

## Investigating the Causes of Febrile Encephalopathy in Elderly Patients Admitted to Imam Reza Hospital in Mashhad during the 2013 to 2014

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### Abstract

**Background:** Encephalopathy is a non-specific clinical syndrome, which if accompanied or followed by fever, its broad range of differential diagnosis will be restricted. As elderly patients with encephalopathy present with non-specific manifestations, the recognition of causes are important for clinicians to manage the disease with more accuracy. This study evaluated the causes of encephalopathy following febrile illness in elderly adults admitted to Imam Reza hospital of Mashhad, Iran.

**Methods and materials:** This prospective cohort study was carried out during January 2013 to January 2014. An application check-list was designed based on the objects of the study and was filled for all admitted patients. Check-list contained data including age, sex, and disease outcome, duration of hospitalization, background disease, and season of admission, performing or not performing brain imaging and lumbar puncture; and the final diagnosis of febrile encephalopathy.

**Results:** The age of all 100 participants were 65 years and over consisting of 39 female and 61 male. Of them, only 34 patients underwent lumbar puncture, among them the cerebrospinal fluid (CSF) analysis was abnormal in 29.4%. Infectious causes were responsible for febrile encephalopathy in 94 patients, of which 84% had an extra-cranial infection and neuro-infectious process was detected in 10%.

**Discussion:** Current study presented extra-cranial infections as the leading cause of febrile encephalopathy in elderly patients. So, it should be considered as an important origin whenever an older patient presents with fever and altered mental status.

**Keywords:** Encephalopathy; Fever; Elderly

### Introduction

Aging is one of the most important indicators in the incidence of various conditions including delirium in the course of a febrile disease [1]. Due to changes in cellular and humoral immunity, physiological changes such as reduced cough reflex, impaired blood circulation, and reduced healing rate of wounds, infectious diseases are more prevalent in the elderly [2,3]. In addition, a variety of infections in the elderly have no outstanding clinical symptoms, and most of physiological responses to these infections are suppressed in these patients [4]. Therefore, special attention to the most common infections is necessary in this susceptible age group. Due to underlying medical conditions and functional defects of vital organs, as well as multiple drug consumption, elderly age group is more susceptible to disorders in the central nervous system (CNS), which can be manifested as encephalopathy and impaired consciousness [4,5]. Infectious diseases in the elderly may have the classic features such as fever and leukocytosis. Fever above 38.3°C in elderly patients might represent a serious and life-threatening infectious disease (e.g. pneumonia, urinary tract infections, bacterial meningitis, viral encephalitis, infections of the biliary tract, etc...) [4]. Fever can cause delirium in the elderly. Further, it causes dehydration, which might exacerbate the delirium in older adults [6].

Encephalopathy is a nonspecific pathology, referring to disorders that affect the cerebral function and cause structural or functional changes in the brain. A wide range of infectious and non-infectious processes can induce encephalopathy. Blood tests, CSF analysis and imaging techniques can be used to distinguish the various causes of encephalopathy. Encephalopathy, if accompanied by fever, limits the diagnostic spectrum, which in most cases are infectious in nature. Encephalopathy is not limited only to a specific entity. Rather, it refers to a disorder induced by a variety of metabolic, septic, ischemic and toxic promoters.

This prospective study was conducted on elderly patients with encephalopathy and fever admitted to Imam Reza hospital, Mashhad, during 2013 to 2014 to study the main causes of febrile encephalopathy in this age group.

### Methods

#### Study population

The study populations were the elderly patients referred to the emergency ward of Imam Reza hospital due to fever and decreased level of consciousness. All patients aged ≥65 years admitted to the hospital with febrile encephalopathy were enrolled in the study. All information of patients including age, gender, duration of

hospitalization, underlying diseases, the results of brain images and/or lumbar puncture (LP) if performed, CNS and non-CNS causes of encephalopathy, infectious and non-infectious causes of encephalopathy, spinal fluid analysis results if available, and the final diagnosis and outcome were recorded. Patients, who did not complete the check-list for any reason, or patients who discharged from hospital with personal motives or died before the diagnostic and therapeutic interventions, were excluded from the study.

