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REVIEW

Early Diagnosis of Herpes Zoster Neuralgia: A Narrative Review

Han-Rui Fan · En-Ming Zhang · Yong Fei · Bing Huang · Ming Yao

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ABSTRACT

Background: Early intervention reduces the incidence of postherpetic neuralgia (PHN). Typical shingles are easy to diagnose; however, there is no clear diagnostic method for neuralgia symptoms manifested before the onset of the rash, which can easily cause misdiagnosis. This not only increases the patient's pain, medical expenses, and mental burden, but more importantly, delays the valuable time for early treatment of shingles, and increases the probability of complications and PHN.
Objective: In this paper, the diagnostic methods of preherpetic neuralgia were summarized and analyzed, and the current challenges were put forward to provide directions for the early diagnosis of herpes zoster (HZ) in the future.
Methods: PubMed, and China National Knowledge Infrastructure (CNKI) libraries were searched using the terms "herpes zoster," "before the blistering," "diagnosis," and "neuralgia." Clinical trials, reviews, and case reports were collected and reviewed. The period of literature search is from 1 January 1980 to 1 October 2022.
Results: The early diagnosis of herpes zoster neuralgia can reduce misdiagnosis and mistreatment, and timely and effective intervention can significantly reduce the incidence of PHN. The body may possess a mechanism that limits the local breakthrough of the virus in the skin, causing blistering later than the onset of pain. Changes in the plasma proteins of patients with varicella-zoster virus shingles neuralgia may be used as an early diagnostic indicator in patients with HZ neuralgia before eruption.
Conclusion: Early diagnosis of HZ neuralgia before eruption can facilitate timely targeted treatment, thereby reducing the incidence of PHN. Proteomic quantitative analysis and validation results can serve as a simple, micro, rapid, and accurate diagnostic method.

Keywords: Herpes zoster; Early diagnosis; Varicella-zoster virus; Polymerase chain reaction; Antibody titer; Biomarker; Thermography; High-frequency ultrasonography

En-Ming Zhang and Han-Rui Fan have contributed equally to this work.

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H.-R. Fan · E.-M. Zhang
Zhejiang Chinese Medical University, Hangzhou, People's Republic of China

Y. Fei (✉) · B. Huang · M. Yao
Department of Anesthesiology and Pain, The Affiliated Hospital of Jiaxing University, 1882 Zhong-Huan-South Road, Jiaxing 314000, People's Republic of China
e-mail: jxfy6666662022@sina.com

INTRODUCTION

Herpes zoster (HZ) neuralgia is among the most common neuropathic pains in the clinic and severely affects quality of life [1–3]. Varicella-zoster virus (VZV) infection in early childhood remains latent in the cranial ganglia, dorsal root ganglion, and other sensory ganglion neurons. When the immunity of the body is reduced, the latent virus is reactivated through peripheral nerve fibers to sensory nerve fibers to induce shingles [4, 5]. Patients with HZ require prompt diagnoses and treatment to avoid severe progression to postherpetic neuralgia (PHN) [6–9]. Currently, most patients with HZ rely on clinical presentations and rashes to obtain a diagnosis [5, 10]. However, most patients initially present with symptoms of neuralgia, such as paroxysmal or persistent pinpricks, knife cuts, burning pain, itching, banding, and ant walking. The rash generally appears 2–5 days after neuralgia onset, and a small number of patients do not develop herpes until 2 weeks after the onset of neuralgia symptoms. These patients are often misdiagnosed with migraine, myocardial infarction, pleurisy, intercostal neuralgia, cholelithiasis, appendicitis, and gastric ulcer, depending on the nerve involved [1, 11–13]. Misdiagnosis not only increases the patient's pain, medical expenses, and mental burden, but more importantly, delays the valuable time for early treatment of shingles and increases the risk of complications and PHN.

Clinicians and researchers have attempted to solve the problems of the early diagnosis of herpetic neuralgia using laboratory diagnostic methods, infrared thermography, and high-frequency ultrasound diagnosis [14–16]. However, most of the previous reviews on the diagnosis of herpes zoster only describe PCR and antibody detection methods, which is not comprehensive enough [5, 17]. Based on some clinical studies published in recent years and related research results of our team, this review summarizes the possible methods for the early diagnosis of herpes zoster, and points out the direction for the research of early diagnosis of herpes zoster. The proteomic quantitative analysis and validation results described in this paper provide a simple, microscopic, rapid, and accurate diagnostic method that allows researchers to conduct further studies and identify proteins that can recognize shingles before the rash appears. This will help clinicians improve diagnosis and reduce misdiagnosis, help patients fight for early treatment time, reduce the pain of patients, and reduce the burden of life caused by frequent medical treatment.

