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Title: Infectious Agents and Stroke: A Systematic Review

Running title: Infectious Agents and Stroke

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ABSTRACT

Introduction: Stroke is one of the main cause of disability and the second cause of death worldwide. Among several infectious agents considered as the risk factor of stroke, some pathogens have shown stronger robust associations with stroke. Proposing an accurate correlation between infectious microorganisms and stroke provides valuable information for early intervention and control of the infections.

Methods: In this study, we searched literature using the Web of Science, PMC/Medline via PubMed, and Scopus databases up to July 2018 with no time and language restrictions. After quality assessment, 16 articles were included in the study. The whole data extraction process was conducted by two reviewers independently.

Results: Based on the results of the studies, it seems that viruses such as human immunodeficiency virus (HIV), Hepatitis B virus (HBV), Hepatitis C virus (HCV), Herpes Simplex virus Type-1, 2 (HSV-1, 2), Varicella-zoster virus (VZV or Chickenpox), and West Nile virus (WNV) are common causes of ischemic stroke. Moreover, the association of other microbial categories such as Streptococcus mutans (in bacteria), Toxoplasma gondii and Toxocara spp. (in parasites), and Rhizopus sp. (in fungi) with stroke was reported.

Conclusion: Considering the adverse role of these microorganisms, it is necessary to implement some prevention measures and methods for stroke treatment.

Keywords: Stroke; Infection; Viruses; Bacteria; Fungi
Introduction

Stroke is one of the major causes of disability in adults and the second cause of death worldwide. Countries with low socioeconomic status account for more than 85% of stroke mortality worldwide. However, not all modifiable risk factors for stroke have been recognized yet (O'Donnell MJ et al., 2010). In this regard, infectious agents are among the supposed risk factors for stroke. In order to deal with traditional risk factors for stroke, some infections could be prevented and their disease incidence could be reduced (Fugate JE et al., 2014).

There are two types of stroke including ischemic and hemorrhagic (Sirven JI & Malamut BL, 2008). In most investigations in this field, ischemic stroke has shown a stronger association with systemic infection (Grau AJ et al., 2010; Fugate JE et al., 2014). Infectious diseases are caused by microorganisms such as bacteria, viruses, fungi, and parasites (Murray P, 2017; Saberi A, et al., 2018). Among microorganisms' categories, common viral and bacterial infections may increase the susceptibility to stroke by promoting atherosclerosis, inflammation, and local thrombosis (Manousakis G, et al., 2009).

The herpesviruses are a family of common persistent viruses that may reactivate periodically from latency to cause substantial morbidity through inducing a range of inflammatory effects (Forbes HJ et al., 2017). To date, more than 130 herpesviruses are known to have been recognized (Brown JC & Newcomb WW, 2011). Nine of these viruses are known to infect humans: herpes simplex viruses 1 and 2 (HSV-1 and HSV-2, also known as HHV1 and HHV2, respectively, which can cause orolabial herpes and genital herpes), varicella-zoster virus (VZV, also called HHV-3 and referred to as the cause of chickenpox and shingles), Epstein-Barr virus (EBV or HHV-4, which lead to several diseases, including mononucleosis and some cancers), human cytomegalovirus (HCMV or HHV-5), human herpesvirus 6A and 6B (HHV-6A and HHV-6B), human herpesvirus 7 (HHV-7), and Kaposi’s sarcoma-associated herpesvirus (KSHV, also known as HHV-8) (Carter J & Saunders V, 2007). West Nile virus (WNV) is a neurotropic flavivirus that has emerged globally as a significant cause of viral encephalitis and is related to other important human pathogens, including dengue viruses, yellow fever viruses, and Japanese encephalitis viruses (Samuel MA & Diamond MS, 2006). WNV infection should be included in the differential diagnosis of unexplained meningitis or encephalitis because a high index of clinical suspicion exists regarding the results of specific laboratory tests (Kemmerly SA, 2003).

