ORIGINAL RESEARCH

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Is Infectious Meningitis/Encephalitis a Notable Problem in Older Adults Admitted to Emergency Department with Altered Mental Status?

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Abstract

Objective: Altered mental status (AMS) is challenging diagnosis. It was aimed to evaluate the underlying causes, reveal laboratory, microbiological and imaging findings, and determine the infectious process in older patients who presented with AMS.

Materials and Methods: This retrospective study was conducted at a training and research hospital. Sixty-five year and older patients who presented with AMS and underwent lumbar puncture, were included.

Results: Among 98 older patients with AMS, the median age was 75.0 years (interquartile range: 69.0-75.0) and 58.2% of patients were female. Of the patients, 26.5% meningitis/encephalitis, 33.6% other infection sources, and 39.8% other disorders were found, respectively. Cerebrospinal fluid (CSF) white blood cell and protein levels were found higher; CSF chloride levels were detected lower in meningitis/encephalitis group. In brain, magnetic resonance imaging ($p<0.001$) and electroencephalogram ($p=0.009$) were found more pathologies suggesting infection in meningitis/encephalitis patients, while brain computed tomography revealed no differences between meningitis/encephalitis and other diagnoses group. The need for intensive care was higher in the other disorder group ($p=0.02$) while admission to service was higher in the meningitis/encephalitis group ($p=0.03$).

Conclusion: Clinical characteristics failed to differentiate between meningitis/encephalitis and other diagnoses in older patients with AMS, and CSF analysis, cranial imaging methods were required for the final diagnosis.

Keywords: Altered mental status, emergency service, encephalitis, meningitis, older adults

Introduction

It is common for older adults to apply to the emergency department (ED) with altered mental status (AMS) (1,2). Up to 50% of hospitalized older patients and 2% of ED patients experience changes in consciousness at different levels (3). The presence of infections, malnutrition, electrolyte imbalance, exacerbation of underlying diseases, drug side effects, delirium, and many other disorders may cause AMS in the older patients (4). Sometimes, the underlying cause may not be found despite all the research.

In the patient who applies to the ED with AMS, the cause is tried to be found by vital signs, a medical history that can be obtained from the patients themselves, relatives or caregivers, physical examination, symptoms and findings, and imaging methods (5). Before the diagnosis is made, peripheral glucose, oxygen level, laboratory parameters such as urinalysis, electrocardiogram, simple electrolyte tests, renal function tests, and complete blood count should be obtained (6,7). Cranial computed tomography (CT) can also be applied for acute intracranial haemorrhage or other mass lesions. If there is no reason to explain the patient's AMS despite all these tests and AMS persists, additional testing

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such as arterial blood gas, thyroid tests, cerebrospinal fluid (CSF) analysis, electroencephalogram (EEG), and brain magnetic resonance imaging (MRI) may be requested. Although obtaining CSF by lumbar puncture (LP) and using it in the differential diagnosis is less and less preferred thanks to brain CT and MRI. However, urgent LP is still used for suspected central nervous system (CNS) infections (6,8).

In this study, it was aimed to 1) evaluate the underlying causes, 2) reveal laboratory, microbiological and imaging findings, and 3) determine the infectious process (meningitis and encephalitis) in older patients who presented to the ED with AMS.

Materials and Methods

Study Design and Population

This study was a single-center, retrospective cross-sectional cohort study. We included all aged 65 years and older patients with AMS who were consulted to infectious diseases (ID) specialists and underwent LP between February 1, 2019 and December 1, 2021. We excluded patients with a lack of data, no indication for LP or those who refuse the LP while in ED. This study was approved by the Medical and Health Research Ethics Committee of Ankara City Hospital (date: 09/06/2021, number: 1756).

Case Definitions and Classifications

Meningitis is an inflammation of the leptomeninges, that can also involve the parenchyma and is defined by the presence of an inflammatory process of the brain (6). Encephalitis is determined by the parenchymal inflammatory process of the brain in association with abnormal brain function (7). We classified patients with AMS meeting the European Society of Clinical Microbiology and ID guidelines recommendations for meningitis, which includes signs and symptoms (headache, fever, neck stiffness), CSF findings [glucose concentration <40 mg/dL, a CSF serum glucose ratio of <0.4, a protein concentration >200 mg/dL, and a white blood cell (WBC) count 1000/microL] and CSF culture results (6,8,9). Viral encephalitis diagnosis was made by the Infectious Disease Society of America Guidelines criteria (7).