METHODS

Study Design

We conducted a narrative review. To comprehensively summarize the methods used for early diagnosis of herpes zoster, we searched PubMed and CNKI databases using the terms "herpes zoster," "before the blistering," "diagnosis," and "neuralgia." Literature was retrieved from 1 January 1980 to 1 October 2022. We analyzed and summarized the retrieved reviews, clinical studies, and case reports, and combined our team's relevant research results and clinical experience to write this paper. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Setting

The settings mentioned in the literature collected were hospitals, neurology departments, pain departments, dermatology departments, and thoracic surgery departments.

RESULTS

Laboratory Test Methods

Polymerase chain reaction (PCR)

PCR is a highly sensitive method for detecting VZV [17–19]. PCR is useful to detect VZV DNA in the blood [including whole blood, serum, plasma, peripheral blood mononuclear cells

(PBMC)], saliva, and cerebrospinal fluid (CSF) of patients for the early diagnosis of atypical HZ in patients without a rash [20–23]. VZV is detectable in the blood from 5 days before eruption to 4 days after eruption, while VZV in T lymphocytes is detectable as early as 8–-10 days before eruption and persists beyond six months [24]. In whole blood, approximately 60% of VZV is present in PBMC and 40% in serum or plasma, and the DNA positivity rate of VZV in PBMC samples detected using PCR is higher than that in plasma and serum samples in patients with HZ. Whole blood is more sensitive for the detection of VZV DNA than PBMC, possibly because it contains VZV DNA from lysed cells [25, 26]. The viral load gradually decreases with treatment of the disease, and real-time PCR can help monitor the effectiveness of treatment in patients with HZ.

Collecting saliva from patients and detecting VZA DNA is more convenient and readily available than collecting plasma. Mehta et al. detected VZV DNA in the saliva of 54 shingles patients (100%) on the day of rash onset [27]. In a study including 70 patients with first-time HZ detected using PCR testing, saliva VZV was detected in 85.7% of patients, and the positive rates on days 1, 8, 15, and 29 were 85.7%, 47.6%, 19.2%, and 23.1%, respectively [28]. Another study reported that in patients with suspected shingles, the sensitivity of salivary DNA PCR for VZV detection (88%) was significantly higher than that of plasma DNA PCR (28%), with no difference in specificity [29]. Nagel et al. detected VZV DNA using PCR in the saliva of a patient with a 12-year history of HZ, indicating that VZV DNA can persist in saliva samples for a long time [30].

CSF samples from patients infected with VZV in the central nervous system were detected using PCR, and the DNA positivity rate of VZV was higher than that of plasma samples and serological detection methods. Grahn et al. retrospectively analyzed 72 patients diagnosed with central nervous system (CNS) VZV infection and neurological symptoms using cerebrospinal fluid VZV DNA testing. Real-time PCR has been used to detect higher levels of VZV DNA in CSF samples than in serum samples [31]. In a study including 34 patients with VZV-infected central nervous system, VZV DNA (67.6%) and VZV-IgG antibodies (32.4%) in the CSF were detected using PCR and enzyme-linked immunosorbent assay (ELISA), respectively [32].

It is meaningful for PCR detection to collect blood and saliva from patients with suspected herpes zoster without eruption. These studies show that VZV DNA is more detectable in saliva than in blood. CSF testing is an invasive procedure that is not suitable for ordinary patients with shingles.

Antibody and Complement Detection

When VZV is reactivated, serum VZV antibody titers remain high and significantly different from those of healthy controls. Serum antibody levels are strongly associated with shingles development, and measurement of serum VZV antibody titers is helpful in the diagnosis of shingles [33, 34]. Kangr et al. used IgM antibody-capture radioimmunoassay (MACRIA) to detect IgM antibodies in the serum of 220 patients, of whom 216 (98%) were diagnosed with shingles, of which 94.4% of serum samples were acquired 2–6 weeks after the rash onset [35]. Serum samples of typical patients with HZ were collected, and 37% of patients with HZ were identified as positive for VZV-IgM antibody with VZV-IgM titer using ELISA. Subsequently, VZV-IgM titers of positive patients were analyzed, and the results revealed that VZV-IgM titers started increasing after the appearance of skin lesions, reached the highest level 6–10 days after the rash onset, and was negative in all patients after 10 weeks. Therefore, VZV-IgM titers are meaningful to detect within 3.5 weeks after the onset of symptoms [36].

In 141 patients with HZ, the positive rates of VZV-IgG antibody, VZV-IgM antibody, and complement fixation (CF) test were 93.9%, 12.0%, and 64.2%, respectively, among which VZV-IgG antibody had a strong correlation with CF titers, and the CF titer largely represented the IgG titer. CF titers tend to increase slowly over time and are weakly correlated with time of onset [37]. In a study including 865 shingles patients who presented with the incidence of VZV-specific CF at their initial presentation to a

dermatological clinic, 66% of patients with HZ showed negative CF. Subsequently, paired complement binding tests performed over a short period of time showed a significantly elevated titer, peaking approximately 2 weeks after the onset, and gradually decreasing after 1 year [38].