Chronic infections presently discussed as stroke risk factors, mainly include periodontitis and infections with Streptococcus mutans (Inenaga C et al., 2018), Helicobacter pylori (Palm F et al., 2009; Ashtari F et al., 2008), and Chlamydia pneumoniae (Palm F et al., 2009; Ashtari F et al., 2007).

Some studies have reported that infection may be associated with the risk of stroke (He Huang et al., 2013-Abdallah A et al., 2018). We performed this systematic review to identify the most common microorganisms related to stroke.

Materials and Methods

Search Strategy:

This research was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Moher D et al., 2009). We searched International databases including Medline/PMC (via PubMed), Scopus, and Web of Science. There was not any limitation in date of articles (except until July 2018), language, and type of documents.

Keywords:

The search strategy is described in Table 1. The search terms with similar meanings were combined using the OR logic and were coupled using the AND logic.
Table 1. Search strategy applied in the PubMed, Scopus, and Web of Science databases

<table>
<thead>
<tr>
<th>Database</th>
<th>Syntax</th>
</tr>
</thead>
<tbody>
<tr>
<td>PubMed</td>
<td>(stroke[Title/Abstract]) AND (bacteri*[Title/Abstract] OR viral[Title/Abstract] OR virus[Title/Abstract] OR fung*[Title/Abstract] OR parasit*[Title/Abstract])</td>
</tr>
<tr>
<td>Scopus</td>
<td>(TITLE-ABS-KEY (stroke) AND TITLE-ABS-KEY (bacteri*) OR TITLE-ABS-KEY (viral OR virus) OR TITLE-ABS-KEY (fung*) OR TITLE-ABS-KEY (parasit*))</td>
</tr>
<tr>
<td>Web of Science</td>
<td>TOPIC: (stroke) AND TOPIC: (bacteri* OR viral OR virus OR fung* OR parasit*)</td>
</tr>
<tr>
<td></td>
<td>TITLE: (stroke) AND TITLE: (bacteri* OR viral OR virus OR fung* OR parasit*)</td>
</tr>
</tbody>
</table>

**Exclusion criteria:**

An article was excluded from our systematic review if it was:

1. A study on Animal Models
2. A study on vectors in therapy
3. An article studying post-stroke infection in patients such as surveying nosocomial infection in patients
4. An article studying one of the strokes along with other neurological diseases such as septic embolism, meningitis, stress, and endocarditis
5. A systematic review and Meta-analysis

**Quality assessment:**

We used the Standards for Reporting of Diagnostic Accuracy (STARD) for assessing the quality of articles. It included the standards for the quality of completeness and transparency of reporting of diagnostic accuracy studies (Scales Jr CD et al., 2008). Two reviewers assessed independently the methodological quality (risk of bias) of the studies using the criteria of Downs & Black (Downs SH & Black N., 1998). Any disagreements were resolved by consensus and checked by a third reviewer.

**Data extraction:**

First, we evaluated the titles and abstracts of the retrieved articles to determine the initial eligibility and, if necessary, studied the full articles in detail to select them for the review. Disagreements in data extraction between authors were resolved by consensus.

The following data were extracted from the chosen articles: first author’s name, year of publication, location of the study, type of study, number of cases participated, age of participants, case group, control group, stroke classification in case group, diagnosis test used for microorganism, infection type, and main results concerning the correlation between infection and stroke in patients.

**Results**

After eliminating the duplicate articles and reviewing the titles and abstracts, 9161 articles remained. After removing 9001 unrelated records, 35 full texts were assessed for eligibility. Fig. 1 demonstrates the search strategy based on the PRISMA Flow Diagram. The summary of the selected articles is presented in Table 2.
Fig. 1. Flow diagram of literature search and study selection

