**Mini-CAT Assignment Worksheet Name\_\_\_JUN\_\_MA\_\_\_\_**

Brief description of patient problem/setting (summarize the case very briefly)

37 y/o female without significant PMH had sudden right side facial droop and right arm numbness. CTA confirmed the diagnosis of ischemic stroke. Pt denied history of HTN, DM, smoking, Afib, carotid disorder, HLD or previous stroke or TIA. But pt had recurrent herpes infection 3 weeks ago without treatment. The PA asked me if recent herpes zoster infection is a risk factor of stroke.

**Search Question:** Clearly state the question (including outcomes or criteria to be tracked)

Clinical question: Is recent herpes zoster infection a risk factor of stroke?

PICO question: Are patients with recent infection of human herpes zoster virus at increased stroke risk, compared to those without infection of human herpes zoster virus?

**Question Type:** What kind of question is this? (boxes now checkable in Word)

**Prevalence**  Screening Diagnosis

Prognosis Treatment Harms

Assuming that the highest level of evidence to answer your question will be meta-analysis or systematic review, what other types of study might you include if these are not available (or if there is a much more current study of another type)? **Please explain your choices.**

I got three systematic review articles and one comprehensive review article. If there are not enough review articles, I will choose articles with large, high quality cohort and/or case-control studies because RCT studies are not realistic for this research.

**PICO search terms:**

|  |  |  |  |
| --- | --- | --- | --- |
| **P** | **I** | **C** | **O** |
| patients | herpes zoster | without herpes infection | CVA incidence |
| persons | recent herpes infection |  | stroke incidence |
|  | herpes virus |  | Cerebrovascular Accident |

**Search tools and strategy used:**

Please indicate what data bases/tools you used, provide a list of the terms you searched together in each tool, and how many articles were returned using those terms and filters.   
Explain how you narrow your choices to the few selected articles.

I used PubMed to search for “herpes+ stroke” in “systematic review” and found 128 articles.

I also used Cochrane to search for “herpes+ stroke” in “review”, and found 2 articles.

I also used ScienceDirect to search for “herpes+ stroke” in review articles with open access, and found 32 articles after 2017.

I also used Google Scholar to search for “herpes+Zoster+ stroke”, and found 28 articles.

Then, I read the titles and abstracts of these articles from the most recent article until I found four most related review articles with full text.

**Results found:**

**Identify 3-5 articles (or other appropriate reputable sources) that answer your specific question with the highest available level of evidence.** Please make sure that they are Medline indexed.

**Please post the citation and abstract for each article (to include the journal and authors’ names and date) and say why you chose it.   
Please also note what kind of article it is (e.g. meta-analysis, cohort study, or independent blind comparison with gold standard of diagnosis, etc.).**

**At the bottom of each abstract, please comment on what your key points are from this article (including any points or concepts included in the article, but not present in the abstract – i.e. make the concepts understandable to the reader)**

**Please note that if the evidence is not in the abstract, you must clearly summarize the evidence in your posting.**

**Association of herpesviruses and stroke: Systematic review and meta-analysis.**

**Forbes HJ, Williamson E, Benjamin L, Breuer J, Brown MM, Langan SM, Minassian C, Smeeth L, Thomas SL, Warren-Gash C.**

**PLoS One. 2018 Nov 21;13(11):e0206163. doi: 10.1371/journal.pone.0206163. eCollection 2018.**

**PMID: 30462656**

Abstract:

BACKGROUND:

Herpesviruses induce a range of inflammatory effects potentially contributing to an increased risk of stroke.

OBJECTIVES:

To investigate whether patients with infection, or reactivation of, human herpesviruses are at increased stroke risk, compared to those without human herpesviruses.

DATA SOURCES:

Six medical databases and grey literature sources from inception to January 2017.

STUDY ELIGIBILITY CRITERIA:

Studies where the exposure was any human herpesvirus and the outcome was stroke. We included randomised controlled trials, cohort, case-control, case-crossover and self-controlled case series designs.

METHODS:

Meta-analyses when sufficiently homogeneous studies were available. Quality of evidence across studies was assessed.

RESULTS:

We identified 5012 publications; 41 met the eligibility criteria. Across cohort and self-controlled case series studies, there was moderate quality evidence that varicella infection in children was associated with a short-term increased stroke risk. Zoster was associated with a 1.5-fold increased stroke risk four weeks following onset (summary estimate: 1.55, 95%CI 1.46-1.65), which resolved after one year. Subgroup analyses suggested post-zoster stroke risk was greater among ophthalmic zoster patients, younger individuals and those not prescribed antivirals. Recent infection/reactivation of cytomegalovirus and herpes simplex viruses, but not past infection, was associated with increased stroke risk; however the evidence across studies was mainly derived from small, very low quality case-control studies.

