Meningitis, Meningoencephalitis and Encephalitis in Bern: an observational study of 258 patients

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Abstract

Background

Depending on geographic location causes of encephalitis, meningoencephalitis and meningitis vary substantially. We aimed to identify most frequent causes, clinical presentation as well as long-term outcome of encephalitis, meningoencephalitis and meningitis cases treated in the Inselspital, University Hospital Bern, Switzerland.

Methods

In this monocentric, observational retro- and prospective cohort study, we performed a retrospective review of clinical patient records for all patients treated during 3 years. Patients were contacted prospectively for a telephone follow-up interview and to fill out questionnaires, especially related disturbances of sleep and wakefulness.

Results

We included 258 patients: encephalitis (18%), non-bacterial meningoencephalitis (42%), non-bacterial meningitis (27%) and bacterial meningoencephalitis/meningitis (13%). Herpes simplex virus (HSV) was the most frequent cause of encephalitis (18%), tick borne encephalitis virus (TBEV) of non-bacterial meningoencephalitis (46%), enterovirus of non-bacterial meningitis (21%) and *Streptococcus pneumoniae* of bacterial meningoencephalitis/meningitis (49%). Overall, 35% patients remained without known cause. After a median time of 16 months, 162 patients participated in the follow-up interview, thereof 56% indicated to suffer from neurological long-term sequels such as fatigue and/or excessive daytime sleepiness (34%), cognitive impairment and memory deficits (22%), headache (14%) and epileptic seizures (11%).

Conclusions

In the largest tertiary care University hospital in Switzerland TBEV was the overall most frequently detected infectious cause, with a clinical manifestation of meningoencephalitis in the majority of cases. Long-term neurological sequels, most importantly cognitive impairment, fatigue and headache were frequently self-reported not only in encephalitis and meningoencephalitis but also viral meningitis survivors up to 40 months after the acute infection.

Introduction

Encephalitis/meningoencephalitis is an inflammation of the brain parenchyma with or without involvement of the meningeal structures. Meningitis is either a severe acute bacterial infection or less fulminant of viral origin [1, 2]. Despite being a serious and life threatening disease, mostly associated with long term morbidity, the incidences of encephalitis remain poorly documented - varying between 1 and 14 documented cases per 100.000 inhabitants[3–5]. The most common infectious pathogens vary depending on the geographical region: in Switzerland, tick-borne encephalitis virus (TBEV) is one of the most frequent causes of meningoencephalitis [6], whereas in the United Kingdom, herpes simplex virus (HSV) is the most common infectious cause of encephalitis[3]. Other cases of encephalitis are caused by infectious agents including varicella zoster virus (VZV) and *Mycobacterium tuberculosis* or by cellular or humoral autoimmune processes[3]. In up to 37–67% of patients the cause of encephalitis remains unknown[3–5, 7]. Similarly, in a large observational cohort study from the United Kingdom of non-bacterial meningitis cases, 42% remained without known cause, whereas enterovirus was the most common pathogen[1].

Infectious encephalitis and meningoencephalitis are associated with a high incidence of severe and debilitating long-term sequelae, whereas outcome after autoimmune encephalitis is variable[8–12]. In contrast, viral meningitis is considered a benign, self-limiting illness, however increasing evidence suggest that this may often not be the case[1]. Especially signs and symptoms such as fatigue, excessive daytime sleepiness (EDS) or disturbed night time sleep/insomnia remain understudied despite being frequently reported in clinical routine follow up consultations.

The aims of our study were to (1) determine the most common causes of encephalitis, meningoencephalitis and meningitis in the largest tertiary care university hospital group and to (2) investigate frequency of long-term sequelae with a focus on disorders of sleep and wakefulness (SWD).

Methods

The study was designed as a monocentric, observational retro- and prospective cohort study and contained two parts: First, a retrospective analysis of medical records from all patients diagnosed for any acute encephalitis, meningoencephalitis or meningitis treated in the largest tertiary care university hospital with a population base of 1.5 million inhabitants, the University Hospital Bern, Inselspital. Ethical approval was given by the local Ethics Committee (Kantonale Ethikkommission Bern ID 2018-01523). Research governance approval was given at the University Hospital Inselspital, Bern, Switzerland. Medical records were only used if a written general consent for research projects were available or if patients gave oral and written informed consent in the course of the telephone interview. In the second part, patients were contacted prospectively for a telephone follow-up interview and were asked to fill out and return questionnaires by mail. Oral informed consent was given on telephone interview, written informed consent was obtained from patients returned by mail.

