SCOPE

Journal of Medical Students Reviews is a student-founded, student-administered and student managed digital and free Access journal, under guidance of faculty and staff. Created to give opportunity to develop the critical thinking skills needed to carry out a well-sustained investigation.

MISSION

Our mission is to give the opportunity to develop critical thinking skills needed to carry out a well-sustained investigation, in order to spread knowledge with great responsibility in the constant search for academic, scientific and research excellence that science demands worldwide.

VISION

By 2023 we will be an international magazine included in the most important indexes of quality and quotation in the area of health, in constant growth and with publications of the highest quality.

VALUES

Honesty
Medical student empowerment
Compromise
Responsibility
DIRECTIVE COMMITTEE

RECTOR OF THE UNIVERSITY  MANUEL FERMÍN VILLAR RUBIO M Arch
DIRECTOR  ALEJANDRO JAVIER ZERMEÑO GUERRA MD
CHIEF EDITOR  MAURICIO PIerdANT PÉREZ MD, MSc
ASSOCIATE EDITOR  MARÍA ISABEL PATIÑO LÓPEZ MLis

EDITORIAL COMMITTEE

LILIANA ITAMAR CARRILLO BARBA MS
ANDRÉS CASTILLO DIMAS MS
ALEJANDRA DE LA TORRE SOTO MS
ROCÍO DANIELA OCHOA VALTIERRA MS
LIZETH GUADALUPE ORTIZ VÁZQUEZ MS

AREA EDITORS

MORPHOLOGY  BLANCA ARIADNA CARRILLO ÁVALOS MD
BIOCHEMISTRY  MARIANA SALGADO BUSTAMANTE MD, PhD
MOLECULAR BIOLOGY  CHRISTIAN A. GARCÍA SEPÚLVEDA MD, PhD
PHYSIOLOGY  SERGIO SÁNCHEZ-ARMMASS ACUÑA MD, PhD
IMMUNOLOGY  ESTHER LAYSECA ESPINOSA MD, PhD
MICROBIOLOGY  UCIEL RENÉ OCHOA PÉREZ MD MSc
PHARMACOLOGY  ANTONIO A. GORDILLO MOSCOSO MD, PhD
INTERNAL MEDICINE  EMMANUEL RIVERA LÓPEZ MD
SURGERY  DAVID DE DANIEL EMER SÁNCHEZ MD
PEDIATRICS  RAÚL ROQUE SÁNCHEZ MD
GYNECOLOGY  JUAN CARLOS TORO ORTIZ MD
PUBLIC HEALTH  AMADO NIETO CARAVEO MD, MSc
MENTAL HEALTH  MARISOL OROCIO CONTRERAS MD, PhD
Editorial: what's new on systematic reviews?
MEDINA-MORENO URSULA FABIOLA PhD, GORDILLO-MOSCOSO ANTONIO AUGUSTO PhD.

Articles

Gamma waves, a new way for pain measurement?
AGUILAR- FLORES ESBEIDY MS, AGUILLÓN-PÉREZ OSCAR MS.

Use of statins as a protective factor for nephrolithiasis.
CALVA-CASTILLO PEDRO MIGUEL MS.

Etiology of febrile seizures with particular reference to HHV-6 infection.
TAYABAS-CASTILLO MARÍA FERNANDA MS, ORTIZ-ACOSTA SARA LUZ MS, VILLEGAS-HERNÁNDEZ VICENTE EMMANUEL MS, MAYA-FLORES DAVID FRANCISCO MS.

Guide for authors.
JMSR.
EDITORIAL

WHAT'S NEW ON SYSTEMATIC REVIEWS?

Medina-Moreno Ursula Fabiola¹, Gordillo-Moscoso Antonio Augusto¹.

Clinical Epidemiology Department, Faculty of Medicine,
Universidad Autónoma de San Luis Potosí
Av. Venustiano Carranza #2405. San Luis Potosí, SLP, Z.P. 78210. Mexico

During this summer (2018), the 1st Cochrane Mexico Symposium was held at the Children's Hospital of Mexico “Federico Gómez”. The main objective was to bring together students, professionals, teachers of the health area, members of Cochrane Mexico of various entities and experts in the evaluation of evidence and knowledge transfer of Latin America, in a forum that allowed the exchange of experiences and the discussion of challenges, in order to be able to generate new ideas, and to continue fostering research in the day-to-day clinical practice.

One of the tools we discovered was COVIDENCE, presented by Dr. Giordano Pérez G. To be able to present its advantages and disadvantages, remember that, in a systematic way, when carrying out a systematic review, the steps to follow can be tedious or complicated for the researcher inexperienced. We start manually with the search of articles, follow the analysis of these; Once this stage is over, the next step is to know whether or not they meet the criteria that the researcher needs and finally, the step that may be even more complex is the final decision, which articles should be included or not. After this preamble, let's talk about COVIDENCE, it is a platform developed by the University of Monash and the Alfred Hospital (Australia), in collaboration with Cochrane (https://www.covidence.org/).
Among the advantages, we highlight that it is an online platform developed to carry out a three-step review in a more user-friendly manner based on the screening of all the studies included in the preparation of the systematic reviews. This screening has support for the selection of your articles through titles and summaries. The steps to follow in the platform are: 1. Quality analysis, which has the option of being carried out in pairs (the same platform tells you the reason); 2. Data extraction and summary, process optimized by the Cochrane reviewers; 3. Interpretation based on quality and results (it is very useful in the case of evaluation of treatment results for a particular clinical condition).

Finally, one of the points in favor is that it allows you to export your results to RevMan (which is the software for Meta Analysis), and to be able to organize and manage your meta-analysis as a final part. This, in a short time and in a totally intuitive platform. Among the disadvantages, the free trial option that they offer is only to perform a single review, which, once discharged, you can not modify until finished. As we can see, the proposal is becoming more relevant in the field of research, since it allows you to create a new ecosystem of systematic reviews in a more practical way, but based on quality.

Another tool that every researcher in training and consolidated should always have at hand, is the tool to assess the risk of bias in clinical trials proposed by the Cochrane Collaboration, presented by Dr. Rendón Macías. The tool was revised, based on the premise that every researcher in the current era must be more careful when reading and evaluating the results of a new SR since, as we have seen, many publications lack internal validity and present numerous biases, so, we make a small summary that we hope will be useful when evaluating them. The main biases to avoid are: the selection, since the appropriate method of randomization and assignment must be described, which justifies that the groups evaluated are really comparable. The realization, describe extensively the measures used in the method of blinding and participating personnel. Detection, how to guarantee the adequate masking of the evaluation or measurement of the results. In addition, how incomplete results were handled due to abandonment of the trial and that could unbalance the groups. Finally, the notification, above all, take care of those selective results, remembering that, for each objective, an outcome or result must be presented. The endpoint of the evaluation of the tool allows you to classify each risk into: Low, when it is unlikely that the bias will alter the results; Unclear, when some doubts have arisen; High, when the biases observed and analyzed, have significantly weakened the results of the SR.

How to cite this article: Medina-Moreno UF, Gordillo-Moscoso AA. What’s new on systematic reviews. JMSR. 2018 Apr-Jun;2(2):1-2.
Gamma waves, a new way for pain measurement?

Aguilar-Flores Esbeidy1, Aguillón-Pérez Oscar2.

1Medical School; Faculty of Medicine, Universidad Veracruzana.
Calle Médicos y Odontólogos s/n, Col. Unidad del Bosque, Xalapa, Ver., C.P. 91010. México.
2Medical School; Faculty of Medicine, Universidad Autónoma de San Luis Potosí.

Abstract

Introduction: Pain is an unpleasant and sometimes annoying sensation that is associated with some type of tissue damage, it is also one of the main reasons why people come to medical consultation. However, despite being a clinical symptom of great presence, its measurement is still based on subjective scales that do not provide a clear idea for its management. It is difficult to quantify an experience conditioned by various environmental and emotional factors, although recently an attempt has been made to demonstrate an association between the perception of pain and brain responses in the frequency range of gamma oscillations in the brain.

Methods: The following metasearchers were used to retrieve the articles quoted: PubMed, BIG y BVS. In addition, multidisciplinary databases were consulted Academic Search Complete, Science Direct, Springer Link, Web of Science and Wiley. Finally, specialized and clinical databases were reviewed like Medic Latina, Ovid, Trip Database, Clinical Key y Nature.

Results: There are different studies that relate gamma waves to pain. The different studies carried out by several researchers use mechanical painful stimuli to lasers to produce pain and in all studies, brain gamma waves are recorded by means of an electroencephalogram; analyzing the statistics of the studies as well as their methodology, we reach our conclusion.

Conclusion: We found that there is a strong relationship between the measurement of brain gamma waves and pain; but there is still a lot to investigate since the measurement of gamma waves is not an easy task and is subject to many variables.

Key Words:
PAIN, PAIN THRESHOLD, GAMMA RHYTHM.

How to cite this article: Aguilar-Flores E, Aguillón-Pérez O. Gamma waves, a new way for pain measurement. JMSR. 2018 apr-jun;2(2):3-15.

Corresponding author:
Aguilar-Flores Esbeidy
ydiebe@hotmail.com
During the clinical practices in the hospital we perceive that one of the symptoms that patients refer most is pain; this sensation can be part of the reason for consultation and for the doctor it is significant both for the diagnosis, prognosis and to become the therapeutic goal. There are many classifications and descriptions about pain: deep, dull, throbbing, among others. Currently his assessment is still done with the Visual Analogue Scale (VAS), but this is totally subjective, so we conduct a search of the available objective methods to quantify this experience. The first review indicated an important relationship with brain responses specifically with gamma waves, so we decided to go deeper into these findings to answer the question: Can pain be measured through gamma waves?

INTRODUCTION

Pain is a vital phenomenon for survival, it allows us to react to situations of danger, the International Association for the Study of Pain define the sensation as: “An unpleasant sensory and emotional experience associated with actual or potential tissue damage or describes in terms of such damage” (1,2), which means that it results from dynamic interactions between sensory and contextual (i.e., cognitive, emotional, and motivational) processes (3,4). The visual analogue scale (VAS) is still being widely used (5,6). The VAS is a subjective pain reporting tool. It is hard to interpret under the same standard across different subjects. That’s why with this investigation we aimed to investigate a more objective way to measure pain to help doctors to objectively evaluate the patient’s pain and thus guide clinical practice accordingly (7). The study of pain has focused on the brain, there it has been seen that the flexibility to direct the flow of information that serves to integrate functions has been favored by the oscillations and synchrony of electrical impulses (8–13), were the noxious stimuli activate an extended network of brain areas (14–16).