- 12,087 records were identified through database searching
- 0 additional record was identified through other sources
- 9,161 records after duplicates removed
- 160 were screened
- 9,001 records were excluded
- 35 full-text articles were assessed for eligibility
- 19 full-text articles were excluded, with reasons:
  - Animal Model
  - Along with other neurological diseases
  - Catching infection after stroke
  - Conference papers
  - Article published before 2000
  - Bacterial, fungal and parasitical study
- 16 studies were included in qualitative synthesis
- 0 studies were identified through bibliographic cross-reference of articles obtained
<table>
<thead>
<tr>
<th>Author, Year, Country</th>
<th>Study type</th>
<th>Number of participant s</th>
<th>Age (year)</th>
<th>Case Group</th>
<th>Control Group</th>
<th>Stroke Classification in the case group</th>
<th>Diagnosis test for microorganism</th>
<th>Infection agent</th>
<th>Main Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topping et al. 2007, South Africa</td>
<td>Cohort</td>
<td>1,023</td>
<td>10-76</td>
<td>HIV-negative stroke patients (n=177)</td>
<td>Ischemia (n=64); Hemorrhagic (n=3)</td>
<td>HIV testing (unknown type of tests)</td>
<td>HIV</td>
<td></td>
<td>- In 20% of HIV-positive patients with stroke, there was radiological evidence of intracranial (9%) or extracranial (11%) vasculopathy. No aneurysmal vasculopathy was seen in HIV-negative stroke patients.</td>
</tr>
<tr>
<td>Benjamin et al. 2007, Malawi</td>
<td>Original</td>
<td>383</td>
<td>–</td>
<td>107</td>
<td>Ischemia (n=48); Hemorrhagic (n=30)</td>
<td>HIV-1 serology, CD4+</td>
<td></td>
<td></td>
<td>- Ischemic stroke in basal ganglia occurred in 58% of HIV-infected stroke patients vs. 42% HIV-negative stroke patients (P = .001).</td>
</tr>
<tr>
<td>Meserve et al. 2009, Farmington</td>
<td>Case report</td>
<td>1</td>
<td>A 55-year-old man</td>
<td>–</td>
<td>–</td>
<td>Ischemic (n=1)</td>
<td>ELISA</td>
<td>Western blot</td>
<td>HIV</td>
</tr>
<tr>
<td>Noury et al. 2009, USA</td>
<td>Case report</td>
<td>1</td>
<td>A 15-year-old girl</td>
<td>–</td>
<td>–</td>
<td>Hemorrhagic (n=1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nogueras et al. 2012, Spain</td>
<td>Observatio n</td>
<td>1</td>
<td>A 31-year-old man</td>
<td>–</td>
<td>–</td>
<td>Ischemic (n=1)</td>
<td>PCR to determine the presence of HSV-integrated DNA in the tissues</td>
<td>HSV</td>
<td></td>
</tr>
<tr>
<td>Hara-Kihus et al. 2000, Japan</td>
<td>Case report</td>
<td>1</td>
<td>A 42-year-old girl</td>
<td>–</td>
<td>–</td>
<td>Ischemic (n=1)</td>
<td>PCR to amplify HSV DNA sequence in her CSF sample</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asefa-Lekid et al. 2016, USA</td>
<td>Review</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Powell et al. 2016, Mexico</td>
<td>Case report</td>
<td>1</td>