Study database

Study data were collected and managed using REDCap electronic data capture tools hosted at the department of Neurology, University Hospital and University of Bern, Inselspital, Bern, Switzerland[13, 14]. REDCap (Research Electronic Data Capture) is a secure, web-based software platform designed to support data

capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources.

Participants and study procedures

Possible and consecutive participants were retrospectively identified in the time from 1.1.2016 until 31.10.2018 by screening the medical record database of the University Hospital Inselspital for ICD-10 Codes A83, A84, A85, B00.4, B01.0, B02.0, B05.0, B26.2, B58.2, G04, G05 referring to all possible causes of encephalitis, meningoencephalitis or meningitis. Patients were either treated at the Department of Internal Medicine, Department of Neurology and/or the Intensive Care Unit.

Patients were eligible if aged 16 and older and had a diagnosis of encephalitis, meningoencephalitis or meningitis in their medical record, confirmed by lumbar puncture with signs of acute inflammation and/or appropriate pathogen identified either on cerebrospinal fluid (CSF) or blood PCR, serology or culture. Diagnosis was reviewed and if necessary revised by two neurologists (A.D. and A.U.) according to published definitions[1, 8, 15]. In detail, patients with acute onset of headache, fever and/or meningism, CSF leucocyte count >4x10^6 cells per L and if possible detection of an appropriate pathogen by either CSF PCR, blood/CSF serology or blood/CSF culture or throat or rectal swab were classified as meningitis[1]. Meningoencephalitis was classified when signs of meningitis were present plus altered consciousness, and/or focal neurological symptoms, and/or abnormal findings in EEG[8]. Encephalitis was defined as altered consciousness for >24 h with no other cause and evidence of CNS inflammation, demonstrated by at least two of the following criteria: fever, seizures or focal neurological findings attributable to the brain parenchyma, CSF pleocytosis (CSF leucocyte count >4x10^6 cells per L), EEG findings suggestive of encephalitis and/or neuroimaging findings suggestive of encephalitis[15]. Preexisting diseases, immune suppressive state as well as signs and symptoms pre- and in hospital were taken from the medical record. Furthermore, findings in the neurological examinations, laboratory findings and microbiological results were taken from the clinical record. At hospital discharge a modified Rankin score (mRS) was taken from the clinical record if available or calculated as described in the clinical record.

Follow-up

Clinical outcome and subjective long-term sequelae were assessed with a standardized interview via telephone from October 2019 until February 2020. Following questionnaires were sent out immediately after the telephone interview to the study participants evaluating sleep-wake-disorders including a set of individual questions regarding SWD, Epworth Sleepiness Scale(ESS)[16], Fatigue Severity Scale(FSS)[17], Insomnia Severity Index(ISI)[18], Beck Depression Inventory II (BDI II)[19]. Cut-offs for pathological scores were set according to literature: ESS >9, FSS >4, ISI > 7, BDI II > 8. Four questions regarding restless legs syndrome (RLS) were included according to diagnostic consensus criteria[20].

Statistical Analysis

Non-parametric continuous data were analyzed by using Kruskal-Wallis tests. Categorical data were analyzed by using c^2 test. Correlation R values were obtained using Pearson Correlation. A *p* value of less than 0.05 was considered statistically significant. Missing data were not imputed. We statistically analysed data using Stata/MP 16.0 and R 3.6.1, graphs were drawn by Graphpad Prism 8, Stata/MP 16.0 and R 3.6.1.

Availability of data and materials

Anonymized data will be shared on request from qualified investigators.

Results

From a total number of 463 screened patient's medical records 258 patients were included in the retrospective analysis of the study (figure 1).

Distribution of diagnoses and causes

In total, as shown in table 1, during the 34 months period 258 patients were treated for encephalitis (46, 18%), non-bacterial meningoencephalitis (109, 42%), non-bacterial meningitis (70, 27%) or bacterial meningoencephalitis/meningitis (33, 13%).

As shown in table 2, most frequent causes overall were of infectious origin (57%), in 5% an immune-mediated cause was found, 36% remained without known cause.