Neurophysiological records have revealed neuronal responses in different frequencies ranging from theta (4–7 Hz) alpha (8–13 Hz) and beta (14–29 Hz) to gamma (30–100 Hz) frequencies (17–21), these brain oscillations refer to rhythmic fluctuations of neural mass signals (22).

Several studies appear to suggest gamma oscillations have a close link to pain perception, however, these vary in the number of patients, the nature of the painful stimulus applied, the duration of the intervention, the correlation that is made between subjective and objective or between variables, so in this review it gathers the findings of the available studies that treat of assessing pain through gamma waves (Fig1).

METHODS

Keywords.
We use key words and synonyms (table 1). Boolean operators.
We used boolean operators “OR” and “AND”. “OR” for joining synonyms of the same key words and “AND” for joining each key word.

Limits.
In the multidisciplinary databases we used the filters “journal” and “health sciences”, but in the rest we included all the results, since we needed to combine all the available information for a more complete review.
Information sources.

The metasearch engines we used for our research were PubMed, BIG and BVS. In addition, multidisciplinary databases were consulted Academic Search Complete, Science Direct, Springer Link, Web of Science and Wiley. Finally, specialized and clinical databases were reviewed like Medic Latina, Ovid, Trip Database, Clinical Key y Nature.

Our general search strategy gathered the keywords of Medical Subject Headings (MeSH) and Descriptores de Ciencias de la Salud (DeCS for hispanic literature) con el operador booleano AND:

(Pain) AND (Gamma Rhythm)

The complete strategy in PubMed included the synonyms that were combined by the OR operator, the repeated terms were only

<table>
<thead>
<tr>
<th>Key words</th>
<th>DeCS</th>
<th>Sinónimos</th>
<th>MeSH</th>
<th>Synonyms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>Dolor</td>
<td>Sufrimiento Fisico</td>
<td>Pain</td>
<td>Pain Burning</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Burning Pain</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pains Burning</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Suffering Physical</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Physical Suffering</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Sufferings Physical</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pain Migratory</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Migratory Pain</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Migratory Pains</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pains Migratory</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pain Radiating</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pains Radiating</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Radiating Pain</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Radiating Pains</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pain Splitting</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pains Splitting</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Splitting Pain</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Splitting Pains</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ache</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Aches</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pain Crushing</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Crushing Pain</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Crushing Pains</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pains Crushing</td>
</tr>
</tbody>
</table>

Table 1. Keywords

Fig 1. The different studies have in common the application of painful stimuli by means of mechanical stimuli, laser among others, registering gamma waves through an EEG.
written once; and the search was extended to the title and abstract sections to detect articles in a recent publication.

((((Pain[MeSH Terms]) OR Pain[Title/Abstract]) OR Suffering[Title/Abstract]) OR Ache[Title/Abstract])) AND ((((Gamma Rhythm[MeSH Terms]) OR Gamma Rhythm[Title/Abstract]) OR Gamma Rhythms[Title/Abstract]) OR Rhythm, Gamma[Title/Abstract])))

Selection Criteria.
From the results obtained in each source of information as the first inclusion criteria, the title was taken into account, in such a way that they were related to the measurement of pain and the use of gamma waves. As a second filter, we read the summary of the articles. Then we eliminate the duplicates with the help of the Zotero reference manager.

Exclusion Criteria.
The complete reading of the articles allowed us to discard those where, when analyzing the methodology more thoroughly, we concluded that it was not useful for our research because it deviated from the general topic.

Evidence evaluation.
To evaluate the original article’s quality, we used OPMER scale. Aguilar Flores and Aguillón Pérez made the same degree of contribution to the review.

RESULTS
An electronic search was performed on June 11-15, 2018. Results of the search and review was 10 original articles, 3 basic and 10 review, which were analyzed to prepare this text (Fig 2).
This review focuses on the search results for pain relation with gamma waves. This relationship is of recent investigation; for a better comprehension in the reading they will be broken down according the year of publication of the article (Table 2).

Link between gamma oscillations and pain perception
In the perception of pain, different neuronal responses subserve interindividual and intraindividual variations in the perception of identical painful stimuli. A time-frequency analysis of the electroencephalographic data from a single test indicates that the gamma responses are related to the short-term modulations of the individual's state (23). Since 2004 De Pascalis managed to determine that phase-ordered gamma oscillation is a reliable indicator of pain sensation, there were more pronounced Z peak scores over the recording sites of Fz and Cz. Differences in hypnotic susceptibility reliably account for more pronounced pain reduction during hypnotic analgesia; and pain reduction is paralleled by reduction in the degree of phase ordered gamma responses (24). In a study conducted by Xiaowu et al with 43 patients, they observed that tonic muscle pain induced significant frontal-central gamma enhancement when compared with both innocuous condition and noxious condition with low stimulus intensity. They also observed positive relationship between gamma oscillations and subjective pain intensity at frontal-central electrode FCz (25). On the other hand De Pascalis again ensures that phase-ordered gamma oscillations recorded over the central sites to be related to the subjective experience of pain (26). Obstructive mental imagery was found to modulate this pain/gamma relation by involving parietal and frontal region, this is because of Gamma activity is thought to play an integral role in information processing (27).
Fig. 2. Methodology electronic search flow diagram.
In relation to what is described by De Pascalis and in the hypnosis literature, it is known that obstructive imagery is a non-pharmacological manipulation for pain modulation in waking and even more in hypnosis and that it can attenuate subjective experience of pain mainly in high hypnotizable or suggestible individuals\(^{(28)}\). Therefore, it is reasonable to assume that the relationship between pain sensation and gamma synchrony may be modulated by hypnotizability\(^{(26)}\).

Through an experimental study with 12 participants to whom painful skin stimuli were applied through a laser at different intensities, Gross et al. was able to demonstrate that amplitudes of induced gamma oscillations and amplitudes of evoked responses from contralateral primary somatosensory cortex (S1) increase with stimulus intensity. This increase in response amplitudes was paralleled by an increase in perceived pain intensity in the same brain zone\(^{(17)}\). In a similar way it has been observed largest gamma time–frequency responses (TFRs) TFRs were consistently found within the S1 region and noxious laser elicited significantly stronger gamma TFRs than innocuous non painful vibratory stimuli\(^{(29)}\).

This relationship between induced gamma oscillations and sensory processing indicates that brain responses may be associated with the already estimated perception of a sensory event beyond the characteristics of the physical stimulus.

The study in deep structures of the brain revealed significant oscillatory responses in the gamma band related to pain caused by laser stimulation within the regions of the amygdala and hippocampus and were stronger in the limbic structures of the right hemisphere\(^{(30)}\). In addition, studies have been conducted in rats where, through electrocorticography, brain waves are recorded produced by the cutaneous application of thermal stimuli, here it was found that the delta band rhythm produced consistent statistical difference upon withdrawal for all cortices studied (left-right motor, right-left somatosensory) in either paw or the tail\(^{(31)}\). Although in another study of brain oscillations induced by nociceptive stimulation the only response that correlated with pain-related behavior between subjects was the gamma-band event-related synchronization\(^{(32)}\).

The comparison of the coding of nociceptive responses between the brain of adults and infants has shown that infants display a distinct, long latency, noxious evoked 18-fold energy increase in the fast delta band (2–4 Hz) that is absent in adults\(^{(33)}\). Li et al demonstrated that frontal-central gamma oscillations showed more specific to tonic muscle pain perception\(^{(25)}\), also Nickel et al. affirms that the amplitudes of these responses also covary with stimulus intensity and pain intensity\(^{(34)}\). In a study by Kim et al they found that distraction from (count back plus laser task) and attention to the painful laser stimuli (count laser task) show gamma-band activation\(^{(35)}\), in the other hand, Wang et al affirm that the gamma activity increased after nociceptive stimulation, and the amplitude of gamma was coupled to the phase of theta frequency oscillations during pain processing\(^{(36)}\); and Li et al suggest that with all this evidence, it exist a possibility to use neural oscillation features to predict pain\(^{(37)}\).