Study Variables

We selected several variables associated with the reasons of AMS, including age, sex, comorbidities including diabetes mellitus, hypertension, malignancies, chronic lung disease, heart disease (arrhythmias, coronary artery disease, congestive heart failure), chronic liver disease, chronic kidney disease and history of stroke, psychiatric disorders, Alzheimer's disease; symptoms and clinical signs on admission (fever, blood pressure, cough, dyspnea, presence of sputum, digestive symptoms, weakness in body parts, dysuria, neck stiffness, headache, Kernig's and Brudzinski's sign, history of seizure, presence of deep and soft tissue infections), intubation and vasopressor use in the ED, laboratory parameter results of blood and CSF, urinalysis, culture results (blood, urine, sputum, CSF), bacterial and viral real-time polymerase chain reaction (RT-PCR) panel, identification of *Mycobacteria* in CSF, imaging technics performed in the ED, outpatient or hospitalized status, the length of hospital stay, causes of AMS and final outcomes from hospital automation systems.

Microbiological Evaluation

For this study, we obtained results of various microbiological laboratory tests available in the database, CSF white and red blood cell, CSF glucose, protein, sodium, chloride and lactate dehydrogenase levels and CSF Gram stain; viral meningoencephalitis pathogen RT-PCR panel [includes, *Herpes simplex virus* type-1 and *Herpes simplex virus* type-2 (HSV-1 and HSV-2), *Varicella-zoster virus* (VZV), *Mumps virus*, *Enterovirus*, *Human parechovirus*]; bacterial meningitis pathogen RT-PCR panel (includes, *Streptococcus pneumoniae*, *Neisseria meningitidis*, *Haemophilus influenzae*) and tuberculosis tests [acid-fast bacillus (AFB) stain and culture], and cultures of CSF, blood, urine, sputum. In our institution, viral and bacterial panels were performed with Siemens, Germany's Fast Tract Diagnostics Multiplex RT-PCR assay. Culture and AFB stain for *Mycobacterium tuberculosis* were performed using Ziehl-Neelsen staining and Middlebrook 7H9 Broth/Löwenstein-Jensen media.

Statistics

Nominal variables were presented as number and percentage, whereas continuous variables were presented as the median and interquartile range (IQR). The distribution of the continuous variables was performed by using the Kolmogorov-Smirnov test where appropriate. Mann-Whitney U test was applied to analyse non-normally distributed data, and Pearson's chi-square or Fisher's Exact tests were applied to examine categorical data. The p-value of <0.05 was considered significant. The IBM Statistical Package for the Social Sciences (SPSS) version 24 (Chicago, USA) was used to perform statistical analysis.

Results

We evaluated 105 older adults with AMS. Seven patients were excluded due to lack of follow-up data, and 98 patients were selected for the study. At least one cause was found to explain AMS in all patients (100.0%) who applied to the ED. The etiologies of patients with AMS were shown in Table 1.

The median age was 75.0 years (IQR: 69-85) in total patients. The median age was lower in the meningitis/encephalitis group [71.0 (66.7-77.2) vs 76.0 (70.2-84.0); p=0.03]. Fifty-seven (58.2%) included patients were female. Ninety-three (94.9%)

patients presented with comorbidities. The most common comorbidity was hypertension in 63 (64.3%) cases. Kernig's and Brudzinski's signs were assessed in 29 (29.6%) patients and were found negative. Ninety-five (96.9%) of patients underwent a neurologic assessment by neurologists. The demographics, clinical characteristics and on admission vitals of patients are presented in Table 2.

Of laboratory values taken during admission, CSF protein and CSF WBC levels were higher; CSF chloride and serum sodium levels were lower in meningitis/encephalitis patients. The CSF culture was sent from all patients, and 14 (14.3%) of patients' culture results were positive (Table 3). All bacteria grown in the culture of the other diagnoses group were skin contaminant, while *S. pneumoniae* (four patients; 15.4%), *Haemophilus influenzae* (one patient; 3.8%) and *Escherichia coli* (one patient; 3.8%) were isolated in CSF cultures of meningitis/encephalitis patients, respectively. CSF viral and CSF bacterial pathogen RT-PCR panels were obtained from 71 (72.4%) and 28 (28.6%) patients, respectively. The viral pathogen panel of 8 (8.2%) patients was positive (five patients, 5.1%, HSV-1 and three patients, 3.1%, VZV) (Supplementary Table 1). The patient with positive bacterial pathogen panel also had positive CSF culture result (one patient, 1.0%, *S. pneumoniae*). Tuberculosis tests were sent from 20 (20.4%) patients, all of them were negative.

