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# Global Study of Viral Meningitis: A Systematic Review and Meta-analysis

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***Abstract***

Meningitis can quickly become a life-threatening sickness and therefore is considered a medical emergency. Viruses, after bacteria, are known as main pathogens involved in meningitis; therefore, we investigated the prevalence of viral meningitis worldwide and evaluated the clinical and preclinical features for rapid detection of viral meningitis. The results showed that the most prevalent viruses in viral meningitis are Enterovirus, Coxaci, Tick-borne encephalitis virus, Herpesviridae family; and the most prevalent viruses in aseptic meningitis are Echovirus, Enterovirus, Coxaci and HSV. The findings revealed differences in the prevalence of various viruses in these two types of meningitis, even though there was no significant difference in clinical manifestations between viral and bacterial meningitis. This indicates the importance of laboratory diagnostic methods for discriminating between these two types of meningitis.

***Key Words:*** Meningitis, Meta-analysis, Virus.

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## 1- INTRODUCTION

Meningitis is known as an inflammation in the meninges (the defensive membranes of brain and spinal cord) (1). A report by the Global Burden of Disease in 2015, showed that almost 8.7 million persons were living with meningitis worldwide which could lead to 379,000 deaths (2). Meningitis can quickly become a life-threatening illness due to inflammation in the central nervous system (CNS); hence, it is considered a health emergency (3). Meningitis can be caused by pathogens such as bacteria, viruses, fungi, protozoa and various non-infectious elements (i.e. drug allergies, chemical reactions, some cancers and inflammatory diseases like sarcoidosis) (4, 5). Several viruses could lead to meningitis, including enteroviruses, Herpes simplex virus type 1 (HSV-1) or 2 (HSV-2), varicella zoster (VZV), mumps virus, cytomegalovirus (CMV), Epstein–Barr virus (EBV), West Nile virus (WNV), Human herpesvirus 6 (HHV-6) and Tick-borne encephalitis virus (TBEV) (6). The term aseptic meningitis refers to patients who have the clinical and laboratory evidence for meningeal inflammation without the growth of pyogenic bacteria in cultures of Cerebrospinal fluid (CSF) (7). The viral meningitis is the most common form of the aseptic meningitis, although it can be caused by other etiologies including fungal infections, syphilis, Lyme disease, tuberculosis, drug allergies, and malignancies (8). Coxsackieviruses and echoviruses, two members of the enterovirus group accounted for almost 50% of aseptic meningitis mainly occur at summer and early fall (9). Although the EBV and HHV-6 cause various illnesses (10-13), diagnosis of acute meningitis is according to the mixture of distinctive clinical symptoms and the CSF outcome which are important in screening meningitis (14). Clinical symptoms and signs (i.e. severe headache, fever, neck stiffness, nausea, vomiting, altered consciousness, seizures, sleepiness, skin rash, and photophobia) are important factors in the screening of meningitis (15). The results of lumbar puncture (a needle is injected into the spinal canal to obtain a specimen of cerebrospinal fluid) can diagnose or rule out meningitis (16). Viral meningitis can be suspected, because of clinical features and CSF findings, but bacterial meningitis and viral meningitis cannot be clinically distinguished. Similarly, CSF results for bacterial and viral meningitis significantly overlap (17, 18). When the clinical symptoms and CSF tests of bacterial and viral meningitis overlap, the etiology is unknown. Therefore, a definitive detection of viral meningitis is based on negative CSF culture for routine bacterial pathogens and positive detection of a viral pathogen in CSF or the other patient specimens (19). In this study, we have tried to evaluate the clinical and preclinical features for detection and screening of viral meningitis. According to the recent studies, reports of the prevalence of viral meningitis are limited to specific geographic areas and till now there is not any comprehensive study regarding the prevalence of viral and aseptic meningitis. Based on our knowledge, there is no collected data regarding the epidemiology of viral meningitis all over the world. The exact data of the prevalence of viral meningitis could be helpful for preventing and controlling this emergent disease. As there is no precise assessment of the prevalence of viral meningitis worldwide, the present systematic review and meta-analysis provides useful insights on the prevalence and epidemiology of viral meningitis worldwide.