**Link between gamma oscillations and objective pain measures.**

In 2015 an experimental study with 41 participants where it was applied tonic painful heat stimuli of varying degree to
<table>
<thead>
<tr>
<th>TITLE</th>
<th>AUTHOR</th>
<th>YEAR</th>
<th>KIND OF ARTICLE</th>
<th># OF PATIENTS</th>
<th>OBJECTIVE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perception and modulation of pain in waking and hypnosis: functional significance of phase-ordered gamma oscillations</td>
<td>Vilfredo De Pascalis, Immacolata Cacace, Francesca Massicotte</td>
<td>2004</td>
<td>Original</td>
<td>38</td>
<td>Aim of the study was to determine whether: (1) phase-ordered gamma oscillation is a reliable indicator of pain sensation; (2) individual differences in hypnotic susceptibility reliably account for more pronounced pain reduction during hypnotic analgesia; (3) pain reduction is paralleled by reduction in the degree of phase-ordered gamma responses.</td>
</tr>
<tr>
<td>Pain perception, obstructive imagery and phase-ordered gamma oscillations</td>
<td>Vilfredo De Pascalis, Immacolata Cacace</td>
<td>2005</td>
<td>Original</td>
<td>40</td>
<td>Evidence for the role of gamma oscillations in the subjective experience of pain. Further, it has provided support for the view that pain reduction during obstructive mental imagery is the product of an inhibitory process involving frontal and parietal cortical regions.</td>
</tr>
<tr>
<td>Gamma Oscillations in Human Primary Somatosensory Cortex Reflect Pain Perception</td>
<td>Joachim Gross, Alfons Schnitzler, Lars Timmermann, Markus Ploner</td>
<td>2007</td>
<td>Original</td>
<td>12</td>
<td>We aimed to identify and to characterize spatially and temporally pain-induced gamma oscillations in human somatosensory cortices.</td>
</tr>
<tr>
<td>EEG indices of tonic pain-related activity in the somatosensory cortices</td>
<td>Robert Dowman, Daniel Rissacher, Stephanie Schuckers</td>
<td>2008</td>
<td>Original</td>
<td>15</td>
<td>To identify EEG features indexing activity in the SI, anterior cingulate cortex, and/or parietal operculum/insula elicited by tonic experimental pain.</td>
</tr>
<tr>
<td>Phase-amplitude coupling between theta and gamma oscillations during</td>
<td>Jing Wang, Duan Li, Xiaoli Li, Feng-Yu Liu, Guo-Gang</td>
<td>2011</td>
<td>Original</td>
<td>8</td>
<td>In the present study, we explored cortical EEGs from behaving rats to study whether there is coupling between theta phase and gamma amplitude after perceived nociceptive stimulation.</td>
</tr>
<tr>
<td>Title</td>
<td>Authors</td>
<td>Year</td>
<td>Type</td>
<td>Page</td>
<td></td>
</tr>
<tr>
<td>----------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------</td>
<td>------</td>
<td>-------</td>
<td>------</td>
<td></td>
</tr>
<tr>
<td>Detection of Thermal Pain in Rodents through Wireless Electrocorticography</td>
<td>Aydin Farajidavar, Shariq M. Athar, Christopher E. Hagen, Yuan B. Peng, and J. Chiao</td>
<td>2012</td>
<td>Basic</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>This preliminary study was performed to investigate alterations in ECoG brain rhythms produced by the cutaneous application of thermal stimuli.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In this study, we delivered the painful laser pulses at random pain-intensity levels (i.e. strong, medium and weak) in a single train to the dorsal hand of six patients with uncontrolled epilepsy.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prefrontal Gamma Oscillations Encode Tonic Pain in Humans</td>
<td>Enrico Schulz, Elisabeth S. May, Martina Postorino, Laura Tiemann, Moritz M. Nickel, Viktor Witkovsky, Paul Schmidt, Joachim Gross, and Markus Ploner</td>
<td>2015</td>
<td>Original</td>
<td>41</td>
<td></td>
</tr>
<tr>
<td>Investigated the neurophysiological encoding of ongoing, tonic pain by using electroencephalography (EEG). We specifically combined tonic painful heat stimuli and a continuous pain rating procedure with time-frequency analyses of EEG recordings to relate time courses of subjective pain intensity and objective stimulus intensity to those of frequency-specific brain activity. We further compared the encoding of tonic pain to that of brief painful stimuli.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Studied the effect of a painful cutaneous laser upon thalamic LFPs and EEG activity, which were recorded during awake thalamic procedures (deep brain stimulation electrode implants) for the treatment of essential tremor.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>We aimed to evaluate the hypothesis that the pain-related gamma band oscillatory responses can be recorded, and are coupled with the</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paul Schmidt, Martina Pastorino, Son Ta Dinh, Joachim Gross, Markus Ploner</td>
<td>2017</td>
<td>Original</td>
<td>Delta and gamma oscillations in operculo-insular cortex underlie innocuous cold thermosensation.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------------------------</td>
<td>-----</td>
<td>---------</td>
<td>---------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Francesca Fardo, Mikael C. Vinding, Maria B. Allen, Troels Saebel, Nanna Brix, Finnur</td>
<td>2018</td>
<td>Basic</td>
<td>Brain oscillations reflecting pain-related behavior in freely moving rats.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weiwei Peng, Xiaoli Xia, Cao, Ming Ye, Gan Huang, Zhirui Zhang, Giandomenico Iannetti, Lü Hub</td>
<td>2018</td>
<td>Original</td>
<td>Is there a correlation between objective and subjective pain measurements and Gamma oscillation frequencies?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table:**

<table>
<thead>
<tr>
<th>Stimulus</th>
<th>Intensity and Pain Intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Painful Heat Stimulation in 39 Healthy Human Participants</td>
<td>Using magnetoencephalography, we identified spatiotemporal features of central cold processing, with respect to the time course, oscillatory profile, and neural generators of cold-evoked responses in healthy human volunteers.</td>
</tr>
<tr>
<td>In the present study, we provide a comprehensive characterization of brain oscillations induced by nociceptive stimulation, as well as their significance in relation to behavior, using direct recording from the cortex of 12 awake and freely moving rats.</td>
<td></td>
</tr>
<tr>
<td>The objective was to establish whether correlation exists between high gamma oscillation frequencies, numeric rating scale (NRS) for pain and pain pressure threshold (PPT).</td>
<td></td>
</tr>
<tr>
<td>Title</td>
<td>Authors</td>
</tr>
<tr>
<td>----------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------</td>
</tr>
<tr>
<td>processing the painful sensory inputs</td>
<td>Cheng, W. Anderson and F. A. Lenz</td>
</tr>
<tr>
<td>Encoding of mechanical nociception</td>
<td>Lorenzo Fabrizi, Madeleine Verriotis, Gemma Williams, Amy Lee, Judith Meek, Sofia Olhede &amp; Maria Fitzgerald</td>
</tr>
<tr>
<td>Differs in the adult and infant brain</td>
<td>Linling Li, Xiaowu Liu, Chuan Cai, Yan Yang, Disen Li, Lizu Xiao, Donglin Xiong, Li Hu, Yunhai Qiu</td>
</tr>
<tr>
<td>Changes of gamma-band oscillatory activity to tonic muscle pain</td>
<td>Linling Li, Xiaowu Liu, Chuan Cai, Yan Yang, Disen Li, Lizu Xiao, Donglin Xiong, Li Hu, Yunhai Qiu</td>
</tr>
<tr>
<td>Extracting Neural Oscillation Signatures of Laser-Induced Nociception in Pain-Related Regions in Rats</td>
<td>Xuezhu Li, Zifang Zhao, Jun Ma, Shuang Cui, Ming Yi, Huailian Guo and You Wan</td>
</tr>
<tr>
<td>Alpha and Gamma oscillation amplitudes synergistically predict the perception of forthcoming nociceptive stimuli</td>
<td>Yiheng Tu, Zhiguo Zhang, Ao Tan, Weiwei Peng, Yeung Sam Hung, Massieh Moayedi, Gian Domenico Iannetti, and Li Hu</td>
</tr>
<tr>
<td>Brain oscillations differentially encode noxious</td>
<td>Moritz M. Nickel, Elisabeth S. May, Laura Tiemann</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
healthy human subjects, demonstrated that neuronal gamma oscillations at frontal electrodes encoded the subjective intensity of tonic pain, was observed dissociation between the encoding of stimulus intensity and pain intensity. In contrast, for phasic pain, it found qualitatively similar patterns for the encoding of both stimulus intensity and pain intensity. Secondly, the subjective intensity of phasic pain was encoded by brain activity at different frequencies, whereas that of tonic pain was encoded by prefrontal gamma oscillations only. Thirdly, the subjective perception of phasic pain was encoded by right-lateralized activity at central electrodes, whereas the subjective perception of tonic pain was encoded by gamma activity recorded from mid-frontal electrodes. Affirming that the area with the strongest relationship between pain intensity and gamma oscillations was located in the mid-prefrontal cortex adjacent to the premotor and cingulate cortices (38).

A recent study has found a strong correlation between gamma oscillations and Pain Pressure Threshold (PPT) con ($r^2=0.91$, 95% CI 0.83 to 0.96, $p<0.0001$) where an objective measure of pain is used using an algometer. (39) In addition, the relationship between the Numerical Rating Scale was again found as a predictor of variability of oscillations ($p <0.05$) and found higher levels in women.

DISCUSSION

Future research should combine a more representative sample, to prove a stronger relationship, particularly in healthy people, since most of the articles analyzed did not justify the sample size, in fact the population section was one of the most deficient in the OPMER evaluation.

It should also be mentioned that a large part of the studies used a special analysis to quantify gamma waves, which makes it difficult to understand their data. Another aspect to take into account is the control of the variables that can alter the emission of this frequency range such as the mental state, emotions, external noise and the movement of the patient (40–43). Measuring them is complicated because it is susceptible to erroneous measurements and artifacts (44), for example muscle activity is picked up in the EEG and can show up in the gamma frequency range. Because of this particular care has thus to be taken to obtain high-quality data. Although a growing number of research groups have been able to record these induced gamma activities, some authors still deny their existence at the scalp level (43).

If there is still a correlation between pain and gamma waves, strategies could be used to manipulate it and become possible therapeutic targets in the treatment and monitoring of chronic pain.

CONCLUSIONS

When performing the review of the literature, we can say that there is a relationship between pain and its intensity with brain gamma waves. But it is important to clarify that the measurement of gamma waves is not an easy task, since it requires eliminating many artifacts in their measurement and they are not waves that are measured routinely in an electroencephalogram, so it will be of vital importance in future studies control the measurement of the waves and explore the different types of painful stimuli that can generate gamma waves.
Also for its measurement will be important the location, since as we learned from the literature, there are areas in the brain where these waves are most easily recorded. Although there is still a lot to investigate about gamma waves and pain, we believe that in the future it will be possible to use the gamma wave measurement to know the true intensity of the pain referred by the patient in the doctor's office in order to be able to refer the patient to the best treatment. For the time being, the Analog Visual Scale will be the closest thing we have to the measurement of pain, waiting for the measurement of gamma waves to gain strength and so we can use them to measure pain in a more objective way in the patient.

Conflict of interest: There was no conflict of interest in the realization of this review, the authors respond to no organization, financial disclosure or company.

BIBLIOGRAPHY

Use of statins as a protective factor for nephrolithiasis.

Calva-Castillo Pedro Miguel.

13rd year student; Medical School, Unidad Académica Multidisciplinaria Zona Huasteca, Universidad Autónoma de San Luis Potosí.
Romualdo del Campo #501, Rafael Curiel, Ciudad Valles, SLP, Z.P. 79060. México

Abstract
Renal lithiasis or nephrolithiasis currently represents a public health problem in general population, which could develop end-stage renal disease. One major problem is the recurrence of this disease, generating costs in medical care, as well as negative impact on social and work life from those who suffer from this disease. For this reason, it is of vital importance the study of the etiology of this disease and even more the development or discovery of drugs that decrease the rate of recurrence of nephrolithiasis. Several factors could play key points in the formation of kidney stones, recent investigations suggest that different pathways of development of nephrolithiasis are similar to the pathways of atherosclerosis, as inflammation, oxidative stress, the injury of renal tubular cells and their apoptosis. That is why statins could help prevent or reduce the recurrence of kidney stones.
Although there is little research on this topic, different analyses demonstrated a significant reduction in the development of nephrolithiasis in patients taking statins.

