

Does Varicella Zoster Virus in Children Affect Temporal Artery Structure or Blood Flow?

Fazıl Kulaklı¹  · Muhammet Bulut²  · Tümay Bekçi³ 

¹Department of Physical Medicine and Rehabilitation, Giresun University, Faculty of Medicine, Giresun, Turkey

²Department of Pediatrics, Giresun University, Faculty of Medicine, Giresun, Turkey

³Department of Radiology, Giresun University, Faculty of Medicine, Giresun, Turkey

Introduction: Varicella-Zoster Virus (VZV) is a member of the Herpesviridae family of viruses and causes two different clinical conditions. The main objective of our study is not to diagnose GCA but instead, we wanted to assess whether there is a structural or flow change following VZV during childhood using US in temporal artery, which is the most commonly affected artery by GCA in advanced age and to review whether the patients show any clinical symptoms related with GCA.

Materials and Methods: The study was designed as a prospective single-blind study and included 30 patients diagnosed with varicella under 16 by the same pediatrician and shows infection characteristics.

Results: None of the patients included in the study showed halo signs. Moreover, none of the patients showed compression signs, occlusion, or stenosis results. The mean value for intima-media complex thickness was measured as 0.25mm (0.18 - 0.27mm) in a common superficial temporal artery.

Conclusion: Chickenpox patients did not show any ultra sonographic changes in their temporal artery and no clinical symptoms related to GCA, yet we think that the relationship between VZV infection and GCA development warrants further studies with larger series and longer follow-up periods.

Keywords: Giant-cell arteritis; varicella-zoster virus; vasculitis; ultrasonography

Introduction

Varicella-Zoster Virus (VZV) is a member of the Herpesviridae family of viruses and causes two different clinical conditions. Varicella, or colloquially known as chickenpox, is a relatively moderate clinical condition characterized by widespread exanthematous rashes, caused by exposure to the virus in people without immunity to the virus. Shingles, or herpes zoster

is the recurrent infection of VZV which lay dormant within the organism after primary infection (1). Chickenpox is easily transmitted from the infectious person through air, droplets, or direct contact (2). Although most varicella infections clear on their own in 7-10 days, complication rates are known to increase with age and cause severe morbidity or even mortality in rare cases.

Corresponding Author: Muhammet Bulut, MD; Department of Pediatrics, Giresun University, Faculty of Medicine, Giresun, Turkey

E-mail: muhammetbulut023@gmail.com

ORCID: 0000-0002-5963-1267

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Giant cell arteritis (GCA) is a systemic type of vasculitis that involves middle-to-large caliber arteries and is usually seen in advanced age. Headache is the most common symptom which can be accompanied by other complaints such as claudication of the jaw, vision problems, and scalp sensitivity. Diagnosis is made by ultrasound (US) and other imaging methods in addition to lab parameters and temporal artery biopsy (3). US was shown to have better sensitivity and specificity in GCA diagnosis when compared to biopsy and it is also proven to be much more cost-effective than biopsy in the literature (4).

VZV complications include post-herpetic neuralgia, meningoencephalitis, myelitis, and vasculopathy (5). Vasculopathies usually affect cerebral arteries and can cause conditions such as transient ischemic attacks or even stroke in some cases (6). Besides, other studies report VZV or VZV vaccine complications in extracranial temporal arteries, ophthalmic and retinal arteries in the form of GCA with its symptoms and results (7, 8). On the other hand, some other studies report no sighting of VZV in the temporal artery and that VZV does not play a role in GCA etiology (9). There are no previous studies that assess whether the temporal artery is affected following varicella infection using the US in the literature. Those contradicting ideas in the literature cause a conundrum whether VZV has a role in GCA etiology. The main objective of our study is not to diagnose GCA but instead, we wanted to assess whether there is a structural or flow change following VZV during childhood using US in temporal artery, which is the most commonly affected artery by GCA in advanced age and to review whether the patients show any clinical symptoms related with GCA.

Materials and Methods

The study was designed as a prospective single-blind study in the University Medical Faculty Departments of Physical Medicine and Rehabilitation, Pediatrics and Radiology. Ethics approval for the study was obtained from the Ethics Committee of the University. All participants and/or their parents signed an informed consent form before participating in the present study.