<td>A 51-year-old man</td>
<td>–</td>
<td>–</td>
<td>Ischemic (n=1)</td>
<td>ELISA to determine HSV immunoglobulin G (IgG) reactivity in CSF B-cell serum; PCR to amplify HSV-specific DNA sequence in her CSF sample</td>
<td>HSV (or HSV-3) or (Chlamydia)</td>
<td></td>
</tr>
<tr>
<td>Arase et al. 2014, Japan</td>
<td>Cohort</td>
<td>7,615</td>
<td>&gt;60 to &lt;65</td>
<td>4,646</td>
<td>–</td>
<td>Hemorrhagic (n=24); Non-hemorrhagic (n=622)</td>
<td>ELISA</td>
<td>PCR to amplifying HHV-6B Tag/ELISA HCV test to determine HCV RNA</td>
<td>HCV</td>
</tr>
<tr>
<td>Lui et al. 2016, Taiwan</td>
<td>Cohort</td>
<td>20,471</td>
<td>20-75</td>
<td>4,046</td>
<td>16,576</td>
<td>none</td>
<td>none</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Song et al. 2007, Korea</td>
<td>Cohort</td>
<td>531,451</td>
<td>10-64</td>
<td>13,962 HIV-1-positive men with normal LFT and normal clinical history. 203 HIV-1-1 positive men with abnormal LFT (136 (64%), a clinical history of liver dysfunction (35%), or both (54%); and 28 772 HIV-1-seropositive men with normal LFT and no clinical history of liver dysfunction (27%); 435 HIV-1-seronegative men with normal LFT and no clinical history of liver dysfunction (28%)</td>
<td>Ischemia (n=85); Hemorrhagic (n=219)</td>
<td>Reverse hemagglutination</td>
<td>ELISA</td>
<td>HIV</td>
<td></td>
</tr>
<tr>
<td>Tsang et al. 2016, Taiwan</td>
<td>Cohort</td>
<td>1,000,000</td>
<td>13-30</td>
<td>229,355</td>
<td>79,212</td>
<td>Ischemic (n= 125)</td>
<td>ELISA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ekkad et al. 2016, New York</td>
<td>Original</td>
<td>306</td>
<td>5.1-14.3</td>
<td>306</td>
<td>Ischemic (n=187)</td>
<td>IgM/IgG antibodies to herpes simplex virus (HSV-1) and 2</td>
<td></td>
<td></td>
<td>- Past infection with HSV did not increase the risk of stroke.</td>
</tr>
<tr>
<td>Sun et al. 2009, The Netherlands</td>
<td>Case report</td>
<td>1</td>
<td>A 3-year-old girl</td>
<td>–</td>
<td>–</td>
<td>Ischemic (n=1)</td>
<td>PCR to amplify HIV-1 DNA sequence in her CSF and serum sample</td>
<td>HIV-1</td>
<td></td>
</tr>
<tr>
<td>Terazi et al. 2013, Italy</td>
<td>Case report</td>
<td>1</td>
<td>A 10-year-old girl</td>
<td>–</td>
<td>–</td>
<td>Ischemic (n=1)</td>
<td>ELISA (lg M and lg G to HSV1)</td>
<td>HIV-1</td>
<td></td>
</tr>
<tr>
<td>Alexander et al. 2006, USA</td>
<td>Case report</td>
<td>1</td>
<td>A 9-year-old girl</td>
<td>–</td>
<td>–</td>
<td>Ischemic (n=1)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** HIV: Human immunodeficiency virus; CSF: cerebrospinal fluid; VZV: Varicella zoster virus; HBV: Hepatitis B virus; HCV: Hepatitis C virus; HSV: Herpes simplex virus; HBV: Hepatitis B virus; HCV: Hepatitis C virus; HSV: Herpes simplex virus type 1, 2, 3; EIA: Enzyme-linked immunosorbent assay; ELISA: enzyme immunoassay; PCR: polymerase chain reaction.
Discussion