CONCLUSIONS:

Our review shows an increased stroke risk following zoster and suggests that recent infection or reactivation of other herpesviruses increases stroke risk, although better evidence is needed. Herpesviruses are common and potentially preventable; these findings may have implications for reducing stroke burden.

Key points:

* Zoster was associated with a 1.5-fold increased stroke risk four weeks following onset.
* Post-zoster stroke risk was greater among ophthalmic zoster patients, younger individuals and those not prescribed antivirals.

I chose it because it is new (2018) and most relevant. It is a systematic review and meta-analysis article, including 13 cohort studies, 1 case control study and 3 self-controlled case series studies for herpes zoster.

Link: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6248930/>

**A meta-analysis of stroke risk following herpes zoster infection.**

**Marra F, Ruckenstein J, Richardson K.**

**BMC Infect Dis. 2017 Mar 7;17(1):198. doi: 10.1186/s12879-017-2278-z.**

**PMID: 28270112**

Abstract:

BACKGROUND:

The incidence of herpes zoster (HZ) is increasing and poses a significant health concern to aging populations. Several studies suggest an increased risk of stroke following zoster infection, but the results are conflicting. We conducted a systematic review and meta-analysis to determine if stroke risk is increased following HZ infection.

METHODS:

A search of MEDLINE, EMBASE, Google scholar, Web of Science, CAB Direct, Cumulative Index to Nursing and Allied Health Literature, and Evidence Based Medicine Reviews was conducted for observational studies of adults with HZ infection that examined stroke and TIA risk from January 1, 1966 to May 31, 2016. Adjusted relative risks reported for similar follow-up durations were pooled across studies separately using random-effects inverse variance models.

RESULTS:

Data were pooled from nine studies. Relative risk for stroke after zoster was 1.78 (95% CI 1.70-1.88) for the first month following herpes zoster, dropping progressively to 1.43 (95% CI 1.38-1.47) after 3 months, to 1.20 (95% CI 1.14-1.26) after 1 year. We found that stroke risk increases by a larger margin during the first month after a herpes zoster ophthalmicus episode: relative risk 2.05 (95% CI 1.82-2.31). The risk remains elevated one year after the acute episode.

CONCLUSIONS:

Herpes zoster is an established risk factor for increasing the risk of stroke, especially shortly after infection. Vaccination should be encouraged in patients at high risk of cardiovascular disease.

Key points:

* Herpes zoster is an established risk factor for increasing the risk of stroke, especially shortly after infection.

I chose it because it is new (2017) and most relevant. It is a systematic review and meta-analysis article, including 7 cohort studies and 2 self-controlled case series studies with sample size from 2632 to 4620980.

Link: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5341420/>

**Herpes zoster and the risk of ischemic and hemorrhagic stroke: A systematic review and meta-analysis.**

**Lian Y, Zhu Y, Tang F, Yang B, Duan R.**

**PLoS One. 2017 Feb 8;12(2):e0171182. doi: 10.1371/journal.pone.0171182. eCollection 2017. Review.**

**PMID: 28178287**

Abstract:

BACKGROUND:

Herpes zoster infection and stroke are highly prevalent in the general population; however, reports have presented inconsistent findings regarding the relationship between herpes zoster infection and stroke. In this meta-analysis, we aimed to clarify this association.

MATERIAL AND METHODS:

The PubMed and Embase databases were searched for studies published from their inception to January 2016. Two investigators independently extracted the data. The pooled relative risk (RR) was calculated using a random effects model.

RESULTS:

A total of 8 studies met the inclusion criteria. During the first 1 month after herpes zoster infection, the pooled RRs for ischemic stroke and hemorrhagic stroke were 1.55 (95% CI, 1.46-1.65) and 1.70 (95% CI, 0.73-3.96), respectively, and within 3 months after infection, the corresponding RRs were 1.17 (95% CI, 1.12-1.23) and 2.05 (95% CI, 1.17-3.60), respectively. At 1 year and more than 1 year after herpes zoster infection, a significant relationship was not observed between herpes zoster infection and the incidence of ischemic and hemorrhagic stroke. Publication bias was not observed.

CONCLUSION:

The accumulated evidence generated from this systematic review indicates that an increased risk for ischemic stroke occurred in the short term after herpes zoster infection, whereas a significant relationship was not observed in the long term after infection. With respect to hemorrhagic stroke, the association was not significant. With respect to hemorrhagic stroke, the association between was not significant except within 3 months after a herpes zoster infection.