### Data analysis

For data analysis, T-test, Chi-square and non-parametric tests were performed using SPSS statistical software. In all measurements,  $p < 0.05$  was considered as statistically significant. The Mann-Whitney test was used to compare the mean quantitative variables in the two groups with regard to the small size of one of the studied groups.

### Results

In this study, 100 patients aged  $\geq 65$  years with fever and impaired consciousness referred to the emergency department of infectious diseases during January 2013 to December 2014 were participated. Of the studied population, 61 were male and 39 were female. The mean age of patients with CNS-associated encephalopathy was  $77.6 \pm 6.5$ , while the mean age of patients whose encephalopathy did not related to the CNS, was  $81.2 \pm 7.3$  years ( $P=0.14$ ). On the other hand, the mean age of patients with encephalopathy due to infectious and non-infectious causes was  $72.4 \pm 9.1$  and  $80.08 \pm 7.2$  years, respectively. The difference was statistically significant ( $P=0.005$ ).

No significant correlation was found between the duration of hospitalization in patients with CNS-associated and unassociated encephalopathy ( $P=0.973$ ). Also, there was no significant association between the duration of hospitalization and infectious and non-infectious encephalopathy ( $P=0.707$ ). As well, no significant correlation was observed between the infectious and non-infectious encephalopathy and the seasonal changes of the year ( $P=0.095$ ).

The mean duration of consciousness impairment before the admission was  $46.8 \pm 5$  hours with the minimum and maximum

Brain Imaging	CNS-associated	CNS-unassociated	P value	Infectious Diagnosis	Non-infectious Diagnosis	P value
Abnormal	3	10	0.327	2	11	0.251
Normal	9	44	0.327	4	49	0.251
Not performed	4	30	-	24	10	-

**Table 1:** The results of brain imaging were not significantly different between CNS-associated/unassociated or infectious/non-infectious causes of febrile encephalopathy.

As a result, according to the amount of P-value, the imaging result does not show a significant correlation with final diagnosis. The results also showed a significant correlation between the signs of meningeal irritation and the CNS-associated disorders ( $P=0.007$ ) (Table 2).

In this study, no significant correlation was found between sex and the cause of febrile encephalopathy ( $P=0.240$ ). So that, CNS and non-CNS disorders as well as infectious and non-infectious causes of encephalopathy were observed in both gender almost equally. The relationship between gender and the cause of encephalopathy has not been fully reviewed in the previous studies, but in most of studies, the risk of febrile encephalopathy has been mostly reported in men. In this

period of 2 and 336 (14 days) hours, respectively. The results of brain CT scan and MRI of 66 patients whom their documents were available showed that 53 had normal imaging.

The frequency of underlying diseases in this study showed that of all included participants, 46 patients had blood hypertension, 40 patients had a chronic neurological disorder, 27 had diabetes mellitus and 25 patients suffered from ischemic heart disease. In addition, 19 patients were in bed ridden status, 5 patients had secondary immunodeficiency and there were 4 cases of cancer. 66 patients had more than one underlying disease. Statistical analysis showed that no significant difference exists between any of the underlying medical conditions and CNS-associated and CNS-unassociated encephalopathy, as well as infectious and non-infectious encephalopathy.

Blood cultures were performed in 59 out of 100 patients, of whom 9 cases (15.3%) had positive and 50 cases (84.7%) had negative results. Urine analysis performed in 91 patients that was normal in 63 cases (69.2%), while urine cultures were positive in 26 (28.3%). Toxicological assessment showed positive results in 4 of 100 patients.

Of the patients participating in this study, the etiology of febrile encephalopathy in 94 cases including 10 cases with intra-cranial pathology (10%) was infectious. Direct CNS involvement was ruled out in all other 84 cases (including one with disseminated tuberculosis and one with systemic brucellosis). In 6 cases, non-infectious conditions (6%) caused fever and loss of consciousness.