Key Words:
STATINS, HYDROXYMETHYLGLUTARYL COA REDUCTASE INHIBITORS, Nephrolithiasis, Kidney Stones.

How to cite this article: Calva-Castillo PM. Use of statins as a protective factor for nephrolithiasis. JMSR. 2018 Apr-Jun;2(2):16-23.

Corresponding author:
Pedro Miguel Calva-Castillo.
e-mail: pedromiguelcalva@gmail.com
At the Nephrology class we approached the topic of nephrolithiasis, more specifically, recurrent renal lithiasis. During this class it was mentioned all about this disease, its epidemiology, etiology, physiopathology, treatment and conclusions. After that, our teacher asked us if we had any doubts concerning the main topic, a classmate said that she had found the article "Impact of statins on nephrolithiasis in hyperlipidemic patients; a 10-year review of an equal access health care system by Sur, Masterson, Palazzi et al.", that mentioned a significant reduction on the development of nephrolithiasis in hyperlipidemic patients taking statins (1). The main issue of the article generated me an interest on this topic, without no further information given, I decided to carry out a deeper investigation concerning this topic.

INTRODUCTION

Renal lithiasis or nephrolithiasis currently represents a public health problem in the general population, which could develop end-stage renal disease. One of the major problems that this metabolic disorder presents is recurrence, as a considerable part of the population becomes more of an episode of renal lithiasis during the course of their life; since there is evidence that there is a recurrence rate as high as 35 and 50% at 5 and 10 years, respectively (2-4), generating costs in medical care, as well as negative impact on the social and work life of those who suffer from this disease. For this reason it is of vital importance the study of the etiology of this disease and even more the development or discovery of drugs that decrease the rate of recurrence of nephrolithiasis to improve the quality of life of the patients and to avoid possible comorbidities.

In the last decade studies have been carried out that describe a possible reduction in the development of nephrolithiasis, or in the recurrence of it, in people who have been prescribed the use of statins. These investigations are very small because at present the etiology of the disease is not known exactly. In this systematic review we will address the key points of the role of statins in this disease and its possible protective effect for nephrolithiasis.

METHODS

Search strategy:

To research this topic, I established the Mesh and Decs terms. Those words were: nephrolithiasis, statins. Also, I use the synonyms of these terms, those words were: kidney stones, Hydroxymethylglutaryl CoA Reductase Inhibitors, and additionally I added the word atorvastatin because it belongs to statins.

The Boolean operators used were AND/OR.

There were no limits for this search.

Information sources consulted were PubMed, BVS, Trip database, Ovid SP. And the Databases were Medic Latina, Science Direct, Springer link, Academic Search Complete (Table 1).

<table>
<thead>
<tr>
<th>No</th>
<th>Source of information</th>
<th>No. Identified articles</th>
<th>No. recovered items</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PUBMED</td>
<td>16</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>BVS</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>BIG</td>
<td>54</td>
<td>12</td>
</tr>
<tr>
<td>4</td>
<td>OBVID SP</td>
<td>440</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>SCIENCE DIRECT</td>
<td>410</td>
<td>3</td>
</tr>
<tr>
<td>6</td>
<td>ACADEMIC SEARCH COMPLETE</td>
<td>781</td>
<td>2</td>
</tr>
<tr>
<td>7</td>
<td>SPRINGER LINK</td>
<td>231</td>
<td>1</td>
</tr>
<tr>
<td>8</td>
<td>MEDIC LATINA</td>
<td>260</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 1. Source of information
The exclusion criteria were only for those articles that did not focus on the main topic according to the keywords or for those who only addressed the topic of only one keyword. At the end I retrieved seven articles because a relative number of original and basic articles were duplicated in different electronic sources of information. I also only had access to the abstract of the article “Do statin medications reduce the incidence of Nephrolithiasis in patients with hyperlipidemia?” (5), (Figure 1 and Table 2).

**RESULTS**

**ETIOLOGY OF THE DISEASE.**
At present the etiology of this disease is little known. Several factors could play key points in the formation of kidney stones. Sur et al (1), reported that the pathophysiology of urolithiasis is multifactorial, with genetic, dietary, and intrinsic abnormalities playing a part with spontaneous crystallization of supersaturated urine.

Temiz et al. mentions that various
molecular events such as inflammation and oxidation, as well as metabolic changes can be determinant in the etiology of urolithiasis (4). Tsujihata et al. mentions that it is considered that the lesion to the renal tubular cells promotes the crystalline union to the renal tubular cells and the oxidative stress derived from apoptosis of the cells is involved in lesions of the renal tubular cells. They observed cell injury in calcium oxalate urolithiasis formation process and it appears that the process of renal tubular cell injury is of key importance in renal stone formation (2). In another article by the same author, it is mentioned that the lesion of the renal tubular cells and inflammation seem to play significant roles in the development of calcium oxalate (CaOX) urolithiasis (3). Formation of calcium oxalate stones and atherosclerosis have common pathways involving cell injury, apoptosis, and oxidative stress (6). Tsujihata et al. cite an article that indicated that the exposure of renal tubular cells to oxalate leads to the production of reactive oxygen species (ROS) and the development of oxidative stress, followed by injury and inflammation (3). The inflammation hypothesis suggest that inflammation leads to hypoxia and renal tubular injury, thereby leading to kidney stone formation; this role of inflammation and deposition of renal tubular crystals was further demonstrated in a mouse model metabolic syndrome according to the described by Cohen et al (6). A vascular etiology has been proposed to be in part responsible for stone formation (5). The theory suggests that the precipitation event of the stone formation is vascular, with the stone nidus beginning within the vasa recta of the urinary papilla (1). This hypothesis suggests that atherosclerotic plaques in the vasa recta of the kidney ultimately erode and are exposed to urine serving as a nidus for stone formation (6), this is also bolstered by the presence of cholesterol in nephroliths and renal papillary histology (1). As mentioned in the same article, the incorporation of cholesterol in the stones is logical, since the lipid droplets have been documented in interstitial cells of the innermost medulla. These cells are intimately associated with the loop of Henle; Randall’s plaques are theorized to originate from the basement membrane of the loop of Henle. Renal histology supports this theory: descending vasa recta make a hairpin turn in the medulla; a hostile, hypoxic and hyperosmolar environment. At this turn, there is a transition from a laminar to turbulent flow that potentiates a vascular injury (1). This atherosclerotic-like reaction in the kidney may result in calcification of damaged vessel walls which erodes into renal papillary interstitium and then into ducts of Bellini functioning as a nidus for calculus formation (6) or further enhancing the potential for stone growth (1).

ROLE OF STATINS WITHIN THE CONTEXT.

The casual relationship between statin treatment and urolithiasis or nephrolithiasis has not been firmly established and the role of statins in kidney stone formation less clear (4). However, dyslipidemia is a known independent risk factor for urolithiasis, and emerging evidence suggests common biological pathways; also, it is confirmed that triglycerides is associated with kidney stone risk (6). Statins, also known as 3-hydroxy-3-methylglutaryl coenzyme a reductase inhibitors, are drugs used to lower cholesterol. These agents have clinical benefits that could be related to improvement
<table>
<thead>
<tr>
<th>Title</th>
<th>Author</th>
<th>Year</th>
<th># of Patients</th>
<th>Objective</th>
<th>Kind of Article</th>
<th>OPMER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin Inhibits Renal Crystal Retention in a Rat Stone Forming Model</td>
<td>Masao Tsujihata, Chikahiro Momohara, Iwao Yoshioka, Akira Tsujimura, Norio Nonomura and Akihiko Okuyama</td>
<td>2008</td>
<td>24 ten-week-old specific pathogen-free male Wistar rats</td>
<td>...investigated whether atorvastatin can prevent renal tubular cell injury by oxalate and inhibit renal crystal retention.</td>
<td>ORIGINAL</td>
<td>10</td>
</tr>
<tr>
<td>Why does atorvastatin inhibit renal crystal retention?</td>
<td>Masao Tsujihata, Iwao Yoshioka, Akira Tsujimura, Norio Nonomura, Akihiko Okuyama</td>
<td>2011</td>
<td>24 ten-week-old specific pathogen-free male Wistar rats</td>
<td>...investigated the mechanism by which atorvastatin inhibits renal crystal retention.</td>
<td>BASIC</td>
<td>11</td>
</tr>
<tr>
<td>Effects of statin treatment with atorvastatin on urolithiasis-associated urinary metabolic risk factors: an experimental study.</td>
<td>Mustafa Zafer Temiz, Emrah Yuruk, Kasim Ertas, Oguzhan Zengi, Atilla Semercioz.</td>
<td>2017</td>
<td>Sixteen adult male Sprague-Dawley rats</td>
<td>To investigate whether atorvastatin has favorable effects on urinary metabolic risk factor associated with urolithiasis.</td>
<td>ORIGINAL</td>
<td>15</td>
</tr>
<tr>
<td>Impact of Statin Intake on Kidney Stone Formation</td>
<td>Andrew J. Cohen, Melanie A. Adamsky, Charles U. Nottingham, Jaclyn Pruitt, Brittany Lapin, Chi H. Wang, Sangtae Park</td>
<td>2018</td>
<td>101,259</td>
<td>To determine whether statin intake affects nephrolithiasis risk, and whether higher lipid levels correlate with stone risk.</td>
<td>ORIGINAL</td>
<td>14</td>
</tr>
<tr>
<td>Do statin medications reduce the incidence of Nephrolithiasis in patients with hyperlipidemia?</td>
<td>James H. Masterson, Jason R. Woo, David C. Chang, James O. L’Esperance, Marshall L Stoller, Roger L. Sur.</td>
<td>2013</td>
<td>7,742</td>
<td>...investigated whether HLD patients on statins had reduced incidence of nephrolithiasis.</td>
<td>ORIGINAL</td>
<td>---</td>
</tr>
<tr>
<td>Study: Statin users less likely to develop kidney stones.</td>
<td>Randy Dotinga.</td>
<td>2016</td>
<td>---</td>
<td>---</td>
<td>REVIEW</td>
<td>---</td>
</tr>
</tbody>
</table>

Table 2. Articles
in endothelial dysfunction, decreased blood thrombogenicity, antioxidant action and anti-inflammatory activity (1). As mentioned above, the etiology of nephrolithiasis is unclear, but it has been observed that play an important role in various factors such as inflammation, oxidative stress, the injury of renal tubular cells and their apoptosis (2–4,6).