The study included 30 patients diagnosed with varicella under 16 by the same pediatrician and shows infection characteristics. Varicella characteristics were defined as lesions initially starting as erythematous macules and changing into vesicles with clear liquid inside, halo-formed erythema around vesicles, and that lesions showed polymorphic properties (different staged lesions on the same region)(4). Sociodemographic property of the participants (age, gender, education), varicella immunization history, comorbidity, medications, temporal artery-related symptoms (claudication of jaw, headache, vision issues, earache, sensitivity on temples), whether they received any symptomatic treatment against chickenpox and developed any complications during follow-up (skin infections, CNS involvement, pneumonia, rhabdomyolysis, hepatitis, myocarditis, nephritis, hemorrhagic diathesis) were all recorded in detail. Patients with conditions that might affect vascular structures (vasculitis, hypertension, diabetes mellitus), severe infection, fever and malaise, limited cooperation or mental retardation, malignancies, and open wounds in the procedure site were excluded.

The pediatrician, who made the chickenpox diagnosis by using the criteria stated above, assessed clinical symptoms in those patients such as fever, newly started headaches, and

its localization, temporal artery sensitivity and pulse, presence of jaw claudication, vision loss, and pulse changes. Gray-scale and colored Doppler US were used to assess temporal artery during the initial diagnosis and on their 6th-month follow-up visit by a radiologist with 10 years of experience (T. B) who was blind to the patients' initial diagnosis and the reason for their assessment (10). US assessment was done using Toshiba Aplio 500 US device (Toshiba Medical System Corporation, Tokyo, Japan), with a high-frequency linear probe (PLT-1005 BT [4-14 MVZV]) which supports Doppler mode. Doppler frequency was set as 10MVZM, PRF 2-3 kVZV, focus setting at 5mm, and depth setting as 1-2 cm. Common superficial arteries and their frontal and parietal branches were bilaterally reviewed on longitudinal and axial planes. GCA characteristic signs such as halo sign, compression sign, occlusion, and stenosis presence were assessed (4). Moreover, intima-media complex measurement, which is known to show increased values in vessels with vasculitis, was done using Schäfer VS et al.'s study as reference (11). "Compression sign" was defined as artery not being compressed following pressure application by US probe, "occlusion" was defined as temporal artery filled with hypoechoic material despite decreasing PRF and increasing color gain setting and inability to obtain Doppler signal and finally, "stenosis" was defined as the presence of turbulent colored pattern and persisting diastolic filling in Doppler US, accompanied by increased maximum systolic flow in pressure-waved Doppler US, and were all recorded as either "positive" or negative" (11).

Statistical Analysis

The Statistical Package for Social Sciences (SPSS), Version 22.0 (Chicago, IL, USA), was

used for the statistical analysis. The descriptive data are presented as means $\pm$ standard deviation and medians (minimum-maximum).

Results

Table-1 shows the demographic values of the patients. None of the 30 patients included in the study showed halo signs. Moreover, none of the patients showed compression signs, occlusion, or stenosis results. The mean value for intima-media complex thickness was measured as 0.25 mm (0.18 - 0.27mm) in a common superficial temporal artery.

Table 1. Patient characteristics

Characteristics	Mean (min-max)
Total number of patients	46
Age	7.7 (1-15)
Gender	
▪ Male	25
▪ Female	21
Vaccination	29
Jaw claudication	0
Headache	4
Earache	5
Temporal artery tenderness	3
Visual problems	0
Visceral complications	0
B-mode and Doppler US	
▪ Baseline	0
▪ 6 th month	0
Type of VZV treatment	
▪ A*	15
▪ B*	18
▪ C*	8
▪ D*	5

(*) A: lotion; B: lotion+antipyretic; C: lotion+antipyretic+ antihistamine drugs; D: lotion+antipyretic+ antihistamine drugs+ antiviral drugs

Discussion

There are contradicting studies in the literature about the relationship between VZV infection and GCA development. In our study, none of the patients diagnosed with chickenpox showed any clinical or US results that can be

attributed to GCA in the short or long term, and that there were no clinical or US connections between childhood varicella infection and GCA development later on in life.