## 2- METHOD

### 2-1. Search strategies

From January 1, 2000 to January 1, 2017 all related studies were searched and collected by two independent reviewers from major databases including Embase, Medline (via PubMed), and Cochrane library. The gray literature and unpublished data were searched on the Web of Science, Cumulative Index to Nursing and Allied Health Literature (CINAHL), and WHO databases. The following search terms containing Medical Subject Headings (MeSH) keywords and their synonyms in title, abstract, or text were utilized: "Viral meningitides or viral meningitis'', "Meningitis", "Meningitis, Aseptic", "Central nervous system viral infections'', "Central Nervous System Viral Diseases'', "Cerebrospinal fluid or CSF". Furthermore, we explored the references (forward citation) and citation lists (backward citation) of the regain reviews and original articles afterwards, we picked any extra scientific study (recommended with the Cochrane guideline) (20). Studies extracted through the search strategy were evaluated for eligibility using the titles and abstracts and by two independent researchers. The complete manuscripts of the articles collected by the title and abstract were checked by the same researchers (**Table 1**). The discrepancies were resolved by disquisition. This systematic review was updated in May 2017. This study was performed based on PRISMA guidelines (21).

### 2-2. Study selection

#### 2-2.1. Inclusion criteria

Every published original article in English and other languages regarding the viral meningitides in patients with suspected meningitis with confirmatory standard lab tests were considered. We also found research studies in other languages rather than English and translated them by Google Translate (http://translate.google.com). Standard laboratory examinations for viral meningitides included: culturing, different molecular tests such as polymerase chain reaction (PCR), reverse transcriptase PCR, real-time PCR, nested PCR, nested real-time PCR (NRT PCR), multiplex PCR, restriction fragment length polymorphism (RFLP), serological assays such as enzyme-linked immunosorbent assay (ELISA), neutralization, and sequencing. The following laboratory feature analyses of viral meningitis were found in fifty eight studies: thirteen studies on CSF glucose (22-34), eight studies on CSF leukocyte (24, 27, 30-35), fifteen studies on CSF protein (22-25, 28-33, 35-39), five studies on CSF WBC (22, 28, 31, 36), twelve studies on the duration of hospitalization (30, 36, 37, 40-48) and five studies accounted for PMN (neutrophil) (22, 24, 32, 39, 49) (**Table 1**).

### 2-3. Exclusion criteria

Patients with normal CSF were considered sub-acute or chronic meningitis. Articles which were not retrievable in full text and did not comprise adequate data in their abstracts like including only individual groups of patients, surveying other infectious meningitis rather than viral meningitis such as bacterial or fungal, and those that had not used standard methods were excluded. Twenty-five studies were excluded from epidemiological studies because their reports of meningitis were not separated from the other virus infections (29, 39, 45, 50-71). Also, Thirty-two studies were ruled out because of inappropriate data (26, 31, 42, 54, 72-99). This study focused on viruses and aseptic meningitis; therefore, studies on Mollaret's meningitis (a form of meningitis known as recurrent benign lymphocytic meningitis) were excluded.

### 2-4. Data extraction and Data collection

The papers were assessed for eligibility and were double-checked by two researchers to remove any eligibility error; finally, the appropriate articles were

included in our meta-analysis. The data was extracted by 2 pundit independent researchers and were rechecked by a third professional researcher. Remarkably, contradictions between the investigators were discussed to obtain a distinct agreement. The following data were extracted from the chosen articles: first author's name, publication date, min, max, and mean age, number of participants and sample size, viral meningitis diagnostic methods, time period and where the experiment took place, the season of sample collection, methodological quality, and study design. Evidently, if any of the mentioned data were not found in the publications, they were marked as "UNKnown, UN". Data extraction and the finally chosen articles were assessed independently by two reviewers, and the differences were resolved by agreement.