For these reasons, both the physiopathology of nephrolithiasis and pharmacodynamics of statins, is that these drugs could play a key role in the reduction or prevention of this disease. The diverse articles documented in this systematic review detail in different ways the pathways in which statins act on the formation of kidney stones according to the aforementioned etiologic theories. According to the pathway of renal tubular cells injury, Tsujihata et al. found that Urinary N-acetyl-β-D-glucosaminidase (NAG) excretion, a biochemical marker of renal tubular cell injury, was decreased significantly by atorvastatin treatment in their stone forming rat model (2). Also they exposed that in the same rat group the levels of 8-hydroxy-2′deoxyguanosine (8-OHdG), the most frequently detected DNA lesion in urine and an oxidative stress marker, were decreased significantly, unlike the stone forming rat group not treated by atorvastatin, in which those 8-OHdG levels were increased (1). For these reasons, it is deduced that atorvastatin has an inhibitory effect on the oxidative damage of DNA in renal tubular cells.

According to the studies of Tsujihata et al. the superoxide dismutase (SOD), an enzyme that alternately catalyzes the dismutation of the superoxide radical into either ordinary molecular oxygen or hydrogen peroxide, and catalase levels were significantly higher in atorvastatin positive stone-forming rats than in the atorvastatin negative stone-forming rats. The mechanisms by which atorvastatin inhibits the renal tubular cell injury and oxidative stress caused by reactive oxygen species (ROS) is that atorvastatin stimulates the production of SOD which converts reactive oxygen into H2O2 and catalase which converts H2O2 into H2O and O2 (2,3). Another mechanisms by which atorvastatin inhibits the renal tubular cell injury and oxidative stress caused by ROS is the inhibition of NOX-1, a reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase subunit (2). A predominant source of ROS production is the NADPH oxidase system (3). Also, transforming growth factor-β1 (TGF-β) is reported to participate in ROS production through the activation of NADPH oxidase; in addition activated TGF-β may have enhanced interstitial inflammation, which would promote CaOX stone formation (2). Tsujihata et al. reported that atorvastatin treatment significantly decreased the expression of TGF-β in kidney tissue (2,3).

FROM THEORY TO PRACTICE.

Based on the above, several researchers have put into practice theories about the protective factor of statin use for nephrolithiasis. Researchers found that subjects who took statins were less likely to develop stones, and they spotted an especially dramatic effect among recurrent stone formers (7).

In the study by Tsujihata et al. was found that the formation of renal crystal deposits in kidney tissue were decreased by atorvastatin treatment stone forming rats (2). In another study, was detected a statistically significant decreased 24-h Urinary uric acid (UUa) level in an atorvastatin group (atorvastatin given rats), whereas it was increased in the
control group, in contrast to baseline levels (P = 0.012 and P = 0.025, respectively). But was noted a significantly increased Urinary calcium (UCa) levels in the atorvastatin treatment group (4).

Currently only have been carried out, based on the found in metasearch and the sources of information, three clinical studies on the use of statins as a protective factor for nephrolithiasis. In the study of Masterson et al. whose population was 7,742 hyperlipidemic patients, found that statin medications reduced the incidence of nephrolithiasis. The risk of nephrolithiasis in these hyperlipidemic patients treated with statins was OR=0.67 (p<0.001) [OR=0.81 (p<0.194) for men; OR=0.53 (p<0.001) for women] (5).

Sur et al. conducted a study, where the population was 52,232 subjects with hyperlipidemia, of which 1,904 suffered nephrolithiasis. They performed univariate and multivariate analyses. In univariate analysis, patients taking statin medications had significantly less stone formation compared to patients not taking statin medications (3.1% vs. 3.7%, p<0.001), corresponding to a 19% decreased risk (OR=0.828, 95% CI 0.756-0.907, p<0.001). This reduction was significant for females (OR=0.609, 95% CI 0.519-0.715, p<0.001) but not males (OR=0.971, 95% CI 0.868-1.086, p=0.609).

In multivariate analysis, the use of statin medications remained protective against stone formation (OR=0.514, 95% CI 0.462-0.572, p < 0.001) when adjusting for age, sex, obesity, hypertension, diabetes mellitus and cardiovascular disease. In subgroup analysis of the statin cohort, both females (OR=0.383, 95% CI 0.318-0.461) and males (OR=0.589, 95% CI 0.518-0.671) had reduced risk of stones on multivariate analysis. When they analyzed the subgroup of patients without hypertension, diabetes, or obesity, the OR of statins associated with stone disease was 0.69.

This indicates that statins are associated with a reduced incidence of stones even in populations without other lithogenic comorbidities (1).

The most recent study I found was the one made by Cohen et al. their population was 101,259 patients. Their univariate analysis revealed a 20% decrease in incidence of nephrolithiasis for patients prescribed statins without a prior history of stones. There was a more dramatic 36% decrease in the incidence of nephrolithiasis for patients prescribed statins with a prior history of stones.

On multivariable analysis, adjusting for history of kidney stones, statin therapy, age, body mass index, gender, race, osteoporosis, hemiplegia, paraplegia, immobility, thiazide prescription, calcium, and maximum creatinine, they found a protective effect of statins on incident stone risk (OR=0.57, 95% CI 0.53-0.61). Again, this protective effect was more pronounced among those patients with a history of stones and treated with statins (OR=0.53, 95% CI 0.42-0.66).

That is why they encountered a protective association between statin use and incident kidney stone formation (6).

CONCLUSIONS

Formation of kidney stones and atherosclerosis have common pathways, that is why statins could help prevent renal stone formation.

The different studies showed that taking statin had 19-25% decreased risk of urinary stone formation. Moreover, they believe that
atorvastatin could help prevent and treat renal crystal formation and reducing the uric acid stone recurrence by decreasing de UA levels. 

Retrospective analyses demonstrated a significant reduction in the development of nephrolithiasis in hyperlipidemic patients taking statins. And these results were even more profound in women.

**Points to take home.**

- Statins may be protective against kidney stone formation.
- The protective association between statins and nephrolithiasis has been found in different patient populations.
- Women who take statin had a significant decrease in stones compared to men.
- It is necessary to carry out a controlled clinical trial in patients with nephrolithiasis without hyperlipidemia or other comorbidities.

**Conflict of interest:** I declare no conflicts of interest.

**BIBLIOGRAPHY**


Etiology of febrile seizures with particular reference to HHV-6 infection.

Tayabas-Castillo María Fernanda 1, Ortiz-Acosta Sara Luz 1, Villegas-Hernández Vicente Emmanuel 1, Maya Flores David Francisco 1

1 Faculty of Medicine. Universidad Autónoma de San Luis Potosí

Abstract

Introduction. During childhood, 3-5 children in every 100 have at least one episode of febrile convulsions. Febrile seizures occur in children ages 6 months to 5 years with fever ≥100.4°F (38°C) and absence of underlying neurologic abnormality, metabolic condition or intracranial infection. Recently, researches have focused on human herpes virus type 6 (HHV-6) as the etiology of 20-25% of the FC cases.

Methods. The following metasearchers were used to retrieve the articles quoted: PubMed and BVS. Also, we used the following data bases: Wiley, Academic Search Complete, ScienceDirect and OvidSP. For our exclusion criteria, at first, we read all the titles and abstracts of the articles we found, and then we read the full articles.

Results. Febrile seizures occur in children with fever, they have a prevalence of 2-4% and affected children are typically between 6 months and 5 years of age. The etiology is still unknown but it has been shown that viruses play an important role, among them; HHV-6 is a primary cause. The vast majority of isolates associated with febrile status epilepticus, are predominantly HHV-6B. Febrile seizures are related to the degree of fever and family history of febrile seizures correlated with genetic susceptibility for immunological factors.

Conclusion. The etiology of febrile seizures is still unknown but it has been shown that viruses play an important role, prominently the HHV-6. A factor that distinguishes children who develop febrile seizures is the family history of febrile convulsions; these can be related to low immunoglobulin especially IgA and IgM that play an important role in the onset of a viral infection. The degree of fever seems to correlates with the risk of febrile seizures, but it is still uncertain. It was found that primary infection with HHV-6 does not seem to be a risk factor for recurrent febrile seizures.

Key Words: SEIZURES, FEBRILE CONVULSION, HERPESVIRUS 6, HUMAN

How to cite this article: Tayabas-Castillo MF, Ortiz-Acosta SL, Villegas-Hernández VE, Maya-Flores DF. Etiology of febrile seizures with particular reference to hhv-6infection. JMSR. 2018 Apr-Jun;2(2):24-37.

Corresponding autor.
Ortiz-Acosta Sara Luz
sara.ortiz@alumnos.uaslp.edu.mx
QUESTION AND CONTEXT

What is the role of HHV6 infection in the etiology of febrile seizures in pediatric patients under 5 years? Febrile seizures are a cause of frequent hospital admission to pediatric emergency services and they generate an alarming situation for parents. The ethiopathogenesis is unknown but has been correlated to factors as genetic and viral infections. Reason for which we want to know the role of HHV6 in the etiology of febrile seizures, that this virus is frequent in the range of age that this type of crisis presents.

INTRODUCTION

During childhood, particularly from 6 months to 3 years of age, 3-5 children in every 100 have at least one episode of febrile convulsions (FC). Each episode causes a definite small but unquantified risk of permanent brain damage. Recently, researchers have focused on human herpes virus type 6 (HHV-6) as the etiology of 20-25% of the FC cases (1).

Human herpesvirus 6 (HHV-6) causes sixth disease, also known as roseola infantum or exanthem subitum. Ninety percent of children have been infected by 2 years of age, with peak incidence occurring between 9 and 21 months of age (2). HHV-6 is most likely transmitted via the saliva of healthy individuals and enters the body via a mucosal surface. One percent of HHV-6 infection is acquired congenitally without known sequelae. After an incubation period of 10 to 15 days, sixth disease is characterized by a prodrome of mild rhinorrhea, sore throat, and conjunctival redness, followed by a high fever (100.4° F to 104° F). Cervical, postauricular, or occipital lymphadenopathy usually develops. Other symptoms are usually absent but may include abdominal pain, vomiting, or diarrhea. After 3 to 5 days, the fever abates and the rash of roseola may begin—if at all—as tiny, erythematous, raised papules on the trunk that spread to the neck and extremities, lasting 1 to 3 days. Interestingly, while 93% of those infected are symptomatic (fevers, fussiness, rhinorrhea), only 20% of those infected exhibit the rash of roseola. Fifteen percent of infected children have febrile seizures.