Key points:

* An increased risk for ischemic stroke occurred in the short term after herpes zoster infection (within 3 months), whereas a significant relationship was not observed in the long term after infection (1 year and over).
* With respect to hemorrhagic stroke, the association was not significant.

I chose it because it is new (2017) and most relevant. It is a systematic review and meta-analysis article, including 5 cohort studies and 3 self-controlled case series studies with sample size from 4478 to 124462.

Link: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5298244/>

**Does Herpes Zoster Increase the Risk of Stroke and Myocardial Infarction? A Comprehensive Review.**

**Wu PH, Chuang YS, Lin YT.**

**J Clin Med. 2019 Apr 22;8(4). pii: E547. doi: 10.3390/jcm8040547. Review.**

**PMID: 31013629**

Abstract:

Herpes zoster (HZ) caused by varicella zoster virus (VZV) reactivation is characterized as a vesicular rash of unilateral distribution that can also cause multiple complications; such as post-herpetic neuralgia; ophthalmic zoster; and other neurological issues. VZV can also increase incident hemorrhagic or ischemic complications by causing inflammatory vasculopathy. Thus; emerging epidemiological and clinical data recognizes an association between HZ and subsequent acute strokes or myocardial infarction (MI).

This study reviewed published articles to elucidate the association between HZ and cerebrovascular and cardiac events.

Individuals exposed to HZ or herpes zoster ophthalmicus had 1.3 to 4-fold increased risks of cerebrovascular events. Higher risks were noted among younger patients (age < 40 years) within one year after an HZ episode. The elevated risk of CV events diminished gradually according to age and length of time after an HZ episode. The putative mechanisms of VZV vasculopathy were also discussed. Several studies showed that the development of herpes zoster and herpes zoster ophthalmicus increased the risks of stroke; transient ischemic attack; and acute cardiac events.

The association between VZV infection and cardiovascular events requires further studies to establish the optimal antiviral treatment and zoster vaccination to reduce zoster-associated vascular risk.

Key points:

* An increased risk for cerebrovascular events occurred in individuals exposed to HZ or herpes zoster ophthalmicus.
* Higher risks were noted among younger patients (age < 40 years) within one year after an HZ episode.
* The elevated risk of CV events diminished gradually according to age and length of time after an HZ episode.

I chose it because it is new (2019) and most relevant. It is a comprehensive review article, including 15 published epidemiological studies and 6

meta-analysis reports with sample size from 2324 to 4620980.