IgM appears first but does not last long and is a marker of recent infection; therefore, VZV-IgM antibodies testing is only beneficial in confirming the diagnosis of acute-phase shingles. The relationship between complement titer and time of VZV onset remains controversial and requires further elucidation. IgG appears and persists at the initial infection with the VZV virus and is of little significance in the early diagnosis of shingles.

Inflammatory Cytokines

VZV is caused by the dorsal root ganglia, which causes nerve root inflammation and changes in cytokine levels in the body. Galectin-3 is a member of the β-galactose-bound lectin family, secreted by monocytes, phagocytes, and epithelial cells, and is involved in biological processes, such as cell interactions, cell cycle, regulation of cell growth, splicing of mRNA precursors, and angiogenesis. After VZV infection, the mRNA and protein expression of galectin-3 in the dorsal horn of the spinal cord of mice was significantly increased. Galectin-3 gene deletion in mice, or intrathecal injection of galectin-3 antibody, significantly reduced tactile pain, suggesting that galectin-3 is involved in PHN production [39]. Wang et al. reported that plasma galectin-3 and IL-6 levels in patients with HZ neuralgia were significantly higher than those in healthy physical examiners, and galectin-3 levels could be used as a new biochemical marker for patients with pre-HZ and PHN [40, 41].

Reduced immunity is a predisposing factor for shingle development. The immune response to shingles is thought to be dysfunctional and mainly manifested by specific cellular immunosuppression [42, 43]. In a case analysis including 83 patients with multiple myeloma, patients with multiple myeloma infected with HZ had elevated serum $CD3^+$ and $CD4^+$ levels and significantly lower $CD8^+$ levels after treatment [44]. Jung et al. found that VZV induces a broad immune response by affecting the release of immunoactive substances such as cytokines, neurotrophic factors, and chemokines in vivo, leading to T-lymphocyte immunosuppression [45]. Zhu et al. reported that shingles patients had elevated levels of IL-6 in the acute phase; $CD3^+$, $CD4^+$, and $CD8^+$ levels were lower than normal and were closely associated with the occurrence of PHN [46]. Many markers of inflammation are used clinically to detect herpetic neuralgia but is rarely diagnosed before eruption. Gal-3, IL-6, and T lymphocytes detected in the above study were all conducted in patients with post-diagnosis herpes zoster. Studies on differences in blood levels of inflammatory factors between pre-eruption and healthy patients are lacking. The specificity of these inflammatory factors for the diagnosis of shingles also needs further study.

Proteomic Analysis and Non-coding RNA

Wang et al. reported 44 differentially expressed proteins found in the plasma of patients with HZ, and the main pathways in which these molecules were involved included the MAPK signaling pathway, neuroactive ligand-receptor interactions, acute myeloid leukemia, and transcriptional regulation disorders in tumors. Six key molecules were selected as candidate molecules for further study, and plasma from 40 patients with HZ and 40 healthy participants was validated using ELISA, immunoblot assay, and receiver operating characteristic curve analysis. Finally, three proteins, PLG, F2, and VTN, were found and can be used as biomarkers for the detection of early patients with HZ [47].

Non-coding RNA refers to RNA that does not code for proteins, including rRNA, tRNA, snRNA, snoRNA, and microRNA with a variety of known functions, as well as RNA with unknown functions. MicroRNAs are a class of endogenous non-coding RNAs found in eukaryotes with regulatory functions; they are involved in maintaining normal cell function, host-virus interactions, and restricting the replication of certain virus types. In a study including 41 patients with HZ for the detection of microRNAs, serum miRNA levels were analyzed using TaqMan low-density array and

confirmed using quantitative reverse transcription PCR (RT-qPCR) analysis. The expression levels of six miRNAs, including miR-190b, miR-571, miR-1276, miR-1303, miR-943, and miR-661, were significantly increased in patients with HZ; therefore, it may be used as a biomarker to detect potential HZ infection [48]. Markus et al. reported VZV-encoded small non-coding RNAs (sncRNAs), with at least one VZV sncRNA expressed in productive infections in neurons and fibroblasts, which may reduce viral replication. Since sncRNAs are considered potential targets for antiviral therapy, identifying these molecules in VZV may provide a new direction for the development of HZ pain treatments [49].

Whether it is proteomic analysis or non-coding RNA research, large samples, multicenter research, and repeated validation are required. In addition, the acquisition of blood samples from patients before eruption is the focus and difficulty of this study. Based on previous studies, our research team will continue to investigate changes in blood protein expression in patients with preeruption.