Febrile seizures occur in children aged 6 months to 5 years with fever ≥100.4°F (38°C) and absence of underlying neurologic abnormality, metabolic condition, or intracranial infection.

METHODS

SEARCH STRATEGY:

Keywords:
In the search strategy we use the Boolean operators: OR to link all those synonyms that correspond to the same MeSH descriptors; as well as AND to link the MeSH descriptors used to perform the search.

Limits:
Human, idioma, articles.

Information sources:
Meta search engines: PuMed, BVS, Trip database, Ovid SP.

Databases:
Medic Latina, Science Direct, micromedex, Springer link, Wiley.

Result:
We also recovered 6 original articles by secondary recovery from the bibliography of the titles we had (Figure).
RESULTS

An electronic search was performed on May 15, 2018. Results of the search are presented in a flow diagram in Table 1. This review focuses on the search results for HHV-6 relation with febrile seizures.

During childhood, particularly from 6 months to 3 years of age, 3-5 children in every 100 have at least one episode of febrile convulsions (FC). Recently, researchers have focused on human herpes virus type 6 (HHV-6) as the etiology of 20-25% of the FC cases (1). Human herpesvirus 6 HHV-6) causes sixth disease, also known as roseola infantum or exanthem subitum. Ninety percent of children have been infected by 2 years of age, with peak incidence occurring between 9 and 21 months of age (2). HHV-6 is most likely transmitted via the saliva of healthy individuals and enters the body via a mucosal surface. One percent of HHV-6 infection is acquired congenitally without known sequelae.

After an incubation period of 10 to 15 days, sixth disease is characterized by a prodrome of mild rhinorrhea, sore throat, and conjunctival redness, followed by a high fever (100.4°F to 104°F). Cervical,
postauricular, or occipital lymphadenopathy usually develops. Other symptoms are usually absent but may include abdominal pain, vomiting, or diarrhea. After 3 to 5 days, the fever abates and the rash of roseola may begin—if at all—as tiny, erythematous, raised papules on the trunk that spread to the neck and extremities, lasting 1 to 3 days. Interestingly, while 93% of those infected are symptomatic (fevers, fussiness, rhinorrhea), only 20% of those infected exhibit the rash of roseola. Fifteen percent of infected children have febrile seizures. Febrile seizures occur in children aged 6 months to 5 years with fever \(\geq 100.4^\circ\text{F} (38^\circ\text{C})\) and absence of underlying neurologic abnormality, metabolic condition, or intracranial infection. More than 2 children in every 100 will experience one or more such seizures in the first 5 years of life. Each episode causes a definite small but unquantified risk of permanent brain damage\(^3\).

Seizures comprise the majority of emergency cases in pediatric neurology \(^4\). Studies have shown that HHV-6 is a primary cause of febrile seizures in children, the most common neurological problem during childhood \(^5\). Febrile seizures have a prevalence of 2-4% of children who are between 6 months and 5 years of age \(^5\). Each
episode causes a small but not quantified risk of permanent brain damage (6). The etiology of these is not known, but series have been reported in which viruses play up to 67.7% in cases with febrile seizures (1). Three major pathogenic mechanisms of virus-associated encephalopathy have been proposed: metabolic error, cytokine storm, and excitotoxicity (7). Among viral infections, an important role of HHV-6 in febrile seizures has been suggested (4). Up to 18% of the children seen in emergency departments with first episode of febrile seizures experienced primary infection with HHV-6. It was also found that some viruses can cause seizures more frequently than others (8).

The average age of children who present febrile seizures attributed to HHV-6 vary according to the different studies: 9.11 months (9), 9.4 months (10), 9.9 months (11), 15.6 months (5), 17.2 months (8), 20 months (12) compared to the average age of children with febrile seizures for other causes that was 15 months (11).

Approximately one third of the patients, mainly those children under one year of age, were infected with HHV-6 (9). In another study, half (56.5%) of children under one year of age were infected (13). By two years of age, 90% of the children were infected (2). The majority of children with febrile seizures due to other causes had specific HHV-6 IgG, indicating previous exposure to the virus. By three years of age, 87.1% had been exposed to the virus (11). Serological tests for IgM HHV-6 antibodies were positive in 8.5% of children and intermediate results in 42.7%. Serological tests for IgG HHV-6 antibodies showed positive results in 69.5% and intermediate results in 12.2% (14).

Acute infection with HHV-6 was associated with febrile seizures in 31% of patients (15). 84.9% of patients presenting with the febrile crisis had viremia either by HHV-6B or HVV-7. Only genotype 6B was detected in febrile patients due to HHV-6 (11). In 32% of the patients, they presented viremia due to this genotype. No HHV-6 infection was identified (10). The finding of HHV 6 represented 45% of febrile status epilepticus and 64% of cases of afebrile epileptic status (12). The ability to diagnose PCR infection during the acute phase of the disease could facilitate clinical trials of antiviral agents with activity against any virus (16).

Infections by HHV-6 are the main cause or factor associated with seizure status, whether febrile or non-febrile (12). It was reported that 31% of cases of febrile seizures were associated with acute infection by HHV-6 (13). A significant percentage of febrile seizures occurred in children with primary infection with HHV-6 (17). Primary infection with HHV-6 was found in 20% of patients with febrile seizures (13). In another study, HHV-6 infection occurred in 16.1% of children with febrile seizures, a little lower than the previously reported 26.1% (11). A similar percentage was found in another series in which 15% of infected children had febrile seizures (12). Between 3 and 18% of patients with primary HHV-6 infection had febrile seizures during the period of acute disease (18). A significantly higher proportion of children with fever between 12 and 15 months of age with primary HHV-6 infection had febrile seizures (36%) compared to control subjects without HHV-6 infection (13%) (8). The highest incidence (76.3%) of febrile seizures in children was in children infected by HHV-6 in the age group > 24 months (19). In another study HHV-6 was found in 33% and 57% of patients with HHV6 infection had febrile seizures (9). HHV-6 was
found in 35.4% of cases of febrile seizures and in 54.2% of cases without febrile seizures (1).
Infections by HHV-6B and HHV-7 are commonly associated with febrile status epilepticus, predominantly with HHV-6B (10). The primary infection by HHV-6 was verified in 18% of those who presented their first febrile crisis (20). In contrast to these reports, in one study the 10 children with primary HHV-6 infection experienced febrile seizures. This difference between current findings and previous reports could be attributed to differences in methodology, study design, or heterogeneity of the populations studied (8).
On the other hand, in another study seizures were found in 52% of patients. No significant association was found between seizures and positive results for HHV-6 (43% in patients without seizures and 57% in cases that developed seizures [p > 0.05]) (9).
A factor that distinguishes children who develop febrile seizures from those in the control group is family history, 65% of patients infected with HHV-6 who had febrile seizures had a family history of FC (1,4). It is known that the appearance of febrile seizures is related to genetic susceptibility, some of these factors can be explained by the genetic background to the immune response to HHV-6 (21). Children who develop FC infected with HHV-6 have low immunoglobulin, especially IgA and IgM that play an important role in the onset of a viral infection (1). The lack of significance of a lower IgA and IgM in children who did not have a family history of febrile seizures shows a certain correlation between family history and immunological factors (1). A family history of febrile seizures was found more frequently in those with primary HHV-6 infection. In comparison, risk factors were found among which are: family history of seizures, early age of onset of the first febrile seizure or a complex or prolonged seizure (5). On the other hand, it was also found that there were no significant differences between the group studied and the control group with respect to age, gender, development, history of previous febrile crisis, family history of febrile seizures or epilepsy (10). Other studies reveal that the relationship between family history and complex febrile seizures remains unfinished (22) And multiple factors are involved: 1) temperature (usually > 39 °C) 2) encephalitis and 3) viral neurotropism (encephalopathic factor of HHV-6) (14).
HHV-6 can infect the CNS latently in the interictal period in patients with recurrent febrile seizures and can be reactivated by factors such as fever. It is speculated that HHV-6 invades the brain during the acute phase of epileptic status and establishes latent infection in the CNS, the new seizures are due to its reactivation (21). The incidence of seizures within the first hour of onset of fever was more frequent in the group infected with HHV-6 (22). It was shown that seizures usually developed during the first two days of fever (92.7%) and were mostly simple (90.2%) (14). Children who were infected with HHV-6 at the time of their first febrile seizure had a slightly higher maximum temperature than the negative controls for HHV-6. (39.93 °C vs. 39.68 °C) (5). The degree of fever correlates with the risk of febrile seizures, this seems to be influenced by intracranial metabolic changes, increased concentration of glutamate and GABA. These processes can be induced by fever (22). On the other hand, it was found that the body temperature level does not play a role in febrile seizures (4). Another study showed that HHV-6 infection is a frequent cause of fever in children (25.8%) compared
to previously found that HHV-6 infection is not a frequent cause of fever (8.5%) \(^{(20)}\). These data demonstrate that the onset of a first or second febrile seizure is caused by febrile illness rather than the neurotropic properties of HHV-6 \(^{(4)}\).

Previous studies have suggested that children who experience a higher temperature in their first febrile seizure were at reduced risk for a recurrent seizure. The presence of the genome of HHV-6 in the CNS at the time of initial infection, however, has been reported to increase the risk of recurrence of febrile seizures. The recurrence rate of seizures is 34%, 20% in children positive for HHV-6 and 40% in children negative for HHV-6. During the first twelve months of the first febrile seizure, few children with HHV-6 infection had a recurrent seizure compared to children without HHV-6 infection (20% vs 40%). The children whose first seizure was complex, showed an increased risk of recurrence \(^{(5)}\). In another study it was found that the primary infection with HHV-6 does not seem to be a risk factor for recurrent febrile seizures \(^{(8)}\).

Children with febrile seizures had a greater leukocyte count and circulating neutrophils \(^{(4)}\). In contrast, patients with febrile seizures due to HHV-6 had a lower mean leukocyte count (9.5 cells / mm\(^3\) vs. 11.3 cells / mm\(^3\)) and an absolute neutrophil count (4.5 cells / mm\(^3\) vs. 7.8 cells / mm\(^3\)) \(^{(17)}\). This is in accordance with previous results suggesting that viruses that induce leucopenia may be a frequent cause of febrile seizures, although in a more recent series the opposite was demonstrated \(^{(6)}\). More indicative are immunoglobulin levels, which are lower in children with febrile seizures \(^{(4)}\).