TBEV was the most frequently detected cause of meningoencephalitis or meningitis (65/258 cases, 25%) in our overall patient population, thereof 58 (89%) presented as meningoencephalitis (including 9 cases of meningoencephalomyelitis and meningoencephalomyeloradiculitis), 6 (9%) as meningitis and 1 (2%) classified as encephalitis. In the group of meningoencephalitis, 6 patients were classified as meningoencephalomyelitis (causes: 2 VZV and 4 TBE) and 7 as meningoencephalomyeloradiculitis (causes: 5 TBE, 1 unknown and 1 suspected parainfectious cause with *Bartonella henselae* infection). In the group of encephalitis, in 13/46 (28%) patients an autoimmune cause was found. Recurrent meningitis was seen in 4 patients.

Clinical presentation

As shown in detail in table 1, median time from onset of signs and symptoms until hospital admission was 5.5 days in encephalitis, 7 days in non-bacterial meningoencephalitis, 4 days in non-bacterial meningitis and shortest with 2 days in bacterial meningoencephalitis/meningitis.

Follow-up

The telephone follow-up interview took place at median 16 months (range 2-40 months) after hospital discharge (supplementary table 1). All interviewed patients were living at home, and the majority (96-100%) were able to cook their own meal, do the laundry, use public transport unaided independently of the diagnostic group. However, only 50% of encephalitis, 75% of bacterial meningoencephalitis/meningitis, 81% of non-bacterial meningoencephalitis and 94% of non-bacterial meningitis survivors were able to restart work or studies in the same extent compared to before the acute illness. Overall, 37% of patients indicated not feeling completely fit again (respectively encephalitis 65%, non-bacterial meningoencephalitis 39%, non-bacterial meningitis 16%, bacterial meningoencephalitis/meningitis 53%). When asked whether to still feel more rapidly exhausted physically or mentally compared to before the acute illness 47% of patients agreed (respectively encephalitis 70%, non-bacterial meningoencephalitis 45%, non-bacterial meningitis 32%, bacterial meningoencephalitis/meningitis 71%).

Persisting neurological manifestations were reported by 56% of patients irrespectively of elapsed time since acute illness (respectively encephalitis 83%, non-bacterial meningoencephalitis 54%, non-bacterial meningitis 42%, bacterial meningoencephalitis/meningitis 71%, supplementary table 1). The most frequent manifestations were EDS and/or fatigue (34%, 95% CI 27-41, supplementary figure 1), cognitive impairment (22%; 29-16), headache (14%; 9-20) and epileptic seizures (11%; 6-16). Regarding headache, 9% (4-13) indicated to suffer from headache less than 15 days per months and 6% (2-9) more than 15 days per months.

Follow-up questionnaires

Overall 97 patients returned questionnaires (figure 2), including the Epworth Sleepiness Score (ESS), Fatigue Severity Score (FSS), Insomnia Severity Index (ISI) and Beck Depression Index II (BDI II). Overall, proportions of pathological scores were: 23% (95% CI 15-32) for ESS (cutoff >10), 24% (16-33) for FSS (cutoff >4), 40% (31-50) for ISI (cutoff >7) and 31% (23-41) for BDI II (cutoff >8). Proportion of pathological scores were not statistically significant different between groups (ESS p = 0.258, FSS p = 0.06 ISI p = 0.403, BDI II p = 0.077). Time since hospital discharge did not significantly influence any score value (ESS R=0.0002, 95% CI -0.86-0.1, p=0.885; FSS R=0, 95% CI -0.04-0.04, p=0.967; ISI R=0.012, 95% CI -0.206-0.061, p=0.285; BDI II R=0.0001, 95% CI -0.148-0.16, p=0.08).

In a set of questions regarding SWD 39% and 42% (95% CI 30-49 and 33-52 respectively) indicated to suffer from EDS (agreed to questions: "I am tired during the day and I have to fight to stay awake and against sleeping in" and "It happens frequently, that I am forced to take a nap."). However, 54% (95% CI 44-63) also indicated to suffer from fatigue (agreed to question: "During the day I feel exhausted and tired, however I am not able to sleep in when given a possibility to nap."). New onset of daytime SWD such as fatigue and EDS since suffering from the acute illness was indicated by 25% (95% CI 17-34), 33% (24-43) indicated to have been suffering from the same problems already before the acute illness and 42% (33-52) couldn't indicate clear onset of fatigue or EDS.