To find the etiologies in patients with AMS, investigated in other suspected areas with imaging methods (thorax CT and abdominal imaging technics). Brain MRI showed abnormalities in patients with meningitis or encephalitis, while brain CT revealed no differences (p=0.01 vs p=0.48). In brain MRI and EEG, more pathologies suggesting infection were found in meningitis/encephalitis patients (p<0.001; p=0.009, Table 3).

The median time from admission to outcomes (i.e., discharge, intensive care unit admission, inpatient follow-up and death) was longer in the CNS infections group [17.5 days (IQR: 10.7-24.2) vs 10.5 days (IQR: 4.0-18.7)]. The admission rate to service for following-up was higher in meningitis/encephalitis patients (p=0.03), whereas patients with other diagnoses needed intensive care more frequently (p=0.02). The hospital admission rates among all patients and mortality rates among meningitis/encephalitis patients were 87.8% and 23.1% (total seven patients; six of them encephalitis, one of them meningitis), respectively (Table 3).

While the diagnosis of meningitis was made by culture results in 6 (75.0%) patients and a combination of clinical signs and symptoms, CSF findings and brain MRI in two (25.0%) patients; the diagnosis of encephalitis was made by CSF viral pathogen RT-PCR panel in 8 (44.4%) patients, brain MRI and EEG findings in 6 (33.3%) patients, and clinical signs and symptoms and CSF findings in four (22.2%) patients respectively. The patients' characteristics were summarised in Supplementary Table 1.

Discussion

In older adults, admission to the ED with AMS are frequently seen due to many conditions. Specific signs, such as fever, neck stiffness, headache and, nausea is less common in older adults with meningitis. In our study, clinical signs and symptoms different from other disorders that cause AMS were not observed in patients diagnosed with meningitis and encephalitis. Our results were coherent with other studies (10,11). In light of this, it is not possible to distinguish CNS infection in older people with AMS by only assessing signs and symptoms.

Meningitis/encephalitis patients were younger [71.0 years (IQR: 66.7-77.2) vs 76.0 years (IQR: 70.2-84.0)]. The risk of encephalitis and meningitis, and other CNS infections were increasing in individuals aged 65 years and over and had been

Table 1. Etiologies of elderly patients with AMS

Meningitis/encephalitis	n (%)	Non-infectious disorders	n (%)
Total	26/98 (26.5)	Total	39/98 (39.8)
Meningitis	8 (30.8)	Psychiatric disorders	12 (30.8)
Encephalitis	18 (69.2)	Cerebrovascular diseases	12 (30.8)
Other infections	n (%)	Kidney diseases	5 (12.8)
Total	33/98 (33.6)	Pulmonary diseases	4 (10.2)
Urinary tract infection	10 (30.3)	Cardiovascular diseases	3 (7.7)
Sepsis	8 (24.2)	Liver disease	1 (2.6)
Pneumonia	5 (15.1)	Endocrinological disorder	1 (2.6)
Viral infections	4 (12.1)	Dehidydration	1 (2.6)
Bacteremia	2 (6.1)		
Sinusitis	2 (6.1)		
Cellulitis	1 (3.0)		
Lung abscess	1 (3.0)		

Data were presented as n (%), AMS: Altered mental status

associated with worse clinical outcomes in other studies (10-13). To our knowledge, there were no other studies shown that patients who applied to the ED with AMS and were diagnosed with meningitis/encephalitis were younger.

CSF chloride [115.0 mEq/L (IQR: 114.0-121.0)] was lower whereas CSF protein [715.6 mg/dL (IQR: 421.0-1701.0)], and CSF WBC counts [0.5/microL (IQR: 0-125.0)] were higher in patients with meningitis/encephalitis. In studies, older meningitis patients had lower CSF glucose and higher median CSF WBC count and CSF protein (10,14,15). Elevated protein levels and red blood cell counts in CSF were also detected in patients with viral encephalitis (14-16). Studies have shown that lower chloride levels (<120 mEq/L) might be seen in tuberculous, cryptococcal and bacterial meningitis (17,18).