Link: <https://www.mdpi.com/2077-0383/8/4/547/htm>

**Summary of Evidence**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Author (Date) | | Level of Evidence | | Sample/Setting  (# of subjects/ studies, cohort definition etc. ) | | Outcome(s) studied | | Key Findings | | Limitations and Biases | |
| Forbes HJ, Williamson E,  Benjamin L, Breuer J, Brown MM, Langan SM, Minassian C, Smeeth L, Thomas SL, Warren-Gash C.  (2018) | | systematic review and meta-analysis | | 13 cohort studies, 1 case control study and 3 self-controlled case series studies  sample size from 2324 to 4620980. | | Primary: stroke or  TIA  Secondary:  ischaemic,  haemorrhagic or  unspecified stroke | | Zoster was associated with a 1.5-fold increased stroke risk four weeks following onset (summary estimate: 1.55, 95%CI 1.46-1.65), which resolved after one year. Subgroup analyses suggested post-zoster stroke risk was greater among ophthalmic zoster patients, younger individuals and those not prescribed antivirals. . | | limitations included having little data from low-income countries, which make  up around 75% of stroke deaths worldwide whether different populations have different  susceptibilities to stroke following herpesvirus infections is unclear. Some meta-analyses combined very few studies, limiting the strength of our pooled results. subgroup analyses were underpowered, limiting confidence in the findings. | |
| Marra F, Ruckenstein J, Richardson K.  (2017) | | systematic review and meta-analysis | | 7 cohort studies and 2 self-controlled case series studies sample size from 2632 to 4620980. | | Primary: stroke or  TIA | | Relative risk for stroke after zoster was 1.78 (95% CI 1.70-1.88) for the first month following herpes zoster, dropping progressively to 1.43 (95% CI 1.38-1.47) after 3 months, to 1.20 (95% CI 1.14-1.26) after 1 year. We found that stroke risk increases by a larger margin during the first month after a herpes zoster ophthalmicus episode: relative risk 2.05 (95% CI 1.82-2.31). The risk remains elevated one year after the acute episode. | | Occasionally we observed heterogeneity amongst studies results potentially due to different study designs, as previously mentioned. All of the studies except Yawn et al., relied on electronic medical records to ascertain both the HZ and the stroke outcome. Administrative data has been reported to overestimate herpes zoster by 10–15%. Studies varied as to whether their stroke definition included TIA or not, and those including TIA would have potentially overestimated risk as TIA is more common than stroke. | |
| Lian Y,  Zhu Y, Tang F, Yang B, Duan R.  (2017) | | systematic review and meta-analysis | | 5 cohort studies and 3 self-controlled case series studies  sample size from 4478 to 124462. | | Primary: stroke or  TIA  Secondary:  ischaemic or  haemorrhagic | | During the first 1 month after herpes zoster infection, the pooled RRs for ischemic stroke and hemorrhagic stroke were 1.55 (95% CI, 1.46-1.65) and 1.70 (95% CI, 0.73-3.96), respectively, and within 3 months after infection, the corresponding RRs were 1.17 (95% CI, 1.12-1.23) and 2.05 (95% CI, 1.17-3.60), respectively. At 1 year and more than 1 year after herpes zoster infection, a significant relationship was not observed between herpes zoster infection and the incidence of ischemic and hemorrhagic stroke. | | Certain limitations should also be acknowledged when interpreting the results from this  study. Our study is a meta-analysis of included observational studies,it is vulnerable to bias  introduced by methodological and clinical heterogeneity in the primary studies.First, because  of the observational nature of the included studies, loss to follow up was evitable. Second, due  to limited data, we were unable to analyse possible significant differences in the associations by  conducting subgroup analyses. Finally, the observed association between HZ and stroke risk  may have been affected by unevaluated or residual confounding factors. Persons with HZ may  have diabetes, cardiac disease and hypertension. Most of the studies included in the meta-analysis but not all adjusted for these and other potential confounders. | |
| Wu PH, Chuang YS,  Lin YT.  (2019) | | comprehensive review | | 15 published epidemiological studies and 6  meta-analysis reports  sample size from 2324 to 4620980 | | Primary: stroke or  TIA  MI | | Individuals exposed to HZ or herpes zoster ophthalmicus had 1.3 to 4-fold increased risks of cerebrovascular events. Higher risks were noted among younger patients (age < 40 years) within one year after an HZ episode. The elevated risk of CV events diminished gradually according to age and length of time after an HZ episode. | | The limitations of the observational studies included a lack of randomization and a risk of bias. The review studies were controlled for important confounders, such as demographics and CVD risk factors. Some studies were flawed by a small number of enrolled subjectof HZ (Hosamirudsari et al.), few HZO identified patients (Langan et al.) , small events numbers (Kang et al., Lin et al., and Sundström et al.), and misclassification of HZ and herpes simplex (Sreenivasan et al.). Furthermore, several studies implemented a self-controlled case series design to provide stronger confounding control. However, the possibility of residual confounding, such as stressful life events or mental health, could not be ruled out. Furthermore, few of the studies evaluated stroke risk according to use of antiviral treatment, which may solidify the evidence of risk association and provide clinical recommendations for adults with high CVD risk after HZ. Correspondingly, only one study evaluated the effect of vaccination on stroke risk after an HZ episode with low power. Additional studies of CVD outcomes among patients vaccinated against HZ could provide a better understanding of HZ as a possible risk factor for CVD. Future cohort studies or clinical trials of patients who received the HZ vaccine could better clarify the association between HZ and CVD or cerebrovascular outcomes. The risk of CVD may depend on whether the HZ outbreak occurs in dermatomes that share innervation with the coronary and cerebral arteries. Although the meta-analysis results demonstrated the association between HZ or HZO and stroke, heterogeneity was observed in the study designs, geographic areas, characteristics of populations, and variant confounding factors’ adjustment. Furthermore, positive result bias may reveal an association between HZ and selected CVD events. | |

**Conclusion**

Question: Are patients with recent infection of human herpes zoster virus at increased stroke risk, compared to those without infection of human herpes zoster virus?

Answer: The first study showed zoster was associated with a 1.5-fold increased stroke risk 4 weeks following onset. So the answer is that patients with recent infection of human herpes zoster virus are at increased stroke risk, compared to those without infection of human herpes zoster virus.

The second study showed that herpes zoster is an established risk factor for increasing the risk of stroke, especially shortly after infection. So it also supports that patients with recent infection of human herpes zoster virus are at increased stroke risk, compared to those without infection of human herpes zoster virus.

The third study showed that an increased risk for ischemic stroke occurred in the short term after herpes zoster infection (within 3 months), whereas a significant relationship was not observed in the long term after infection (1 year and over). Besides, for hemorrhagic stroke, the association was not significant. So it supports that patients with recent infection of human herpes zoster virus are at increased stroke risk, compared to those without infection of human herpes zoster virus.