### 2-5. Quality assessment

The quality of the articles was assessed by two independent researchers according to the adapted Critical Appraisal Checklist suggested via the Joanna Briggs Institute, and the discrepancies were decided upon, through agreement. The researchers answered a checklist containing seven enquiries for each paper. Each Yes-answered item acquired one score. Therefore, the total score for each paper varied from zero to seven.

### 2-6. Analysis

The outcomes were analyzed by the Comprehensive Meta-Analysis (V2.0, Biostat) software. The assessment points of the effect size, the prevalence of viral and aseptic meningitis, and its 95% confidence interval (95% CI) in all studies were evaluated. In addition, we analyzed the proportion of laboratory and clinical features. The controversial data was analyzed by Cochran's Q-statistic I2 squared. Some of the analyses demonstrated significant heterogeneity. Therefore, we used subgroups (meta-regression), and sensitivity tests to identify causes of heterogeneity. The modeling of random effects was conducted to assess pooled effects because of high heterogeneity. With the purpose of assessment of possible publication bias, Egger weighted regression was performed. The P-values less than 0.05 were considered significant for publication bias.

## 3- RESULT

### 3-1. Selection of the studies

A total of 50349 publications were reviewed in a systematic search and 49771 papers were excluded after the first screening. Finally, 464 studies were included in the meta-analysis (**Table 1**).

### 3-2. Various virus proportions in viral and aseptic meningitis

Overall, the virus proportions in viral meningitis were 68.3 % (48-83.3) Enterovirus, 11 % (95% CI, 0.4-80) Coxaci, 10.6 % (95% CI, 0.7-65.3) Tick-borne encephalitis, 9 % (95% CI, 5-15.7) HSV, 5.3 % (95% CI, 1.3-19) Mumps, 4.6 % (95% CI, 1.9-1.-0.5) HHV6, 4.5 % (95% CI, 2.3-8.8), 4.2 % (95% CI, 2.4-7.3) VZV, and 3.4 % (95% CI, 0.9-12.4) EBV (Fig. S1, S2, S3, S4, S5, S6, S7, S8, S9, S10 in the supplementary materials).

The virus proportions in aseptic meningitis were 49.3 % (95% CI, 40.3-58.3) Enterovirus, 51.1 % (95% CI, 29.5-72.3) Echovirus, 26.4 % (95% CI, 9.6-55) Coxaci, 9.3 % (95% CI, 6.3-11.5) Mumps,7.3 % (95% CI, 5.8-9.2) VZV, 6.1 % (95% CI, 3-12) HHV1, 6 % (95% CI, 2.9-12) HHV2, 2.9 % (95% CI, 0.5-15.5) CMV, and 2.1 % (95% CI, 0.7-6.5) HHV6 (**Table 2**).

### 3-3. Proportion of Clinical features in viral meningitis

The clinical presentation of viral meningitis was characterized by, headache 84.7 % (95% CI, 79-89), nausea 56% (95% CI, 48.4-63), seizures 8.3% (95% CI,

4.5-14.7), photophobia 45.8% (95% CI, 38.3-53.4), rash 17% (95% CI, 12-23), neck stiffness 52.6% (95% CI, 46.4-58.7), vomiting 65.3% (95% CI, 60-70), and fever 72% (95% CI, 67.3-76). In addition, the duration of hospitalization was 4.23 % (95% CI, 3.1-5.27) days (**Table 3**).

### 3-4. Mean of laboratory findings in viral meningitis

Laboratory findings in CSF-culture positive samples were characterized by the increased CSF leukocytes counts [173.7 (cells/mm3), 95% CI 134-213], increased CSF protein [52.9 (mg/dl), 95% CI 40-65.8], decreased CSF glucose [57.15 (mg/dl), and 95% CI 25. 55-59.3], increased CSF WBC [246.17 (mm3), 95% CI 108.7-383.5], and increased PMN (neutrophil) [45.9 (106/l), 95% CI 30.8-61] (**Table 4**).