Some authors consider that HHV-6 is the most important etiological causative agent for febrile seizures \(^{(12)}\). All patients with complex HHV-6 seizures were without neurological sequel \(^{(7)}\). There are no definitive conclusions about the presence or absence of the neuroinvasion by HHV-6B or HHV-7 that can be extracted from the studied data \(^{(10)}\). Oxidative DNA damage in the brain caused by HHV-6 infection is involved in febrile seizures and may be independent of inflammatory reactions and subsequent axonal damage \(^{(7)}\). It was reported that local inflammatory or edematous changes occur temporarily in brain tissues with encephalitis or encephalopathy, presumably in association with viral infection. HHV-6 can invade the CNS during primary infection, infect neural and glial cells, and result in a more severe form of febrile seizures. Febrile seizures associated with HHV-6 infection can result from direct invasion of the virus into the CNS and not simply from fever \(^{(13)}\). Although HHV-6 has been postulated to have neurotropic properties, it does not seem to appear more commonly in young children with a first or second febrile seizure compared to young children with febrile illness in the absence of seizures \(^{(4)}\).

Tau protein is a sensitive biomarker that can help diagnose HHV- encephalopathy, but it is difficult to make an early diagnosis for acute encephalopathy using this biomarker \(^{(7)}\). In another study, no evidence of pleocytosis was found in CSF, so their hypothesis is that febrile seizures are not induced by a direct viral attack to the brain, but are the result of vasculitis by virus bodies or secretion\(^{(8)}\), (Table 2).
<table>
<thead>
<tr>
<th>Title</th>
<th>Author</th>
<th>Year</th>
<th>No. of Patients</th>
<th>Objective</th>
<th>Kind of Article</th>
<th>OPMER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human Herpes Virus Type 6 and Febrile Convulsion</td>
<td>Houshmandi MM, Moayedi AR, Rahmati MB, Nazemi A, Fakhrai D, Zare Sh.</td>
<td>2015</td>
<td>53</td>
<td>The aim of this study was to investigate the prevalence of HHV-6 infection in FC admitted patients of Bandar Abbas Children Hospital, southern Iran.</td>
<td>Original</td>
<td>11</td>
</tr>
<tr>
<td>A study of childhood febrile convulsions with particular reference</td>
<td>Maria Francesca Bertolani Marinella Portolani Francesca Marotti Anna</td>
<td>1996</td>
<td>89</td>
<td>Accordingly, we set out to identify which viruses are mainly involved in FC and to discover whether there are elements differentiating children who develop FC from those who do not during viral infections in general and in the case of HHV-6 infection in particular, whether different amounts of cytokines are present in children with FC than in other, nonconvulsive, children, and finally, whether different types of viruses pose different levels of risk of recurrent FC.</td>
<td>Original</td>
<td>13</td>
</tr>
<tr>
<td>HHV-6 infection: pathogenic considerations</td>
<td>Maria Sabbattini Claudio Chiossi Maria Rosa Bandieri Giovanni Battista Cavazzuti</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case-Control Study of Primary Human Herpesvirus 6 Infection in Children With Febrile Seizures</td>
<td>Juliette Hukin, MB*; Kevin Farrell, MB*; Laurie M MacWilliam, MSc*; Margaret Colbourne, MD*; Eiko Waida, MD*; Rusung Tan, MD; Larry Mroz, MSc; and Eva Thomas, MD, PhD</td>
<td>1998</td>
<td>86</td>
<td>Human herpesvirus 6 (HHV-6) has been demonstrated to be the causative agent in roseola infantum. It has been suggested that HHV-6 may have neurotrophic properties and be involved in the pathogenesis of febrile seizures in infants. We describe a case-control study to examine the hypothesis that acute HHV-6 infection occurs more commonly in children with febrile seizures than in controls.</td>
<td>Original</td>
<td>15</td>
</tr>
<tr>
<td>Febrile seizures: Current understanding of pathophysiological mechanisms</td>
<td>S. Auvin, L. Valle´e</td>
<td>2009</td>
<td>-</td>
<td></td>
<td>Review</td>
<td></td>
</tr>
<tr>
<td>Diagnosis of primary human herpesvirus 6 and 7 infections in febrile infants by polymerase chain reaction</td>
<td>Duncan A Clark, I Michael Kidd, Kathryn E Collingham, Michael Tarlow, Titi Ayeni, Andrew Riordan, Paul D GriYthns, Vincent C Emery, Deenan Pillay</td>
<td>1997</td>
<td>41</td>
<td></td>
<td>Original</td>
<td>10</td>
</tr>
</tbody>
</table>

Table 2. Articles
<table>
<thead>
<tr>
<th>Title</th>
<th>Authors</th>
<th>Year</th>
<th>Citations</th>
<th>Abstract</th>
</tr>
</thead>
<tbody>
<tr>
<td>Febrile Seizures and Primary Human Herpesvirus 6 Infection</td>
<td>Ioanna Laina, MD, Vassiliki P. Syriopoulou, MD, George L. Daikos, MD, Eleftheria S. Roma, MD, Foteini Papageorgiou, PhD, Talia Kakourou, MD, and Maria Theodoridou, MD</td>
<td>2010</td>
<td>13</td>
<td>The aim of this study was to describe the clinical characteristics of children with febrile seizures during primary HHV6 infection and to investigate the frequency of primary HHV-6 infection in children with febrile seizures in Greece.</td>
</tr>
<tr>
<td>Human Herpesvirus 6 Infection in Febrile Children: Frequency in an Iranian Referral Hospital</td>
<td>H. Farshadmoghadam, B. Pourakbari, S. Mahmoud, R. H. Sadeghi &amp; S. Mamishi</td>
<td>2014</td>
<td>17</td>
<td>The aim of this study is to determine the frequency of HHV6 infections in children aged two years or under with an initial diagnosis of fever during an evaluation in the paediatric emergency department of the Children’s Medical Center, an Iranian referral hospital.</td>
</tr>
<tr>
<td>Causes of fever in children with first febrile seizures: How common are human herpesvirus-6 and dengue virus infection?</td>
<td>Chitsanu Pancharoen, Thaworn Chansongsakul and Parvapan Bhattarsakosol</td>
<td>2000</td>
<td>7</td>
<td>We have conducted this research in order to evaluate the etiologies of fever in children with first febrile seizures.</td>
</tr>
<tr>
<td>The Incidence of Human Herpesvirus 6 Infection in Children with Febrile Convulsion admitted to the University Hospital Kuala Lumpur</td>
<td>K. B. Chua MRCP, S. K. Lam FRCPath, S. AbuBakar PhD, M. T. Kohn MRCP, W. S. Lee MRCP</td>
<td>1997</td>
<td>14</td>
<td>This study was undertaken to determine the proportion of children with febrile convulsion admitted to the University Hospital, Kuala Lumpur that could be attributed to HHV 6 infection and whether there are specific clinical features that may help to differentiate seizures due to HHV 6 from those due to other causes.</td>
</tr>
<tr>
<td>Title</td>
<td>Authors</td>
<td>Year</td>
<td>PubMed ID</td>
<td>Summary</td>
</tr>
<tr>
<td>----------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------</td>
<td>------</td>
<td>-----------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Three or more infantile febrile seizures and HHV-6.</td>
<td>Westarp Martin Eson, Kleiser Bernhard, Bechinger Doris and Kornhuber Hans Helmut</td>
<td>1995</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>HHV-6 and Seizure: A Systematic Review and Meta-Analysis</td>
<td>Fatemeh Mohammadmour Touserkan, Marina Gainza-Lein, Saba Jafarpour, Katelyn Brinegar, Kush Kapur and Tobias Loddenkemper.</td>
<td>2017</td>
<td>-</td>
<td>The current review aims to address this gap in knowledge by assessing the prevalence of HHV-6 infection and its relationship with seizure disorders, as reported in the literature.</td>
</tr>
<tr>
<td>Clinical characteristics of febrile convulsions during primary HHV-6 infection</td>
<td>Sadao Suga, Kyoko Suzuki, Masaru Ihira, Tetsushi Yoshikawa, Yuji Kajita, Takao Ozaki, Keiji Iida, Yumiko Saito, Yoshizo Asano</td>
<td>2000</td>
<td>105</td>
<td>In our study, we evaluated the involvement of primary HHV-6 infection in patients with febrile convulsions in childhood and compared the clinical features and backgrounds of these patients with those without evidence of primary HHV-6 infection to ascertain the clinical characteristics of children with febrile convulsions during primary HHV-6 infection.</td>
</tr>
<tr>
<td>Risk of recurrent seizures after a primary human herpesvirus 6-induced febrile seizure</td>
<td>EE, Sandra H. BA; Long, Christine E. MPH; Schnabl, Kenneth C. MBA; Sehgal, Neeru MD; Epstein, Leon G. MD; Hall, Caroline Breese MD</td>
<td>1998</td>
<td>2913</td>
<td>To test the hypothesis that children experiencing first febrile seizures caused by human herpesvirus 6 (HHV-6) have an increased risk for recurrent seizures when compared with children experiencing first febrile seizures attributed to other illnesses.</td>
</tr>
<tr>
<td>Title</td>
<td>Authors</td>
<td>Year</td>
<td>Page</td>
<td>Abstract</td>
</tr>
<tr>
<td>----------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------</td>
<td>------</td>
<td>------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Viruses in febrile convulsions</td>
<td>M. J. Stokes, M. A. P. S. Downham, J. K. G. Webb, Joyce Mcquillin, And P. S. Gardner</td>
<td>1977</td>
<td>276</td>
<td>We report the virus findings in a consecutive series of children admitted to hospital with febrile convulsions, and discuss the significance of the associations shown.</td>
</tr>
<tr>
<td>Fifth and sixth diseases: More than a fever and a rash</td>
<td>Jason S. O'Grady, MD</td>
<td>2014</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Changes in Cerebrospinal Fluid Biomarkers in Human Herpesvirus-6-Associated Acute Encephalopathy/Febri te Seizures</td>
<td>Naoyuki Tanuma, Rie Miyata, Keisuke Nakajima, Akihisa Okumura, Masaya Kubota, Shin-ichiro Hamano, Masaharu Hayashi</td>
<td>2014</td>
<td>42</td>
<td>In the present study, we measured the levels of oxidative stress markers (8-hydroxy-2′-deoxyguanosine: 8-OHdG and hexanoyl-lysine adduct: HEL), tau protein, and cytokines in cerebrospinal fluid (CSF) obtained from patients with HHV-6-associated encephalopathy and complex FS associated with HHV-6 infection.</td>
</tr>
<tr>
<td>Human herpesvirus 6 infection and febrile seizures</td>
<td>J Gordon Millichap</td>
<td>2010</td>
<td>130</td>
<td>-</td>
</tr>
<tr>
<td>Febrile seizures in 1–5 aged infants in tropical practice: Frequency, etiology and outcome of hospitalization</td>
<td>Mahmood Dhahir Al-Mendalawi</td>
<td>2015</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Human herpesvirus 6 and 7 in febrile status epilepticus: The FEBSTAT study</td>
<td>Leon G. Epstein, Shlomo Shinnar, Dale C. Hesdorffer, Douglas R. Nordli, Aaliyah Hamidullah, Emma K. T. Benn, John M. Pellock, L. Matthew Frank, Darrell V. Lewis, Solomon L. Moshe, Ruth C. Shinnar, Shumei Sun; and the FEBSTAT study team</td>
<td>2012</td>
<td>199</td>
<td>In a prospective study, Consequences of Prolonged Febrile Seizures in Childhood (FEBSTAT), we determined the frequency of human herpesvirus (HHV)-6 and HHV-7 infection as a cause of febrile status epilepticus (FSE).</td>
</tr>
</tbody>
</table>