Overall, 22 patients out of 97 answered all 4 diagnostic RLS questions positively and accordingly fulfilling diagnostic criteria of RLS. Thereof 12 patients indicated, to have experienced new onset of RLS since the acute illness.

Five out of 97 patients indicated to have new onset of hypnogogic or hypnopompic hallucinations since the acute illness. No patient reported new onset of episodes indicating REM-sleep behavior, sleep paralysis or cataplexy since surviving the acute illness.

Discussion

There were three main findings in this study: First, in the largest tertiary care university hospital in Switzerland, TBEV is the most important overall infectious cause of encephalitis, meningoencephalitis and meningitis, presenting as meningoencephalitis in the majority of patients. Second, only one third of patients remain without a detectable cause of acute illness. Third, neurologic sequelae, most importantly cognitive impairment, fatigue and headache were self-reported in a significant proportion not only of encephalitis, meningoencephalitis and bacterial meningitis survivors but also non-bacterial meningitis patients up to 40 months after surviving the acute illness.

HSV was the most common cause of encephalitis, followed by immune-mediated causes. Therefore, together with VZV encephalitis, almost three quarter of our encephalitis cases had a treatable cause. Depending on geographic location these findings are in line with other European countries[1, 3, 21, 22]. While early detection and treatment of herpes encephalitis is essential for prevention of fatal outcome[23], also recognition of autoimmune causes is of utmost importance since they belong to an expanding group of potentially treatable and curable causes of encephalitis and require immediate immunosuppressive treatment regimens[24, 25]. Non-bacterial meningoencephalitis was most importantly caused by TBEV, since it is endemic in most parts of Switzerland with an estimated incidence of 6.63 cases per 100,000 inhabitants in 2020[26]. In line with large European studies, *Streptococcus pneumoniae* was the main detected cause of bacterial meningitis/meningoencephalitis[2]. Finally, in line with other studies including a large cohort study from the United Kingdom[1], enterovirus were the most important cause of non-bacterial meningitis.

At follow up – independently of elapsed time of up to 40 months after acute illness – more than a third of patients indicated to have not regained full fitness and more than half complained about neurological sequelae, despite functioning well in everyday activities such as cooking, doing laundry and financial affairs. However, only half of encephalitis, 75% of bacterial meningitis/meningoencephalitis, 82% of meningoencephalitis and 94% of non-bacterial meningitis patients were able to continue their work. Comparable findings have been described for encephalitis and meningoencephalitis, including TBE[10, 11, 27]. Our results are also in line with studies on viral meningitis, demonstrating long lasting sequelae despite its ostensibly benign course[1, 28–30].

To our knowledge, our study is the first to apply standardized questionnaires on EDS, fatigue and insomnia in the field of encephalitis, meningoencephalitis and meningitis. In our study, especially EDS and/or fatigue was frequently reported in the follow up, however, a precise discrimination between the two clinically different symptoms was not possible. Insomnia/disturbed night-time sleep was less frequently reported.

Limitations of our study are the retrospective analysis of clinical cases in the acute phase with less precise data on clinical signs and symptoms and therefore diagnostic classification. Furthermore, the telephone follow up may have introduced a bias towards survivors with better outcome, since it is mostly not possible to contact severely disabled patients via telephone – potentially accounting for our number of lost-for follow up patients. Therefore, it has to be postulated that the true overall outcome of our full study population may be worse than described in our study. The relative low return rate of questionnaires might introduce a response bias. Moreover, via telephone interview, we can only rely on subjective signs and symptoms and no objective examination (e.g. neurological examination) took place to underline the subjective complaints. The lack of discrimination between EDS and fatigue might be due to the nature of a telephone interview and could be easily clarified and specified in a personal follow-up consultation. In future prospective studies this point needs to be further addressed. Unfortunately, patients were not asked to fill out life-quality questionnaires, which would have better reflected the general impact of persisting signs and symptoms on everyday life.

Future prospective studies should resume standardized investigation of sleep-wake disorders as well as impact of sequelae on life quality and professional life.