## 4- DISCUSSION

Among the elements mentioned, the virus is considered to be the leading cause of meningitis. Therefore, this study examined the prevalence of viral meningitis worldwide, and evaluated clinical symptoms quickly detecting viral meningitis. According to the previous studies, enteroviruses accounted for 85 to 95% of cases of viral meningitis (100), while group B coxsackieviruses and parechoviruses mainly associated with aseptic meningitis in infants under three months of age (99, 101, 102). Our results showed that the highest proportion of viruses in viral meningitis belongs to Enterovirus, Coxaci, Tick-borne encephalitis, HSV, Mumps, HHV6, CMV, VZV and EBV, respectively and the highest proportion of viruses in aseptic meningitis belongs to Echovirus, Enterovirus, Coxaci, HSV, Mumps, VZV, CMV, and HHV6. These results showed a difference in virus incidents in these two types of meningitis. Despite a lack of report for some herpes viruses, this virus family significantly causes viral and aseptic meningitis. Thus, since effective commercial medications are available for the treatment of herpes viruses such as acyclovir for HSV1, HSV2 and VZV and ganciclovir for CMV, a rapid and correct diagnosis could lead to the prevention of further disorders and the treatment of this infections (103).

Before the introduction of mumps vaccine in 1967, this virus was a common cause of viral meningitis, accounted for 10 and 20 percent of all cases but the results of this meta-analysis show that the virus accounts for 5.3% of viral meningitides.

Although bacterial meningitis and viral meningitis overlap in clinical symptoms, but one retrospective cohort study reported that nausea, vomiting, headache and neck stiffness were more common in viral meningitis in comparison to bacterial meningitis (viral versus bacterial: nausea: 79% versus 48%, P = 0.005; vomiting: 81% versus 52%, P = 0.009; headache: 78% versus 10%, P < 0.0001; neck stiffness: 88% versus 62%, P = 0.006) (104). This analysis showed that headache, fever, vomiting, nausea and neck stiffness were the most common clinical symptoms of viral meningitis. Therefore, the presence of them can somewhat contribute to the screening of viral meningitis.

In regard to the high heterogeneity, these clinical symptoms of viral meningitis cannot be used as an important factor in diagnosing this type of meningitis. Fever, nausea, vomiting and imbalance are the most common clinical symptoms of bacterial meningitis. There is no significant difference in the clinical manifestations of viral and bacterial meningitis (105), which indicates the importance of laboratory diagnostic methods for discriminating these two types of meningitis.