*Letters to the editor*
<table>
<thead>
<tr>
<th>Title</th>
<th>Authors</th>
<th>Year</th>
<th>Volume</th>
<th>Page</th>
<th>Type</th>
<th>Abstract</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human herpesvirus-6 infection in children with first febrile seizures</td>
<td>Stephen R. Barone, MD, Mark H. Kaplan, MD, and Leonard R. Krilov, MD</td>
<td>1995</td>
<td>42</td>
<td></td>
<td>Original</td>
<td>Our prospective study was designed to examine children seen in an emergency department with a febrile convulsion for evidence of acute HHV-6 infection.</td>
</tr>
<tr>
<td>Human Herpesviruses Types 6 and 7 and Febrile Seizures</td>
<td>Stephen J. Teach, MD, MPH, Howard L. Wallace, MS, Mary Jo Evans, PhD, Patricia K. Duffner, MD, John Hay, PhD, and Howard S. Faden, MD</td>
<td>1999</td>
<td>174</td>
<td></td>
<td>Original</td>
<td>To further examine the role of HHV-6, HHV-7, and other neurotropic viruses in the pathogenesis of febrile seizures, the current study used PCR to search for DNA from multiple herpesviruses, including HHV-6 and HHV-7, and for RNA from enteroviruses in the CSF of an unselected case series of children with febrile seizures and age-, sex- and race-matched control subject</td>
</tr>
<tr>
<td>Association of Human Herpesvirus 6 Infection of the Central Nervous System with Recurrence of Febrile Convulsions</td>
<td>Kazuhiro Kondo, Hiroshi Nagafuji, Atsuko Hata, Chieri Tomomori, and Koichi Yamanishi</td>
<td>1993</td>
<td>25</td>
<td></td>
<td>Original</td>
<td>Determine the relationship of human herpesvirus-6 (HHV-6) infection to febrile convulsions, cerebrospinal fluid (CSF) from patients with a history of febrile convulsion were tested by polymerase chain reaction (PCR) amplification for HHV-6 DNA.</td>
</tr>
<tr>
<td>Role of Viral Infections in the Etiology of Febrile Seizures</td>
<td>J. Gordon Millichap, MD*, and John J. Millichap, MD</td>
<td>2006</td>
<td>-</td>
<td></td>
<td>Review</td>
<td></td>
</tr>
</tbody>
</table>
CONCLUSIONS

Febrile seizures comprise the majority of emergency cases in pediatric neurology. Is common in children aged 6 months to 5 years, with a greater incidence at 9 months, each episode causes a definite risk of permanent brain damage. The etiology is still unknown but it has been shown that viruses play an important role, prominently the HHV-6. A factor that distinguishes children who develop febrile seizures is the family history of febrile convulsions; these can be related to low immunoglobulin especially IgA and IgM that play an important role in the onset of a viral infection. It is speculated that HHV-6 invades the brain during the acute phase of epileptic status and establishes latent infection in the CNS, but these need further study. The degree of fever seems to correlates with the risk of febrile seizures, but it is still uncertain. Oxidative DNA damage in the brain caused by HHV-6 infection may be involved in febrile seizures. It was found that primary infection with HHV-6 does not seem to be a risk factor for recurrent febrile seizures.

POINTS TO REMEMBER

1. Febrile seizures occur in children with fever, they have a prevalence of 2-4% and affected children are typically between 6 months and 5 years of age (5).
2. The etiology is still unknown but it has been shown that viruses play an important role, among them, HHV-6 is a primary cause (4,5).
3. Human herpesvirus 6 (HHV-6) infects 90% children by two years of age (12).
4. The ability to laboratory identification during the acute phase of the disease may be necessary only in specific circumstances (16).
5. The vast majority of isolates associated with febrile status epilepticus, are predominantly HHV-6B (10).
6. Febrile seizures are related to the degree of fever and family history of febrile seizures correlated with genetic susceptibility for immunological factors (4,22).

CONFLICT OF INTEREST

There was no conflict of interest in the realization of this review, the authors respond to no organization, financial disclosure or company.

BIBLIOGRAPHY

8. Laina I, Syriopoulou VP, Roma ES, Papageorgiou F,


The research work to be submitted for review should contain the following items organized as shown below:

1. MAIN PAGE, WHICH WILL CONTAIN

1.1 Title.
It is necessary that you generally reflect the content of your work in an attractive way.

1.2 Name of the authors.
It is recommended to analyze how they will be identified because it is necessary to standardize their name for future publications and have a first name, must include the full name, putting together the surnames with a hyphen.
Example: Mauricio Pierdant-Pérez.

1.3 Adscription.
Record the degree of studies; career to which belong; Faculty and/or University of which you are student, fully registering the name of the institution. Separated with semicolons (;).
Example: 2nd year student; Medical School; Faculty of Medicine, Autonomous University of San Luis Potosí.

1.4 ORCID
Relate your registration to obtain your Digital Identifier, in order to obtain a profile as a researcher and integrate links in each of your works.

1.5 Summary.
It should reflect a general description of the work with the most important points, with a maximum extension of 300 words.

1.6 Keyword.

1.7 Corresponding author.
Name and e-Mail.

2. QUESTION AND CONTEXT
Research questions arise through reading, academic or social conversations, in classes or in a clinical context, so in this section a brief explanation of how your research question and / or problem arose, guiding to the reader the need that has arisen to carry out the development of his work.
In case the origin arises within classes, the topic seen in class will be mentioned as well as the degree of information (sufficient or null) that allows to create the question mark.

3. SEARCH STRATEGY
It consists of the following elements:

3.1 Keywords.
It is necessary to identify the keywords of the subject that is being sought, as well as their synonyms. You need to use MeSH to perform searches.

3.2 Boolean operators.
Structure the MeSH term conjugations with the boolean operators, using AND to join two or three terms, OR so that the scope of the search is greater, and NOT to exclude unwanted terms.

3.3 Limits.
It is important to establish them to delimit our search, these tools will be found within each source of electronic information that identifies.
3.4 Information sources.

The electronic sources of information consulted divided into:
Meta search engines: PuMed, BVS, Trip
database, Ovid SP
Databases: Medic Latina, Science Direct,
micromedex, Springer link, Wiley, etc.

3.5 Results.

The total result of each search will be displayed, specifying the total number of articles identified and the total number of articles retrieved (used).
Example:

<table>
<thead>
<tr>
<th>No</th>
<th>Source of information</th>
<th>No. Identified articles</th>
<th>No. Recovered items</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PubMed</td>
<td>200</td>
<td>34</td>
</tr>
<tr>
<td>2</td>
<td>Ovid Sp</td>
<td>140</td>
<td>10</td>
</tr>
</tbody>
</table>

4. EVIDENCE EVALUATION

For the analysis of the retrieved literature, OPMER will be used, a format that allows the methodological evaluation of the articles, as well as the selection of those that will be used in the work according to a scale.

5. INTRODUCTION

It gave a general description of the subject, the results that you found.

6. STATE OF THE ART/RESULTS

In this section you will begin to describe what is found in the literature previously selected, the aspects to be considered are:
- Authors
- Previous research
- Results of other similar investigations
- Identify Theories
- Years in which the selected theme has had a greater impact

7. CONCLUSIONS

It will include the conclusion reached by the authors about the content of the subject to investigate, answering the question concretely, coherent and relevant.

8. POINTS TO TAKE HOME

In this section the students will expose the difficulties with which found developing the topic, leading to the development of new research related to the work developed. They can make recommendations within their area to prevent and / or treat certain diseases in case of being a clinical issue.

9. BIBLIOGRAPHY

It will be in Vancouver-style bibliography based on Citing Medicine, the NLM Style Guide for Authors, Editheors and Publisers. Available in: https://www.ncbi.nlm.nih.gov/books/NBK7256/
As well as the Quick Reference Guide: Vancouver Style available at: https://es.slideshare.net/CICBI/guia-rapida-para-la-redacción-de-referenciasestilo-vancouver

10. TABLES AND GRAPHICS

The images, tables and graphics will be presented in JPG or PNG format presented at the end of the article. They should be mentioned within the article at the end of the paragraph in parentheses, named and listed consecutively with Arabic numerals.
Example: (Image 1. Search methodology).
For this journal considers as an image that photograph and / or figure that support the understanding of a paragraph; tables like those figures that are columns and rows that
are recommended for organize and present relevant information in the investigation. The Graphs will be used to represent the numerical data using circles, lines or bars the relationship between the data presented.

10. CONFLICT OF INTEREST

Authors must state that they do not have any type of conflict at the personal, institutional that compromise to a secondary benefit, nor to be obligatorily committed by third parties and be signed by each of them.
Check our guide: How to write a review for the JMSR, where you will find more information about how to publish in our Journal.

Available in: http://www.medicina.uaslp.mx/Paginas/JMSR/ManualJMSR.pdf