With this retro- and prospective cohort study including 285 patients, we demonstrate the importance of TBEV as the major cause of encephalitis, meningoencephalitis and meningitis cases in our geographic region and its primary clinical presentation as meningoencephalitis. Furthermore, we were able to assess long-lasting neurological sequelae not only after encephalitis, meningoencephalitis or bacterial meningitis but also after non-bacterial meningitis in a relevant proportion of patients up to 40 months post infection.

Declarations

Ethics approval

Kantonale Ethikkommission Bern ID 2018-01523

Consent to participate

Retrospective data was used if a written general consent was available, all participants of the prospective part of the study gave written informed consent or agreed to the general consent.

Availability of data and material

Anonymized data will be shared on request from qualified investigators.

Conflict of Interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

Study Funding

Authors' Contributions:

Anamaria Ungureanu: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis and interpretation of data

Julia van der Meer: Revision of the manuscript for content, including medical writing for content; Analysis and interpretation of data

Antonela Bicvic: Revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data

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Franziska Suter-Riniker: Revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept

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Claudio L. A. Bassetti: Revision of the manuscript for content, including medical writing for content; Study concept or design; Interpretation of data

Anelia Dietmann: Drafting and revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept and design; Analysis and interpretation of data

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Tables

Table 1 Demographics and clinical signs and symptoms

	All	Encephalitis	Non-bacterial Meningo-encephalitis	Non-bacterial Meningitis	Bacterial Meningoencephalitis or Meningitis	p value°
Total n (%)	258 (100)	46 (17.8)	109 (42.2)	70 (27.1)	33 (12.8)	
Sex female n (%)	126 (48.8)	18 (39.1)	53 (48.6)	41 (58.6)	14 (42.4)	0.18
Median age (IQR)	51.5 (33)	60 (24)	56 (36)	38 (28)	53 (19)	<0.0001
Median days from clinical onset to hospital admission (IQR)	5 (8)	5.5 (18)	7 (10)	4 (5)	2 (5)	<0.0003
Symptoms or clinical signs						
Headache*	183 (71, 65-76)	12 (26, 15-41)	85 (78, 69-85)	63 (90, 80-95)	23 (70, 52-83)	
Fever	150 (58, 52-64)	17 (37, 24-52)	73 (67, 58-75)	38 (54, 42-66)	22 (67, 49-81)	
Meningism	77 (30, 25-36)	2 (4, 1-16)	29 (27, 19-36)	27 (39, 28-50)	19 (58, 40-73)	
Photo-/Phonophobia	47 (18, 14-23)	0 (0)	16 (15, 9-23)	27 (39, 9-23)	4 (12, 5-28)	
Nausea/vomiting	98 (38, 32-44)	8 (17, 9-31)	40 (37, 28-46)	40 (57, 45-68)	10 (30, 17-48)	
Epileptic Seizures	73 (29, 23-34)	27 (59, 44-72)	32 (29, 22-39)	2 (2, 1-11)	12 (36, 22-54)	
Sensory/motor deficits	66 (26, 21-31)	12 (26, 15-41)	38 (35, 27-44)	7 (10, 5-20)	9 (27, 15-45)	
Confusion	74 (29, 24-35)	27 (59, 44-72)	31 (28, 21-38)	6 (9, 4-18)	10 (30, 17-48)	
Cognitive impairment	70 (27, 22-33)	24 (52, 38-66)	36 (33, 25-42)	4 (6, 2-14)	6 (18, 8-35)	
Abnormal behavior	53 (21, 16-26)	23 (50, 36-64)	23 (21, 14-30)	3 (4, 1-13)	4 (12, 5-28)	
Aphasia	55 (21, 17-27)	16 (35, 23-50)	35 (32, 24-42)	0 (0)	4 (12, 5-28)	
Vertigo	48 (19, 14-24)	9 (19, 11-34)	28 (26, 18-35)	9 (13, 7-23)	2 (6, 2-21)	
Gait disturbance	45 (17, 13-23)	11 (24, 14-38)	28 (26, 18-35)	2 (3, 1-11)	4 (12, 5-28)	
Cerebellar signs	36 (14, 10-19)	10 (22, 12-36)	24 (22, 15-31)	1 (1, 0-10)	1 (3, 1-19)	
Cranial nerve dysfunction	37 (14, 11-19)	2 (4, 1-16)	24 (22, 15-31)	4 (6, 2-14)	7 (21, 10-38)	
Impaired consciousness	101 (39, 33-45)	27 (59, 44-72)	46 (42, 33-52)	2 (3, 1-11)	26 (79, 62-90)	
GCS <15	91 (35, 30-41)	23 (54, 40-68)	34 (37, 28-46)	1 (0-10)	24 (76, 58-87)	
GCS median (IQR)	9 (6)	8 (9)	10 (6)	13 (0)	9 (3)	
Mechanical ventilation	45 (17, 13-23)	12 (26, 15-41)	17 (16, 10-24)	0 (0)	16 (49, 32-65)	
mRS (IQR)	2 (2)	3 (2)	2 (2)	1 (1)	3 (1)	
CSF results						
Median leucocyte count (x10^6 per L, IQR)	81.5 (190.5)	14 (55)	75.5 (148)	96 (194)	1218.5 (5946)	<0.0001
Proportion lymphocytes of white blood cells (%, IQR)	92 (49.5)	99 (7)	94 (32)	91.5 (25)	10 (23)	<0.0001
Median protein (g/L, IQR)	0.78 (0.61)	0.66 (0.54)	0.79 (0.43)	0.58 (0.41)	3.36 (6.63)	<0.0001
Median lactate (mmol/L, IQR)	2.5 (1.09)	2.2 (0.8)	2.5 (0.75)	2.3 (1)	13 (11.9)	<0.0001