**Table-1:** Flow of literature search and study selection

| Flow | Category | | Herpes family | | | | | | | | Other than Herpes family | | | | | | | Totall |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | HSV | Her 1 | Her2 | Her 6 | EBV | VZV | CMV | Mumps | Coxsackie | Echo | entero | Mix | TOSV | WNV | Tick-borne encephalitis | |
| databases | Medline (via PubMed) | | 721 | 379 | 140 | 103 | 193 | 364 | 300 | 419 | 1820 | 765 | 1767 | 8111 | 60 | 334 | 208 | 15684 |
| | Embase | | 1484 | 2004 | 1884 | 1308 | 445 | 679 | 822 | 902 | 512 | 365 | 2145 | 14493 | 61 | 601 | 293 | 27998 |
| | Others* | | 3241 | 3142 | 2340 | 1742 | 654 | 847 | 1044 | 1541 | 2351 | 864 | 2576 | 26145 | 246 | 1421 | 546 | 48700 |
| | Total (after remove of duplicates) | | 3356 | 2345 | 1841 | 1841 | 712 | 954 | 1121 | 1641 | 2451 | 2641 | 2751 | 26256 | 287 | 1511 | 641 | 50349 |
| Excluded after screening of title and abstract | | | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | 49771 |
| Excluded after full-text screening | Inappropriate Data | | - | 1 | 2 | - | - | 3 | - | - | 3 | 9 | 10 | 2 | 1 | 1 | - | 32 |
| | Reported Number of meningitis between virus infections | | 3 | - | 2 | 1 | - | 4 | - | 3 | - | 3 | 4 | - | 1 | 4 | - | 25 |
| | Total | | 3 | 1 | 4 | 1 | 0 | 7 | 0 | 3 | 3 | 12 | 14 | 2 | 2 | 5 | 0 | 57 |
| Included for Meta-analysis | EPIDEMIOLOGICAL | viral meningitis | 5 | 0 | 0 | 2 | 2 | 4 | 2 | 5 | 2 | 0 | 13 | 0 | 0 | 0 | 0 | 35 |
| | | Aseptic meningitis | 2 | 6 | 6 | 2 | 0 | 11 | 3 | 5 | 2 | 6 | 42 | 0 | 0 | 0 | 2 | 85 |
| | CLINICAL CONSIDERATION | Headache | 2 | 2 | 4 | 0 | 0 | 5 | 1 | 2 | 0 | 6 | 23 | 3 | 1 | 2 | 0 | 51 |
| | | Nausea | 2 | 0 | 4 | 0 | 0 | 3 | 1 | 0 | 1 | 2 | 9 | 1 | 1 | 2 | 0 | 26 |
| | | seizures | 2 | 1 | 1 | 0 | 0 | 2 | - | 2 | 0 | - | 6 | 2 | 0 | 1 | 0 | 17 |
| | | photophobia | 2 | 0 | 4 | 0 | 0 | 3 | - | 0 | 0 | 4 | 10 | - | 0 | 2 | 0 | 25 |
| | | rash | 2 | 0 | 2 | 0 | 0 | 5 | - | 0 | 0 | 2 | 10 | - | 0 | - | 0 | 21 |
| | | Neck stiffness | 2 | 1 | 5 | 0 | 0 | 5 | 1 | 0 | 0 | 4 | 17 | 3 | 1 | 2 | 0 | 41 |
| | | vomiting | 1 | 1 | 4 | 0 | 0 | 2 | 1 | 2 | 1 | 5 | 22 | 5 | 1 | 2 | 0 | 47 |
| | | fever | 2 | 2 | 4 | 0 | 0 | 5 | 1 | 2 | 1 | 6 | 28 | 4 | 1 | 2 | 0 | 58 |
| | | Duration of hospitalization | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | 12 |
| | LABORATORY CONSIDERATION | CSF glucose | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | 13 |
| | | CSF protein | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | 15 |
| | | CSF WBC | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | 5 |
| | | CSF Leukocyte | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | 8 |
| | | PMN | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | 5 |
| | Total | | | | | | | | | | | | | | | | | 464 |

* Cochrane library, Web of Science, Cumulative Index to Nursing and Allied Health Literature (CINAHL), and WHO databases.