The results showed that performing LP made a significant difference between the patients with CNS and non-CNS encephalopathy ( $P=0.001$ ), while it was not the case for infectious and non-infectious encephalopathy ( $P=1$ ). Therefore, according to the reported P-value, LP is significantly correlated to final diagnosis. Abnormal CSF results were seen in CNS-associated causes, suggesting high positive predictive value of LP in these patients (Table 1). On the contrary, the results of brain CT scan and MRI did not make difference between the two groups of CNS and non-CNS ( $P=0.327$ ) or infectious and non-infectious encephalopathy ( $P=0.251$ ).

study, no significant correlation was observed between the prognosis of patients and the cause of febrile encephalopathy ( $P=0.103$ ).

### Discussion

Many studies investigated the causes of febrile encephalopathy in adult patients. Unlike other studies in which the CNS-associated conditions constituted the most important cause of febrile encephalopathy, non-CNS disorders were the main cause of encephalopathy here [7]. Beside bacterial meningitis, other CNS infections such as viral encephalitis and tuberculous meningitis may also be considered as a cause of encephalopathy [8]. In addition, it was

demonstrated that other etiologies such as inflammatory cytokines or metabolic disorders may contribute to febrile encephalopathy [9-11].

All mentioned disorders in previous studies were also reported in the patients of this study with different prevalence rate.

Meningeal signs	Abnormal CSF		Normal CSF		LP not performed	
	CNS-associated	CNS-unassociated	CNS-associated	CNS-unassociated	CNS-associated	CNS-unassociated
Positive	5	1	1	7	0	2
Negative	1	0	0	10	0	47
Unreliable	3	0	0	7	0	16
P value=0.007						

**Table 2:** All neuro-infectious causes of febrile encephalopathy, except one case, had abnormal CSF analysis. So, performing LP had a high positive predictive value for final diagnosis.

It is especially worth mentioning that the results of brain imaging techniques in elderly patients with febrile encephalopathy were not associated with final diagnosis in the present study. However, the results indicated a positive predictive value of performing LP in the elderly with fever and altered mental status. In other words, as showed by Weisfelt et al., although LP has not a high clinical sensitivity in older patients with febrile encephalopathy, it has high specificity [12].

In one of the studies, it was reported that seasonal changes are involved in the prevalence of viral encephalitis and brain malaria [9]. However, current study showed no significant difference between seasonal changes and the diverse causes of febrile encephalopathy in the elderly.

Resistance to passive movement of the neck is a common physical finding in elderly patients because of the presence of cervical spondylosis. Although it is practically difficult to distinguish between the cervical spondylosis and nuchal rigidity resulting from meningitis, some clinical clues have been proposed. For example, it has been noted that in nuchal rigidity, the neck resists flexion but in spinal disease, lateral rotation, extension, and flexion of the neck are all associated with resistance. It has also been suggested that a relatively helpful clinical sign is that with cervical arthritis, in particular, passive flexion of the neck may elicit resistance more at the extremes of range of motion, whereas with meningeal irritation, resistance may be felt more immediately [13]. Present study showed a statistically significance for meningeal irritation (Table 2). However, some studies reported that test of passive flexion of the neck not only is unreliable in elderly patients, but also Kernig and Brudzinski signs are probably of little or no diagnostic value [14]. In a study by Waghdhare et al. physical signs of meningeal irritation were not useful as accurate diagnostic tests for meningitis [age range of participants: 13-81; mean: 38(SD:18)] [15]. Similarly, Breuwer et al. reported low diagnostic accuracy of signs of meningeal inflammation to include or exclude meningitis [16].

In summary, the present study indicated the extra-cranial disorders as the most common cause of febrile encephalopathy in the elderly patients. But to minimize the possible misinterpretation of the fact, it should be noted that this conclusion could be affected by relatively small sample size and the unique properties of the hospital in which the study was conducted. So, it seems reasonable to conduct a well-designed multicenter research study with proper sample size to evaluate the role of age, sex, infectious agents and other CNS pathologies as well as other possible influencing factors in the incidence of febrile encephalopathy.

## Conclusion

Based on the findings of the current study, extra-cranial infection without direct involvement of CNS can be the leading cause of febrile encephalopathy in elderly patients. Hence, it should be considered as a significant possible diagnosis in the elderly present by fever and altered mental status. Furthermore, performing LP for CSF analysis is the most useful single intervention to make a distinction between CNS-associated and CNS-unassociated disorders.

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