Cranial CT should be used in patients suspected of space-occupying lesions, patients with the possibility of brain herniation or according to guidelines recommendations (9,19,20). In this study, 98.0% of patients underwent cranial CT before performing LP, and there was no difference in terms of abnormalities in cranial CT between the two groups. It was

Table 2. The demographics, clinical characteristics and on admission vitals of patients

	Total 98 (100)	Meningitis/encephalitis 26 (26.5)	Other diagnoses 72 (73.5)	p-value
Median age (IQR), years	75 (69-85)	71 (66.7-77.2)	76 (70.2-84.0)	**0.03***
Female gender, n (%)	57 (58.2)	14 (53.8)	43 (59.7)	0.60†
Comorbidities, n (%)	93 (94.9)	24 (92.3)	69 (95.8)	0.61†
Hypertension	63 (64.3)	18 (69.2)	45 (62.5)	0.53†
Diabetes mellitus	34 (34.7)	9 (34.6)	25 (34.7)	0.99†
Malignancies	5 (5.1)	-	5 (6.9)	-§
Chronic lung disease	17 (17.3)	6 (23.1)	11 (15.3)	0.38†
Arrhythmia	11 (11.2)	1 (3.8)	10 (13.9)	0.28†
Coronary artery disease	27 (27.6)	9 (34.6)	18 (25.0)	0.35†
Congestive heart failure	14 (14.3)	6 (23.1)	8 (11.1)	0.19†
Chronic liver disease	4 (4.1)	2 (7.7)	2 (2.8)	0.29†
Chronic kidney disease	15 (15.3)	3 (11.5)	12 (16.7)	0.75†
History of stroke	27 (27.6)	9 (34.6)	18 (25.0)	0.38†
Alzheimer's disease	16 (16.3)	1 (3.8)	15 (20.8)	0.06†
Psychiatric disorder	5 (5.1)	1 (3.8)	4 (5.6)	0.32†
Signs and symptoms, n (%)				
Neck stiffness	11 (11.2)	1 (3.8)	10 (13.9)	0.28†
Seizure	11 (11.2)	4 (15.4)	7 (9.7)	0.47†
Headache	10 (10.2)	3 (11.5)	7 (9.7)	0.72†
Nause	12 (12.2)	3 (11.5)	9 (12.5)	1.0†
Vomiting	15 (15.3)	3 (11.5)	12 (16.7)	0.75†
Sudden weakness in body parts	9 (9.2)	2 (7.7)	7 (9.7)	1.0†
Dysuria	3 (3.1)	-	3 (4.2)	-§
Dyspnea	11 (11.2)	1 (3.8)	10 (13.9)	0.28†
Cough	8 (8.2)	4 (15.4)	4 (4.6)	0.20†
Sputum	7 (7.1)	4 (15.4)	3 (4.2)	0.08†
Soft tissue infection	2 (2.0)	-	2 (2.8)	-§
Vitals on admission, n (%)				
Fever (>38 °C)	35 (35.7)	10 (38.5)	25 (34.7)	0.73†
Arterial blood pressure (>140/80 mmHg)	33 (33.7)	9 (34.6)	24 (33.3)	1.0†
Oxygen saturation below 90%	24 (24.5)	5 (19.2)	19 (26.4)	0.47†
Intubation in ED	14 (14.3)	3 (11.5)	11 (15.3)	0.75†
Vasopressor use in ED	5 (5.1)	1 (3.8)	4 (5.6)	-§

Data were presented as median (IQR) or n (%). Differences between age groups were examined using Pearson's chi square† and Fisher's Exact† test for categorical data, and Mann-Whitney U test* was used to compare medians. §The p-value was not calculated due to the small number of patients. ED: Emergency department, IQR: Interquartile range