**Table-2:** Meta-analysis of various virus proportions in viral meningitis and aseptic meningitis

| | viral meningitis | | | | | aseptic meningitis | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Virus | N of Study | Proportion in Viral meningitis % (95% CI) | n/N | I2 test (%) | Test for heterogeneity P value | N of Study | Proportion in Aseptic meningitis % (95% CI) | n/N | I2 test (%) | Test for heterogeneity P value |
| entero | 13 | 68.3 (48-83.3) | 571/936 | 93.94 | 0 | 44 | 49.3 (40.3-58.3) | 2489/8255 | 97.2 | 0 |
| HSV | 5 | 9 (5-15.7) | 52/535 | 66.38 | 0.018 | 2 | 9.7 (0.7-60) | 79/347 | 86 | 0.007 |
| HSV1 | UN | UN | UN | UN | UN | 6 | 6.1 (3-12) | 22/603 | 59.3 | 0.03 |
| HSV2 | UN | UN | UN | UN | UN | 6 | 6 (2.9-12) | 38/583 | 72.2 | 0.003 |
| HHV6 | 2 | 4.6 (1.9-1.-0.5) | 5/111 | 0 | 0.71 | 2 | 2.1 (0.7-6.5) | 3/145 | 0 | 0.68 |
| EBV | 2 | 3.4 (0.9-12.4) | 9/229 | 50.4 | 0.15 | UN | UN | UN | UN | UN |
| VZV | 4 | 4.2 (2.4-7.3) | 12/292 | 0 | 0.88 | 11 | 5.7 (3.4-9.4) | 67/1141 | 73.2 | 0 |
| Coxaci | 2 | 11 (0.4-80) | 24/339 | 97.8 | 0 | 2 | 26.4 (9.6-55) | 37/164 | 89.7 | 0.002 |
| Mumps | 5 | 5.3 (1.3-19) | 79/532 | 86.7 | 0 | 5 | 9.3 (6.3-13.5) | 25/300 | 5.07 | 0.37 |
| CMV | 2 | 4.5 (2.3-8.8) | 8/178 | 0 | 0.73 | 3 | 2.9 (0.5-15.5) | 6/381 | 77.4 | 0.01 |
| Tick-borne encephalitis | 2 | 10.6 (0.7-65.3) | 89/345 | 87 | 0.005 | UN | UN | UN | UN | UN |
| echo | UN | UN | UN | UN | UN | 6 | 51 (29.5-72.3) | 297/535 | 94.5 | 0 |

**Table-3:** Meta-analysis of the proportions of clinical features in viral meningitis

| | Headache | | Nausea | | seizures | | photophobia | | rash | | Neck stiffness | | vomiting | | fever | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Virus | Proportion | I2 test (%) | Proportion | I2 test (%) | Proportion | I2 test (%) | Proportion | I2 test (%) | Proportion | I2 test (%) | Proportion | I2 test (%) | Proportion | I2 test (%) | Proportion | I2 test (%) |
| HSV | 98 (88-99.7) | 0 | 74.5 (63-83.3) | 0 | 8.3 (0.1-90) | 82.5 | 633 (28-88.6) | 72.5 | 10.3 (0.2-86.3) | 81.8 | 74.5 (63-83) | 0 | 82 (49.3-95.4) | 0 | 78.6 (17.2-98.5) | 76 |
| HSV1 | 65.5 (24-92) | 13.2 | UN | - | 33.3 (4.3-84.6) | 0 | UN | - | UN | - | 12.5 (0.7-73.4) | 0 | 78 (24-96.6) | 0 | 89 (50-98.5) | 0 |
| HSV2 | 94.4 (82.4-98.4) | 0 | 70 (34-91.3) | 83.1 | 16.7 (1-80.6) | 0 | 53 (41.3-64.3) | 0 | 5.6 (0.3-50.5) | 0 | 79 (50-93.3) | 63.25 | 57 (31-80) | 73 | 56 (37-73) | 46 |
| VZV | 88.2 (72-95.6) | 0 | 48.5 (32-65.4) | 0 | 7.5 (1-39) | 0 | 31 (15.5-52.2) | 21.8 | 65.3 (48-79) | 38.4 | 38.4 (25-54) | 0 | 55 (33.5-74.7) | 0 | UN | - |
| Coxaci | - | - | 44.2 (30.2-59) | 0 | UN | - | UN | - | UN | - | UN | - | 58 (43-72) | 0 | 91 (77.7-96.5) | 0 |
| Mumps | 70.6 (50.6-85) | 0 | UN | - | 7.8 (2.7-20) | 0 | UN | - | UN | - | UN | - | 78 (55-91.3) | 17 | 72.4 (47-88.7) | 0 |
| CMV | 83.3 (19.4-99) | 0 | 83.3 (19.4-99) | 0 | UN | - | UN | - | UN | - | 50 (6-94) | 0 | 83.3 (19.4-99) | 0 | 83.3 (19.5-99) | 0 |
| echo | 92 (71-98) | 65 | 82 (44.2-96.3) | 79.7 | UN | - | 59 (35.2-79.2) | 82.2 | 10.6 (2.5-35) | 59.6 | 49.6 (27.6-72) | 83.3 | 73 (60-83) | 42.4 | 77 (58-89) | 68 |
| entero | 85 (74.5-91.5) | 92 | 44 (16.6-76) | 96 | 9.8 (2.8-28.7) | 87.3 | 37 (22-55) | 93 | 9.7 (5.3-17) | 82.5 | 46.6 (38-55.4) | 87 | 64.7 (56-72.4) | 88 | 89 (84-92.5) | 83 |
| tosv | 97.2 (68-99.8) | 0 | 88.2 (36.2-97) | 0 | UN | - | UN | - | UN | - | 53 (30.3-74.5) | 0 | 88 (63-97) | 0 | 76.5 (51.5-91) | 7.2 |
| wnv | 95 (51.7-9.7) | 62.8 | 46.2 (7.4-9) | 78.6 | 2.1 (0.3-13.6) | 0 | 36.7 (20.7-56.3) | 13.6 | 56.6 (14-91) | 72.7 | - | - | 53.4 (36-70) | 15.15 | 67 (85.7-99.4) | 0 |
| Mix | 40 (9.7-80.7) | 94.7 | 9.8 (3.7-23.3) | 0 | 6.4 (0.6-45.8) | 93.7 | UN | - | UN | - | 35.3 (12-68.4) | 90 | 57.4 (37-75.5) | 90 | 56 (46.3-65) | 63 |
| total | 84.7 (79-89) | 87.1 | 56 (48.4-63) | 93.3 | 8.3 (4.5-14.7) | 75.4 | 45.8 (38.3-53.4) | 87.8 | 17 (12-23) | 85 | 52.6 (46.4-58.7) | 82 | 65.3 (60-70) | 82 | 72 (67.3-76) | 84 |