NON-INVASIVE EXAMINATION

Infrared Thermal Imaging

Infrared imaging technology uses thermal infrared with a wavelength of 2–1000 μm to image objects through thermal infrared-sensitive signal transduction materials and has been widely used in clinical research [50–52]. Infrared imaging technology collects infrared radiation from the human body and converts it into a digital signal to form a pseudo-color heat map that can accurately quantify temperature changes in different areas. It has the advantages of being non-traumatic, radiation-free, convenient, fast, and inexpensive [53, 54]. Infrared thermography can detect degenerative necrosis and vasoconstriction of local tissues of the body, which can be manifested as different degrees of local hypothermia; however, metabolically active stages such as granulation tissue proliferation, aseptic inflammation, edema, vasodilation, or tumor invasion can be manifested as varying degrees of local high temperature.

The affected skin area of patients with HZ produces inflammation. Yao et al. reported that infrared thermography is more valuable than visual analog scale scoring for early diagnosis of patients with HZ neuralgia before eruption, and has the advantages of being simple in operation, non-invasive, and without radiation [55]. In a case of 112 patients diagnosed with acute-phase HZ, infrared imaging techniques predicted the progression to PHN in acute patients with HZ, but could not be used as an objective assessment tool for subjective pain [56]. Park et al. reported that infrared thermography can be an effective predictor of PHN [57]. However, some patients may have an impact on infrared thermography because of scratching, patting, or acupuncture treatment in the painful area [55, 58]. In addition, the range of temperature differences between the unaffected and affected sides, and whether this specific value represents the early diagnosis of shingle neuralgia, has not been reported.

High-Frequency Ultrasound Diagnosis

High-frequency ultrasound diagnosis is also a non-invasive technique that can observe the epidermis, dermis, subcutaneous tissue, and cutaneous nerve structure of the skin. It has a good correlation with histopathology and has been widely used in the diagnosis of benign skin tumors, malignant tumors, localized scleroderma, and other diseases [59–61]. The main pathological changes in patients with shingles are inflammatory changes in the affected skin, subcutaneous tissues, nerve roots, and nerve endings.

Zheng et al. reported that in patients with HZ, the skin and subcutaneous tissue on the affected side were more thickened than on the healthy side, and the cutaneous nerve was also significantly thickened, which was associated with demyelinating lesions and edema of the nerve roots. Patients mainly present with symptoms of neuralgia before the eruption, and the affected nerve roots also begin to show pathological changes such as demyelination or

edema; therefore, high-frequency ultrasound images of patients with preeruption neuralgia should be observed clinically. Unfortunately, studies on this topic are rare. However, with the development of neuroultrasound, the diagnosis of preherpanic HZ neuralgia using high-frequency ultrasound is bound to develop profoundly [62].

DISCUSSION

Patients with HZ neuralgia cannot be accurately diagnosed in time before the onset of the rash, which causes misdiagnosis and delay in treatment. PCR detection of VZV has high sensitivity; however, due to equipment requirements and high detection costs, its wide clinical application is limited. Although infrared thermography uses temperature differences to distinguish between the unaffected and affected sides, it is difficult to determine whether patients with neuralgia have HZ. High-frequency ultrasound diagnosis can detect pathological changes, such as demyelination or edema of the affected nerve roots, and combined with clinical symptoms, it can improve the accuracy of diagnosis. However, pathological changes such as demyelination or edema of the nerve roots in preeruptive neuralgia patients are not obvious, which undoubtedly complicates the diagnosis. At present, most of the clinical proteomic analysis and non-coding RNA research are focused on patients diagnosed with shingles. However, future studies should focus on patients who develop shingles and PHN before the onset of rash.

CONCLUSIONS

Early diagnosis of HZ neuralgia before eruption can facilitate timely targeted treatment, thereby reducing the incidence of PHN. Proteomic analysis and non-coding RNA have great research prospects for the early diagnosis of herpes zoster.It is a simple, micro, rapid, and accurate diagnostic method. Our research team will continue to investigate changes in blood protein expression in patients with preeruption. More basic and clinical trials are needed to verify plasma protein expression in patients with herpes zoster neuralgia before eruption.

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Authorship. Han-Rui Fan MD[1], En-Ming Zhang, MD[1], Yong Fei, MD[2], Bing HuangMD[2], Ming Yao, phD[2]. [1]Graduate School of Zhejiang Chinese Medicine University Hangzhou, P. R. China, [2]Department of Anesthesiology and Pain, The Affiliated Hospital of Jiaxing University, Jiaxing, P.R. China. Corresponding author: Yong Fei, MD, Department of Anesthesiology and Pain, The Affiliated Hospital of Jiaxing University 1882 Zhong-Huan-South Road Jiaxing 314,000, P.R. China. Email: jxfy6666662022@sina.com.

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