Table 3. The laboratory, microbiological, imaging findings and outcomes of patients				
	Total 98 (100)	Meningitis/encephalitis 26 (26.5)	Other diagnoses 72 (73.5)	p-value
Laboratory parameters				
CSF sodium (mEq/L)	144.7 (142.0-148.8)	143.6 (141.6-145.8)	145.0 (142.3-149.0)	0.18*
CSF chloride (mEq/L)	120.0 (116.0-124.5)	115.0 (114.0-121.0)	122.0 (118.0-127.2)	**<0.001***
CSF glucose (mg/dL)	75.0 (59.0-98.5)	73.0 (49.2-108.2)	76.0 (63-93)	0.52*
CSF LDH (U/L)	30.0 (22.5-44.5)	32.0 (18.0-77.7)	29.0 (23.0-44.0)	0.83*
CSF protein (mg/dL)	544.0 (378.2-799.1)	715.6 (421.0-1701.0)	496.1 (360.8-762.5)	0.03*
CSF cell count, n (%)	92/98 (93.9)	26/26 (100.0)	66/72 (91.7)	
Positive WBC count (>5 cell/mL)	22 (23.9)	11 (42.3)	11 (16.7)	**0.009†**
WBC count (microL)	0 (0-3.5)	0.5 (0-125.0)	0 (0-0)	**0.001***
Positive RBC count (cell/mL)	57 (58.2)	18 (69.2)	39 (59.1)	0.37†
RBC count (microL)	30.0 (0-240.0)	35.0 (0-382.5)	0 (0-242.5)	0.60*
Serum sodium (mEq/L)	139.0 (136.0-142.0)	137.0 (132.7-140.0)	139.0 (136.0-143.0)	**0.01***
Serum glucose (mg/dL)	135.0 (104.7-176.5)	141.0 (108.7-200.7)	134.0 (101.2-163.7)	0.22*
Serum chloride (mEq/L)	14.0 (14.3)	103.0 (101.0-106.2)	105 (100-114)	0.32*
Serum protein (g/L)	63.0 (58.0-68.2)	65.0 (58.0-71.0)	63.0 (58.0-67.0)	0.23*
Aspartate transaminase (U/L)	30.0 (21.0-46.2)	25.0 (20.5-44.2)	33.0 (21.0-49.0)	0.26*
Alanine transaminase (U/L)	20.5 (15.0-34.5)	20.5 (15.0-47.0)	20.5 (15.0-32.7)	0.32*
LDH (U/L)	285.5 (232.0-338.2)	276.5 (219.2-381.7)	286.5 (233.0-334.2)	0.92*
Creatinine (mg/dL)	1.05 (0.80-1.56)	0.95 (0.73-1.22)	1.15 (0.85-1.64)	0.87*
WBC ($x10^9$/L)	10.4 (8.1-15.1)	9.4 (7.9-19.2)	10.6 (8.2-14.7)	0.79*
Lymphocyte ($x10^9$/L)	1.2 (0.7-1.6)	1.2 (1.0-1.7)	1.1 (0.7-1.6)	0.09*
CRP (mg/L)	38.5 (13.8-97.1)	34.7 (4.7-105.7)	43.5 (17.0-100.4)	0.27*
Procalcitonin (µg/L)	0.14 (0.05-1.09)	0.10 (0.03-0.44)	0.20 (0.06-1.31)	0.09*
WBC in urine (p/HPF), n (%)	33/90 (36.7)	8/24 (33.3)	25/66 (37.9)	0.69†
Cultures, n (%)				
Positive urine culture	24/58 (42.1)	6/16 (37.5)	18/42 (42.9)	0.66†
Positive blood culture	15/61 (24.6)	3/19 (15.8)	12/42 (28.6)	0.35†
Positive sputum culture	6/12 (50.0)	0/1 (0.0)	6/11 (54.5)	1.0†
Positive CSF culture	14/98 (14.3)	6/26 (7.7)	8/72 (11.1)	0.19†
Imaging, n (%)				
Cranial CT taken	96/98 (98.0)	26/26 (100.0)	70/72 (97.2)	1.0†
haemorrhage	4 (4.2)	1 (3.8)	3 (4.3)	-§
Old infarction area	22 (22.9)	4 (15.4)	18 (25.7)	-§
Acute ischemic stroke	7 (7.3)	2 (7.7)	5 (7.1)	-§
Mass	2 (2.1)	1 (3.8)	1 (3.8)	-§
Normal	61 (63.5)	18 (69.2)	43 (61.4)	0.48†
Cranial CT suggests infection	-	-	-	NA
Brain MRI taken	82/98 (83.7)	23/26 (88.5)	59/72 (81.9)	0.55†
Diffusion restriction	14 (17.1)	6 (26.1)	8 (13.6)	-§
Meningeal enhancement	5 (6.1)	2 (8.7)	3 (5.1)	-§
Encephalitis	5 (6.1)	4 (17.4)	1 (1.7)	-§
Haemorrhage	1 (1.2)	-	1 (1.7)	-§
Normal	56 (68.3)	11 (47.8)	45 (76.3)	**0.01†**