This systematic review comprehensively presents studies on both infections with and reactivation of all eight human herpesviruses and the risk of subsequent stroke. An improved understanding of this relationship may help to inform public health stroke prevention strategies.

Human immunodeficiency virus (HIV):

Cerebral stroke is a rare complication of HIV infection (Tipping B et al., 2007). Many case studies have reported a different case of stroke that HIV was found to be the stroke etiology (Manwani B et al., 2016), especially in children or young patients. Thus, in pediatric strokes, especially in the high-risk population, laboratory investigation of HIV is mandatory (Narayan P et al., 2002; Nogueras C et al., 2002). HIV-associated vasculopathy is the reason of stroke in these patients (Tipping B et al., 2007). The HIV-associated vasculopathy subtypes included non-atherosclerotic vasculopathy, accelerated atherosclerosis, and HIV-associated vasculitis (Benjamin LA et al., 2017). Two other proposed mechanisms of vasculopathy are the vessel wall inflammation by an opportunistic infection (Benjamin LA et al., 2017) and rarely the primary angitis of the CNS in HIV-infected patients as leading causes of stroke (Nogueras C et al., 2002).

In a study by Tipping in South Africa on the stroke, 6.1% of stroke patients were HIV infected, 96% were cerebral infarction, and the others were intracerebral hemorrhage (4%). HIV infection as a risk factor for stroke was suggested (OR= 6.4, CI: 3.1 to 13.2). HIV-associated vasculopathy was identified in 20% of patients. Moreover, in 11% of them, it showed extra-cranially (11%) as total or significant carotid occlusion. The autopsy of one patient with occlusion of the extracranial internal carotid artery by thrombus demonstrated fibrosis of atrial adventitia with neovascularisation and lymphoplasmacytic infiltration with positive for neutrophil elastase, CD3, CD8, and CD68 and negative for CD20 and P24. The intracranial vasculopathy in the HIV positive patients was characterized by widespread intracranial vascular degenerative ectasia with superimposed thrombosis. Interestingly, it was shown that in patients with extracranial vasculopathy, CD4 count was preserved compared with intracranial vasculopathy (Tipping B et al., 2007).

In a study by Smith et al. in the United Kingdom conducted on adult ischemic stroke patients (64 HIV-infected and 107 HIV-uninfected), it was reported that the most common etiology was HIV-associated vasculopathy (38%), followed by opportunistic infections (25%). It is of note that patients with accelerated atherosclerotic vasculopathy were not as immunosuppressed as cases with other subtypes of HIV-associated vasculopathy (Smith B, 2017). In a large number (25%) of patients, stroke was observed by the mechanism of the immune reconstitution-like syndrome (IRIS) after antiretroviral therapy (ART) (Benjamin LA et al., 2017). IRIS occurs during immune system recovery after an immunodeficient state. It is associated with a rapid decline (of ≥2logs) in HIV viral load, a low nadir, and then rising CD4+ count following the ART introduction and anemia (Haddow LJ et al., 2009; Johnson TP & Nath A, 2014). This phenomenon can be explained by the mechanism of infiltration of active T cells (Johnson TP & Nath A, 2014).

Herpes simplex virus (HSV):

HSV encephalitis is a rare cause of pediatric arterial ischemic stroke (Askalan R et al., 2001). Elkind et al. assessed the role of HSV in children acute ischemic stroke (AIS) and by serological study found that acute herpesvirus infection especially HSV-1 doubled the odds of childhood AIS, even if the infection is subclinical. However, based on their results, past infection did not have any association with stroke (Elkind MS et al., 2016). Also, there is some limited case report in this field, of which we report two cases below. Sas et al. described a 3-year-old girl who presented with bilateral occipital ischemic stroke, attributable to HSV-1 encephalitis. It was confirmed by HSV-PCR in serum and cerebrospinal fluid and anti-HSV-1 immunoglobulin G seroconversion, which occurred within 5 days after admission. Both findings are compatible with primary HSV-1 infection (Sas AM et al., 2009). Terlizzi et al. also described another arterial ischemic stroke after primary HSV-1 infection in a 10-year-old girl. Ig-M antibodies to HSV1 showed relatively high specificity and positive predictive value. Seroconversion to immunoglobulin G antibodies occurred 16 days after admission, which makes the correlation stronger. CSF-PCR for HSV-1 was negative (Terlizzi V et al., 2014). Elbers et al. described that if CSF test is performed in 3-14 days after symptoms onset, the negative HSV-PCR does not rule out the acute infection (Elbers JM et al., 2007).

