problems related to herpes zoster. The gender specificity, seasonal fluctuations, and regional distribution of herpes zoster need to be confirmed by additional research. Antiviral therapy administered within 72 hours of rash start has been demonstrated to reduce herpes zoster and its consequences. Valacyclovir is proven to be inferior than famciclovir. For patients with acute renal

injury, oral acyclovir and valacyclovir are recommended above famciclovir. Acyclovir works effectively for immunocompromised people, children, and pregnant women.

In addition to oxycodone, vitamin C infusion, and MeB12 infusion, pregabalin and gabapentin have demonstrated notable efficacy in treating post-herpetic neuralgia. Although it is more expensive, spinal cord stimulation is useful in avoiding and lessening post-herpetic neuralgia. Steroids and epidural anesthetics help lessen acute zoster pain. The effectiveness of thalamic stimulation and cryotherapy of the intercostal nerves in avoiding post-herpetic neuralgia needs further investigation. Vaccination against herpes zoster lowers the incidence, morbidity, and burden of illness related to herpes zoster and post-herpetic neuralgia in people over 60. It's unknown if zoster immune globulin can prevent herpes zoster after exposure. Treatment for herpes zoster and its consequences is still difficult despite a number of therapeutic approaches.

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