Table 3. Continued

	Total 98 (100)	Meningitis/encephalitis 26 (26.5)	Other diagnoses 72 (73.5)	p-value
EEG suggesting infection	8/20 (40)	6/8 (75.0)	2/12 (16.7)	**0.009‡**
Abnormal findings on thorax CT	27/77 (35.1)	4/19 (21.0)	23/58 (39.7)	0.09†
Abnormal findings on abdominal imaging	1/38 (2.6)	0/11 (0.0)	1/27 (3.7)	-§
The time from admission to outcomes (IQR), days	12.0 (5.7-20.0)	17.5 (10.7-24.2)	10.5 (4.0-18.7)	**0.009***
Outcomes, n (%)	98 (100)	26 (26.5)	72 (73.5)	
Discharge	12 (12.2)	1 (3.8)	11 (15.3)	0.17†
ICU admission	54 (55.1)	11 (42.3)	43 (59.7)	**0.02‡**
Inpatient follow-up	32 (72.7)	14 (93.3)	18 (62.1)	**0.03‡**
Death	26 (25.5)	7 (26.9)	19 (26.4)	0.74†

Data were presented as median (IQR) or n (%). Differences between age groups were examined using Pearson's chi-square† and Fisher's Exact test‡ for categorical data, and Mann-Whitney U test* was used to compare medians. §The p-value was not calculated due to the small number of patients. LDH: Lactate dehydrogenase, CSF: Cerebrospinal fluid, WBC: White blood cell, RBC: Red blood cell, CRP: C-reactive protein, MRI: Magnetic resonance imaging, EEG: Electroencephalogram, CT: Computed tomography, NA: Not applicable

probably related to the overuse of CT scan and its inability to detect early cerebral changes in viral encephalitis. However, the detection of space-occupying lesions in only 2.1% of the patients in cranial CT scan results reminded us that more rational behavior should be considered in the selection of this imaging method, and that both time and cost-effectiveness should be considered. Management of the patients in line with the recommendations of the guidelines seem to be a more correct approach when choosing CT imaging. On the other hand, unlike our research, many other studies have shown abnormalities on cranial CT scan in patients with encephalitis and meningitis (10,16,21).

Pathological changes were detected in brain MRI in meningitis and encephalitis patients. In encephalitis patients, especially brain MRI and EEG findings may be helpful for diagnosis in our study. These results were similar to the literature; MRI and EEG were significantly more sensitive than brain CT for detecting viral encephalitis (10,16,21,22).

Looking at the outcomes of our study, patients with meningitis and encephalitis were followed-up more in the ward, the need for intensive care developed more frequently in the other diagnoses group, possibly due to exacerbation of the underlying disease and clinical risk factors associated with higher mortality rates such as sepsis, pneumonia, and cerebrovascular diseases. The mortality rate was 26.9% in older patients with CNS infection; results ranged from 14.0% (23) to 28.4% (24) in earlier studies. In addition, the median duration of hospital stay was found to be longer in patients with CNS infection [17.5 days (IQR: 10.7-24.2) vs 10.5 days (IQR: 4.0-18.7)], probably due to extended antibiotic or antiviral treatment duration, and arrangements need to be made to return to daily life.

There are not many studies evaluating the etiologies of AMS in older patients who underwent LP in ED admissions regarding to CNS infections. In the previous studies, all infectious causes were given without specifying age groups (25-27) or etiologies of AMS in older patients (5,28). Our study found infectious causes in 60.2% of the older patients with AMS who underwent LP; meningitis and encephalitis were present in 26.5% of the patients. The reasons for this high infectious causes rate compared to previous studies might be the advanced age of the patients, a low number of the study population, and consultation of ID specialists of patients with suspected infectious etiologies.

53.8% (14 patients) of meningitis and encephalitis patients were diagnosed based on microbiological methods. CSF analysis and imaging methods were required to diagnose older patients properly. This difficulty in diagnosing has been reported in other studies (22,23,29).

Study Limitations

Our findings should be interpreted in the light of several limitations. Single-center and retrospective study with a limited number of patients and lack of other CNS infections in the study population seem to be the main limitations. Also, malnutrition status and frailty in patients were not evaluated. These may have affected the study results. However, the advantage of the study was that older patients with AMS was evaluated by ID specialists and emergency care physicians in the ED. In this way, the diagnosis of CNS infection was made accurately, and the patients were evaluated by both specialists in terms of other foci of infections.

Conclusion

AMS is a challenging diagnosis in older patients admitted to ED and has many etiologies. Since these patients' first point of contact is ED, making an early and accurate diagnosis and prompt appropriate treatment is essential. Physical examination, clinical

signs and symptoms, CSF analysis and imaging methods may all need to be used as diagnostic work-up for urgent stabilization and initiation of treatments.

Ethics

Ethics Committee Approval: This study was approved by the Medical and Health Research Ethics Committee of Ankara City Hospital (date: 09/06/2021, number: 1756).