According to **Table 4**, the level of glucose in the cerebrospinal fluid of patients with viral meningitis is normal, while protein level is slightly higher than the normal range. The amount of white blood cells in the cerebrospinal fluid in people with viral meningitis is significantly higher than the normal range with leukocytes as a significant percentage of it. Our results similar to other studies indicate an increase of leukocytes in the CSF of viral meningitis (106). According to the previous reports, children with a CSF WBC count of <500/microL with >50 percent mononuclear cells, normal or high CSF protein, normal CSF glucose, and negative gram stain are likely suspected viral meningitis (107, 108); hence, this laboratory finding can provide a support for a provisional diagnosis of viral meningitis.

**Table-4.** Meta-analysis of the means of CSF findings in viral meningitis

| Virus | Mean | Standard error | Confidence interval 95% | I2 test (%) | Test for Heterogeneity P value | Normal range |
|---|---|---|---|---|---|---|
| CSF glucose ( mg/dl) | 57.15 | 1.09 | 55-59.3 | 98.6 | 0 | 45–80 |
| CSF protein (mg/dl) | 52.9 | 6.5 | 40-65.8 | 98.8 | 0 | 15 - 45 |
| CSF WBC (cells/mm3 ) | 246.17 | 70.1 | 108.7-383.5 | 86.2 | 0 | 0–10 |
| CSF leukocyte (×106/l) | 173.7 | 20.2 | 134-213 | 81.2 | 0 | 0–10 |
| PMN (neutrophil) (×106/l) | 45.9 | 7.7 | 30.8-61 | 71 | 0.007 | 0–10 |

Due to limitations in the number of publications of prevalence-based studies, we couldn't report the global prevalence of aseptic and viral meningitis. The results of this study indicate that herpes viruses are one of the major causes of viral meningitis; and the presence of antiviral drugs against some of them indicates the importance of their rapid and accurate diagnosis. In addition, clinical signs are helpful in the screening of viral meningitis, but the final diagnosis is based on laboratory methods.

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## 6- CONFLICTS OF INTEREST

None.

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