The fourth study showed that individuals exposed to HZ or herpes zoster ophthalmicus had 1.3 to 4-fold increased risks of cerebrovascular events. So it supports that patients with recent infection of human herpes zoster virus are at increased stroke risk, compared to those without infection of human herpes zoster virus.

Conclusion: Patients with recent infection of human herpes zoster virus are at increased stroke risk, compared to those without infection of human herpes zoster virus.

**What is the clinical “bottom line” derived from these articles in answer to your question?**

I will weigh my studies in the following order: Forbes et al, Marra et al, Lian et al, and Wu et al.

I weighed the first study (Forbes et al) is weighed highest because it is the newest (2018) systematic review and meta-analysis article, including the most studies (13 cohort studies, 1 case control study and 3 self-controlled case series studies for herpes zoster). It did not only show zoster was associated with a 1.5-fold increased stroke risk four weeks following onset, but also showed post-zoster stroke risk was greater among ophthalmic zoster patients, younger individuals and those not prescribed antivirals. Our patient is relatively young (37 y/o), had no antiviral treatment, and the zoster infection was 3 weeks ago, compatible with the description of the population with high risk in this article. Of course, it has limitations. One concern is that studies included having little data from low-income countries, which make up around 75% of stroke deaths worldwide, since whether different populations have different susceptibilities to stroke following herpesvirus infections is unclear.

I weighed the second study (Marra et al) second because it is a pretty new (2017) systematic review and meta-analysis article, including many relevant studies (7 cohort studies and 2 self-controlled case series studies with sample size from 2632 to 4620980). It supports that recent herpes zoster infection (1 month vs 3 months vs 1 year after infection) is a risk factor of stroke. Limitations include the occasional heterogeneity amongst study results potentially due to different study designs, using electronic medical records to ascertain both HZ infection and the stroke outcome in most studies that might overestimate herpes zoster, and different stroke definitions as to inclusion of TIA or not in studies.

Next is the third study (Lian et al) because it is a pretty new (2017) systematic review and meta-analysis article, including 5 cohort studies and 3 self-controlled case series studies with sample size from 4478 to 124462. It showed that an increased risk for ischemic stroke occurred in the short term after herpes zoster infection (within 3 months), whereas a significant relationship was not observed in the long term after infection (1 year and over). Besides, for hemorrhagic stroke, the association was not significant. It supports that recent herpes zoster infection is a risk factor of ischemic stroke. Certain limitations include loss to follow up due to the observational nature of the included studies, inability to analyze possible significant differences in the associations by conducting subgroup analyses due to limited data, and unevaluated or residual confounding factors that might affect the studies.

The last is the fourth study (Wu et al) showed because it is only a comprehensive review article. But it includes 15 published epidemiological studies and 6 meta-analysis reports with sample size from 2324 to 4620980. It showed that individuals exposed to HZ or herpes zoster ophthalmicus had 1.3 to 4-fold increased risks of cerebrovascular events. Higher risks were noted among younger patients (age < 40 years) within one year after an HZ episode. The elevated risk of CV events diminished gradually according to age and length of time after an HZ episode. So it supports that recent herpes zoster infection is a risk factor of ischemic stroke. The limitations of the observational studies included a lack of randomization and a risk of bias.

**Magnitude of any effects**

The three systematic review and meta-analysis articles showed zoster was associated with a 1.5-fold to 1.78-fold increased stroke risk after recent infection. The last article showed that individuals exposed to HZ or herpes zoster ophthalmicus had 1.3 to 4-fold increased risks of cerebrovascular events. All of these effects are statistically significant.

**Clinical significance (not just statistical significance)**

Although large high quality studies need to be further performed, the current studies significantly support that that patients with recent herpes zoster infection are at increased stroke risk, compared to those without herpes zoster infection.

Since herpesviruses are common and potentially preventable, these findings may have implications for reducing stroke burden by preventive herpes zoster vaccination and timely treatment of herpes zoster treatment.

In conclusion, the clinical recommendations are herpes zoster vaccination and timely treatment of herpes zoster treatment, which are very important to decrease the stroke risk, especially for ophthalmic zoster patients and younger individuals.

**Any other considerations important in weighing this evidence to guide practice?**

Although the current studies significantly support that that patients with recent herpes zoster infection are at increased stroke risk, compared to those without herpes zoster infection, many studies included are small and low-qualify. Since for this research, RCT is not realistic, large, high quality cohort and case-control studies need to be performed to confirm the conclusion.