Informed Consent: Informed consent was not obtained because of retrospective nature of the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ç.M.A., F.M.G., Ö.A., Concept: Ç.M.A., S.C., Design: Ç.M.A., S.C., Data Collection or Processing: Ç.M.A., F.M.G., Ö.A., Analysis or Interpretation: Ç.M.A., F.M.G., Ö.A., R.G., Literature Search: Ç.M.A., S.C., R.G., Writing: Ç.M.A., S.C., R.G.

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Supplementary Table 1. Characteristic of meningitis and encephalitis patients

Meningitis	Age/ gender	Co-morbid conditions	Presenting symptoms	CSF analyses	CSF culture result	Blood test results	Head CT	Brain MRI	Outcome
Patient 1	66/F	DM, HT, CAD, CKD, asthma	Fever, nausea, vomiting	Glucose: 1 mg/dL, protein: 3.337 mg/dL, WBC: 1.025 microL	*Streptococcus pneumoniae*	Glucose: 109 mg/dL, WBC: $2.4x10^9$/L, CRP: 85 mg/dL	Normal	Normal	Dead
Patient 2	65/F	DM, HT, psychiatric disorder	-	Glucose: 4 mg/dL, protein: 4.954 mg/dL, WBC: 1.000 microL	*Streptococcus pneumoniae*	Glucose: 215 mg/dL, WBC: $24.7x10^9$/L, CRP: 403 mg/dL	Normal	Diffusion restriction	Alive
Patient 3	70/M	HT, CAD	Neck stiffness	Glucose: 1 mg/dL, protein: 6447 mg/dL, WBC: 640 microL	*Streptococcus pneumoniae*	Glucose: 171 mg/dL, WBC: $19.5x10^9$/L, CRP: 237 mg/dL	Normal	Normal	Alive
Patient 4	71/M	HT, CAD	Fever, headache, cough	Glucose: 4 mg/dL, Protein: 1982 mg/dL, WBC: 100 microL	*Streptococcus pneumoniae*	Glucose: 96 mg/dL, WBC: $30.1x10^9$/L, CRP: 59 mg/dL	Old parenchymal haemorrhage	Normal	Alive
Patient 5	65/M	DM, HT, CAD	-	Glucose: 86, protein: 561 mg/dL, WBC: 8 microL	*Haemophilus influenza*	Glucose: 119 mg/dL, WBC: $8.96x10^9$/L, CRP: 4 mg/dL	Normal	Normal	Alive
Patient 6	67/M	DM, HT, stroke history	-	Glucose: 106 mg/dL, protein: 267 mg/dL, WBC: 40 microL	*Escherichia coli*	Glucose: 193 mg/dL, WBC: $22.1x10^9$/L, CRP: 183 mg/dL	Old infarction area	Diffusion restriction	Alive
Patient 7	67/M	DM, HT, COPD	Fever, headache, nausea, vomiting	Glucose: 21 mg/dL, protein: 2369 mg/dL, WBC: 540 microL	Negative	Glucose: 176 mg/dL, WBC: $13.0x10^9$/L, CRP: 74 mg/dL	Mass	-	Alive
Patient 8	65/F	HT	Fever, seizure	Glucose: 74 mg/dL, protein: 201 mg/dL, WBC: 10 microL	Negative	Glucose: 126 mg/dL, WBC: $6.3x10^9$/L, CRP: 40 mg/dL	Normal	Diffuse pachymeningeal hyperintensity	Alive
Encephalitis	**Age/ gender**	**Co-morbid conditions**	**Presenting symptoms**	**CSF analyses**	**CSF RT-PCR result**	**Head CT**	**Brain MRI**	**EEG**	**Outcome**
Patient 1	77/F	DM, HT	-	Glucose: 147 mg/dL, protein: 722 mg/dL, WBC: 200 microL, RBC:0 microL	*HSV-1*	Normal	Diffusion restriction	-	Dead
Patient 2	68/F	HT, heart failure, stroke history	-	Glucose: 115 mg/dL, protein: 303 mg/dL, WBC: 0 microL, RBC: 0 microL	*HSV-1*	New infarction area	Compatible with encephalitis	-	Dead
Patient 3	65/M	-	Fever, vomiting, cough	Glucose: 77 mg/dL, protein: 438 mg/dL, WBC: 30 microL, RBC: 10 microL	*HSV-1*	Normal	Compatible with encephalitis	Epileptiform activity	Alive
Patient 4	77/M	HT, CAD	-	Glucose: 72 mg/dL, protein: 302 mg/dL, WBC: 0 microL, RBC: 20 microL	*HSV-1*	Normal	Diffusion restriction	Epileptiform activity	Alive