Varicella-zoster virus (VZV):

VZV is a common cause of stroke. Approximately, one-third of arterial ischemic stroke in the pediatric population is associated with varicella (Askalan R et al., 2001), which is a neurotropic alpha-herpesvirus. To our knowledge, chickenpox is the primary infection in childhood, after which virus becomes latent in neural ganglia including cranial nerve, dorsal root ganglia, and autonomic ganglia (Mahalingam R et al., 1990). When cell-mediated immunity to VZV declines with immunosuppression or
increasing age, the virus reactivates and herpes zoster (shingles) and, less frequently, the meningoencephalitis, myelitis, multiple serious ocular disorders, and VZV vasculopathy may occur. All of these complications may develop in the absence of rash (Amlie-Lefond C & Gilden D., 2016). Interestingly, it was demonstrated that in the zoster patients who receive oral antiviral therapy, the risk of stroke declines compared to that in untreated zoster patients (Nagel MA et al., 2017).

VZV-associated stroke can be followed primarily by varicella infection, herpes zoster (HZO), or other forms of herpes zoster in both immunocompromised and immunocompetent individuals. In this regard, different VZV-associated stroke syndromes and vasculitis of the CNS have been explained by Moriuchi et al. in the literature (Moriuchi H & Rodriguez W., 2000).

Study of the different database revealed the increase rate of stroke after zoster especially early after zoster in younger adults and after ophthalmic zoster. Records of Taiwanese National Health Research Institute showed a 30% increased risk of stroke within 1 year after zoster (Kang JH et al., 2009), which increases by 4.5-fold with ophthamlic zoster (Lin HC et al., 2010). Danish National Registry revealed a 126% increased risk of stroke within 2 weeks after zoster, a 17% increased risk from 2 weeks to 1 year after zoster, and a 5% increased risk of stroke after the first year (Sreenivasan N et al., 2013). The data from U.K. Health Improvement Network general practice database revealed the risk of transient ischemic attacks (TIAs) increases 1.15-fold, especially in patients under 40 years of age. In the group of under 40-year-old patients, the risk of stroke and TIAs increases 1.74 and 2.42 folds, respectively (Breuer J et al., 2014). Moreover, the assessment the U.K. Clinical Practice Research Datalink demonstrated that the risk of stroke after zoster decreased over time, with a statistically significant age-adjusted incidence of 1.63 at 1-4 weeks, 1.42 at 5-12 weeks, and 1.23 at 13-26 weeks after zoster, and no decrease at later times (Langan SM et al., 2014). A Swedish register-based cohort study showed a 1.34-fold increased risk of stroke within 1 year after zoster in all age groups (Sundstrom K et al., 2015). In the U.K. study, the risk of stroke in patients under 40 years of age increased 10.3 fold within 1 year after zoster (Breuer J et al., 2014). Another U.K. study showed that the risk of stroke increased 2.4-fold within 2 weeks after zoster (Minassian C et al., 2015). In the first U.S. population-based study, the risk of stroke increased 1.53 fold within 3 months after zoster (Yawn BP et al., 2016).

Several pathophysiologies were proposed for the role of VZV in producing stroke:

- Nonspecific inflammation and transient thrombophilia, especially protein S deficiency (Nguyen P et al., 1994)
- Triggering the immunopathology of giant cell arteritis (Amlie-Lefond C & Gilden D., 2016)
- VZV vasculopathy (the predominant pathophysiology), which causes 2 major patterns: a large vessel (unifocal) and small vessel (multifocal) (Gilden DH et al., 2002). In this regard, large vessel involvement more commonly affects the immunocompetent with obvious neurological deficit, whereas small vessel involvement more commonly affects the immunocompromised individuals with nonspecific central nervous system (CNS) involvement. A case was reported by Powell et al. in this category (Table 2) (Powell DR 2nd et al., 2015).

Pathophysiology of VZV Vasculopathy: The pathophysiology in children and adults is similar. When virus reactivates during zoster, especially after ophthalmic zoster, it spreads trans-axonally to intracerebral arteries from trigeminal or other cranial nerve ganglia, because the intracerebral arteries and veins receive a rich supply of trigeminal afferent fibers. VZV is the only human virus that has been shown to replicate in cerebral arteries. VZV infects all layers of the cerebral arteries and causes the granulomatous arteritis.