GCA etiology is still unclear in the literature. However, it is thought that the relationship between vessel walls and the immune system can play a role in the pathogenesis of the disease (12). Activated vascular dendritic cells collect CD4+ T cells and macrophages towards the vessel wall. Then those cells penetrate through the tissue from the adventitia layer towards the intima layer by vasa vasorum, causing granuloma formation (14). Since intracellular pathogens also frequently cause similar granulomatous inflammation situations, infections are thought to be a trigger in some of the patients (15). As for VZV, VZV was shown to have the ability to cause vasculopathy and the pathology samples of the affected vessels show multi-core giant cell presence, similar to GCA (16). Some other studies reported detecting VZV antibodies and DNA in a detailed review of temporal artery and aorta specimens of GCA patients with positive and negative biopsy results (17-21). On the contrary, some patients reported no VZV detected in temporal artery specimens of GCA patients (22-28). An additional case-control study reported no relation between VZV and GCA (29), yet another case-control study reported an increased risk of GCA following VZV infections (30). After seeing those contradicting results in the literature, it piqued our curiosity whether we would be able to detect any clinical or US findings correlated with GCA patients in children with VZV infections and if there are any ultrasonographic changes caused by VZV infections, which is a childhood disease in general, on temporal arteries during childhood,

even though GCA is a condition seen in elderly patients. The study is a first in that sense, which warrants interest in this subject. The reason that we used US assessment instead of temporal artery biopsy, which is the most used method in GCA diagnosis today, is that our main objective was not to diagnose GCA, but instead, to detect whether there are any ultrasonographic changes in the temporal artery following VZV infections in children and the fact that temporal artery biopsy is an invasive and high-risk procedure with complications and that it only assesses a certain part of the vessels structure and only one single vessel, and finally that US imaging was proven to be a much more cost-effective non-invasive method with higher sensitivity and specificity for GCA diagnosis (4). 4 characteristic pathological signs of GCA can be detected using the US. Those are thickening of the vessel wall (halo sign), inability to compress artery (compression sign), stenosis, and vessel occlusion. Cellular infiltrates and edema can collect on intima and then spread out to media and adventitia layers in GCA. This thickening on the vessel wall shows a hypoechoic view around the vessel and is named as halo sign (30). Even though there are serious studies that show halo sign sensitivity as 55-100% and specificity as 78-100% in the US, this imaging method still did not replace temporal artery biopsy in GCA diagnosis (6). TABUL study, which prospectively compared temporal artery biopsy and colored Doppler US, reported sensitivity as 39% to 54% and specificity as 100% to 81% (10). One of the key points in ultrasonographic assessment is the requirement of an experienced radiologist to make that assessment. In the literature, the majority of the clinicians who perform the US were shown to be incompetent in temporal

artery assessment (10). To avoid this obstacle in our study, we employed an experienced radiologist who is experienced in temporal artery US assessment.

We planned to use US for the assessment of temporal artery in VZV patients for the reasons stated above, however, this also caused some limitations to our study. One of the limitations is that even though performed by experienced radiologist, the ultrasonographic assessment method is still extensively studied for use in definitive GCA diagnosis, although it was shown to be a reliable method and is still discussed today. Another limitation is that we were unable to perform temporal artery biopsy in any of the patients, which is the key point in the diagnosis. However, we don't think that it is ethical to perform temporal artery biopsies just to diagnose or detect VZV on the related tissue in patients without GCA clinical symptoms or lab findings. Finally, our last limitation is the short amount of follow-up periods, which was six months. It is possible that those patients included in the study might develop clinical/ultrasonographic signs of GCA in the future and that we might be able to detect those changes during our routine follow-up periods. Therefore; we think further studies on this subject with those aforementioned limitations are warranted.

Conclusions

Chickenpox patients did not show any ultrasonographic changes in their temporal artery and no clinical symptoms related to GCA, yet we think that the relationship between VZV infection and GCA development warrants further studies with larger series and longer follow-up periods.

Ethical Statement

The study was conducted according to the declaration of Helsinki. The study was approved by the Ethic Committee of Giresun University (Date: 07.11.2018; No:5/1/29) and the patients gave informed consent prior to participation.

Conflicts of Interest

The authors declared no conflict of interest for the present article.

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Contact Details

Fazıl Kulaklı, MD

Department of Physical Medicine and Rehabilitation, Giresun University, Faculty of Medicine, Giresun, Turkey

E-mail: drfzl46@gmail.com

ORCID: 0000-0003-0275-7093

Muhammet Bulut, MD

Department of Pediatrics, Giresun University, Faculty of Medicine, Giresun, Turkey

E-mail: muhammetbulut023@gmail.com

ORCID: 0000-0002-5963-1267

Tümay Bekçi, MD

Department of Radiology, Giresun University, Faculty of Medicine, Giresun, Turkey

E-mail: tmybkci@gmail.com

ORCID: 0000-0002-3147-2786

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