Supplementary Table 1. Continued

Meningitis	Age/ gender	Co-morbid conditions	Presenting symptoms	CSF analyses	CSF culture result	Blood test results	Head CT	Brain MRI	Outcome
Patient 5	72/M	Stroke history	Fever, focal neurologic deficit	Glucose: 57 mg/dL, protein: 847 mg/dL, WBC: 200 microL, RBC: 0 microL	*HSV-1*	Normal	Compatible with encephalitis	Epileptiform activity	Alive
Patient 6	86/M	HT, COPD, heart failure, stroke history	-	Glucose: 52 mg/dL, protein: 544 mg/dL, WBC: 0 microL, RBC: 1.600 microL	*VZV*	Normal	Diffusion restriction	-	Dead
Patient 7	101/F	Heart failure, CKD	Dyspnea	Glucose: 105 mg/dL, protein: 746 mg/dL, WBC: 0 microL, RBC: 0 microL	*VZV*	Normal	-	-	Dead
Patient 8	75/F	DM, heart failure, asthma, stroke history	Fever	Glucose: 151 mg/dL, protein: 976 mg/dL, WBC: 0 microL, RBC: 1.000 microL	*VZV*	Old infarction area	Normal	-	Alive
Patient 9	80/M	HT, CAD, stroke history	Fever, focal neurologic deficit	Glucose: 87 mg/dL, protein: 709 mg/dL, WBC: 2 microL, RBC: 200 microL	-	Normal	Diffusion restriction	Compatible with encephalitis	Alive
Patient 10	71/M	DM, HT, CAD, arrhythmia, asthma	-	Glucose: 83 mg/dL, protein: 1070 mg/dL, WBC: 0 microL, RBC: 120 microL	Negative	Old infarction area	Compatible with encephalitis	-	Dead
Patient 11	78/F	DM, HT, CAD	Seizure	Glucose: 173 mg/dL, protein: 1.607 mg/dL, WBC: 1 microL, RBC: 83 microL	Negative	Normal	Normal	Compatible with encephalitis	Alive
Patient 12	69/F	HT, CKD	-	Glucose: 54 mg/dL, protein: 547 mg/dL, WBC: 0 microL, RBC: 0 microL	Negative	Normal	Prosthesis	Compatible with encephalitis	Alive
Patient 13	71/M	DM, HT, CAD, stroke history	Seizure	Glucose: 159 mg/dL, protein: 368 mg/dL, WBC: 0 microL, RBC: 80 microL	Negative	Normal	Compatible with encephalitis	Epileptiform activity	Dead
Patient 14	85/F	HT	Fever, cough	Glucose: 60 mg/dL, protein: 545 mg/dL, WBC: 0 microL, RBC: 0 microL	Negative	Normal	Normal	Compatible with encephalitis	Alive
Patient 15	76/F	CAD, heart failure, arrhythmia	-	Glucose: 62 mg/dL, protein: 681 mg/dL, WBC: 0 microL, RBC: 1.000 microL	Negative	Old infarction area	Normal	-	Alive

Supplementary Table 1. Continued

Meningitis	Age/ gender	Co-morbid conditions	Presenting symptoms	CSF analyses	CSF culture result	Blood test results	Head CT	Brain MRI	Outcome
Patient 17	65/F	-	Focal neurologic deficit	Glucose: 41 mg/dL, protein: 918 mg/dL, WBC: 0 microL, RBC: 0 microL	Negative	Normal	Normal	-	Alive
Patient 18	91/F	Stroke history, Alzheimer's disease	Fever, cough	Glucose: 64 mg/dL, protein: 1.100 mg/dL, WBC: 32 microL, RBC: 2 microL	Negative	Old infarction area	Normal	-	Alive

CSF: Cerebrospinal fluid, CT: Computed tomography, MRI: Magnetic resonance imaging, F: Female, M: Male, DM: Diabetes mellitus, HT: Hypertension, CAD: Coronary artery disease, CKD: Chronic kidney disease, WBC: White blood cell, CRP: C-reactive protein, COPD: Chronic obstructive pulmonary disease, RT-PCR: Real-time polymerase chain reaction, EEG: Electroencephalography, HSV-1: Herpes simplex virus-1, VZV: Varicella zoster virus, RBC: Red blood cell