Pathology of VZV vasculopathy: As previously mentioned, it inflicts granulomatous arteritis. Its pathological and virological analysis reveals Cowdry A inclusion bodies, multinucleated giant cells, herpes virions, VZV DNA, and VZV antigen, indicating productive arterial infection by VZV.

Virologic Confirmation of VZV Vasculopathy: Positive VZV PCR (30%) or anti-VZV antibody (anti-VZV IgG antibodies) (93%) in CSF verifies the presence of VZV vasculopathy. The absence of cells in the CSF does not rule out VZV vasculopathy. It may be due to CSF examination early within the first weeks after stroke (3-14 days) (Amlie-Lefond C & Gilden D., 2016).

Hepatitis C virus (HCV):

Certainly, there is controversy about the association of HCV infection and atherosclerosis (White DL et al., 2008). However, the mechanisms that can explain its role in stroke are atherogenesis and atherosclerosis in carotid and aortic (Ishizaka N et al., 2002). The RNA of HCV was found in human carotid plaques and it is strong evidence for an association between HCV infection and atherosclerosis (Boddi M et al., 2010). It may be due to a chronic inflammatory process in the carotid wall (Ishizaka N et al., 2002).

In a study by Liao et al. on a longitudinal population-based cohort, they identified 4,094 adults newly diagnosed with HCV and 16,376 matched adults without HCV in 2002-2004 from the Taiwan National Health Insurance Research Database. Events of stroke from 2002–2008 were ascertained. The cumulative risk of stroke for people with HCV and without HCV was 2.5% and
1.9%, respectively (p< 0.0001), with adjusted hazard ratios (HRs) of stroke as 1.27 among HCV patients (95% CI: 1.14 to 1.41) (Liao CC et al., 2012). The role of HCV clearance on the reduction of the development of ischemic stroke was not assessed. It has to be noted that it was assessed in intracerebral hemorrhagic stroke. Due to prothrombin deficit and platelets diminution in liver dysfunction, the hemorrhagic tendency increases and treatment of HCV results in decreasing hemorrhagic stroke (Arase Y et al., 2014). For further information in this regard, it is suggested assessing the role of HCV treatment on the development of thrombotic and atherosclerotic events.

**Hepatitis B virus (HBV):**
Interestingly and contrary to the other studied microorganisms in some studies, HBsAg seropositivity was associated with an increased risk of hemorrhagic stroke and a decreased risk of ischemic stroke (Tong DY et al., 2005). Tseng et al. demonstrated that HBV lowers the risk of ischemic stroke compared with the general population even though with increasing age (Tseng CH et al., 2016).
In addition, Sung et al. estimated the risk of ischemic and hemorrhagic stroke with multivariable-adjusted hazard ratios (95% CIs) of 0.79 (0.68, 0.90) and 1.33 (1.15, 1.52), respectively. With normal liver function, the risks of stroke do not change with HBsAg seropositivity, but with liver dysfunction, the risk of hemorrhagic stroke increases and of ischemic stroke decreases compared with HBsAg-seronegative men. This association, therefore, depends on the liver function, which has no pro-inflammatory effect on the patient’s coagulation condition (Sung J et al., 2007). On contrary, Pearce et al. in a survey assessed serological evidence of prior infection based on immunoglobulin G seropositivity to HBV among 13,904 respondents from the National Health and Nutrition Examination Survey III (NHANES III) and found a correlation between HBV seropositivity and stroke among those aged 20-59 (Pearce BD et al., 2018) with no separation of the ischemic from hemorrhagic stroke that can affect the results.

**West Nile virus (WNV):**
WNV is transmitted to humans through infected mosquitoes, blood transfusions, organ transplantation, and even trans-utero and probably through breastfeeding (Hayes EB & O’Leary DR, 2004). Neurologic signs of WNV infection are a spectrum of meningoencephalitis and WNV poliomyelitis-like syndrome (Sejvar JJ, 2004) and motor neuropathy (Katirji B, 2016). However, isolated vasculitis of CNS due to this infection, which resulted in an ischemic stroke, has also been reported. Alexander et al. reported a young girl with a left middle cerebral artery stroke. Acute and subacute convalescent WNV antibodies (IgG and IgM) in serum and CSF were higher than the normal range. Cross-reactivity with other flaviviruses was ruled out by concurrent monoclonal antibody testing in the state reference laboratory. Based on Centers for Disease Control and Prevention (CDC) criteria, the presence of WNV-IgM antibody in CSF fluid strongly suggests WNV infection. Therefore, the stroke in this child is most likely due to cerebral vasculitis secondary to WNV infection (Alexander JJ et al., 2006).
According to our findings, the frequency of other microorganisms, such as fungi, bacteria, and parasites, was much lower than viruses in patients with stroke. Therefore, we have only explained one or two common cases in each category that were reported in more studies.

**Toxoplasma gondii, Toxocara spp.:**
Although a high cumulative burden of viral and bacterial pathogens may increase the risk of stroke, the contribution of parasitic infections in relation to cumulative pathogen burden and risk of stroke has rarely been examined (Pearce BD et al., 2018). In this regard, few studies have considered the role of parasites in pathogen burden studies and the effect on stroke outcome, even though infections with parasites such as T. gondii and Toxocara spp. are common in the United States (Won KY et al., 2008). Pearce et al. reported a connection between serological evidence of prior infection to T. gondii and Toxocara spp. with stroke (Pearce BD et al., 2018).

**Rhizopus sp.:**
Although invasive fungal infections of CNS are uncommon, the associated morbidity and mortality can be quite high, especially among the immunosuppressed (Panackal AA & Williamson PR, 2015).
Zygomycosis (Mucormycosis) is caused by several genera belonging to the family Mucoraceae such as Rhizopus, Mucor, and Absidia. Rhizopus is the offending organism in 95% of cases (Rhizopus arrhizus and Rhizopus oryzae). Zygomycosis fungi, though can be cultured easily on routine mycological media, are often difficult to recover from clinical samples, as during biopsy procedure or processing in the laboratory the hyphal elements get damaged and thus are rendered non-viable. No standard rapid serological method for diagnosis of zygomycosis is available (Shankar SK et al., 2007). Fu et al. suggested that clinicians
should be aware of invasive sinusitis as a rare cause of stroke in diabetics. Once the subarachnoid space and basal arteries of the brain have been invaded, the prognosis is very poor. The key to improve the outcomes is early recognition and treatment, and examination of the sinuses on neuroimaging in all cases of stroke is vital (Fu KA et al., 2015).

**Streptococcus mutans (SM):**
Among human oral bacteria, particular kinds of SM known as dental caries pathogens contain a collagen-binding protein (CBP), which is determined by the corresponding gene. They show platelet aggregation inhibition and matrix metalloproteinase-9 (MMP-9) activation. Inenaga et al. by sampling and culture of saliva obtained from 429 stroke patients found that both ischemic and hemorrhagic stroke rates increase due to the role of this pathogen (Inenaga C et al., 2018). Nakano et al. showed that CBP-positive SM is a potential risk factor for hemorrhagic stroke, not only by platelet aggregation inhibition but also by activated MMP-9 in injured arteries (Nakano K et al., 2011).

**Conclusion**
Overall, these data add to the growing body of evidence linking different categories of microorganisms, especially viruses to stroke. However, more research is needed to understand the pathogenesis mechanisms of microorganisms in patients as a risk factor for stroke and to determine the impact of treatment on risk.

**Suggestions**
- In order to better clarify this systematic review, we need a meta-analysis.
- In order to be more precise, it is recommended using more specialized keywords and specifically searching with one microorganism’s name.
- Included studies may have substantially different methodologies, which could limit our ability to draw reliable conclusions from the existing evidence base.

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**Conflict of interest**
The authors declare that they have no conflict of interest.

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