Table 2 Confirmed causes of encephalitis, meningoencephalitis or meningitis

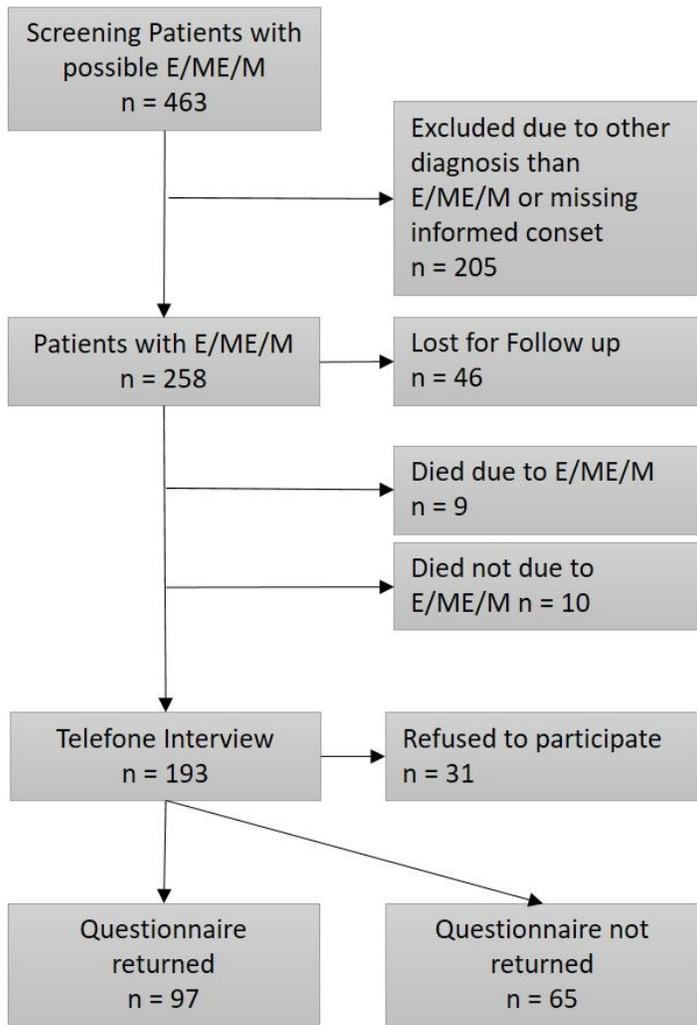|	All	Encephalitis	Meningoencephalitis	Meningitis
Total *n* (%)	258 (100)	46 (17.8)	127 (49.2)	85 (32.9)
Infectious cause	148 (57.4)	15 (32.6)	89 (70.1)	45 (52.9)
Viral	**114 (77)**	**14 (93.3)**	**71 (79.8)**	**30 (68.2)**
Tick-borne Encephalitis Virus	65 (57)	1 (7.1)	58 (81.7)	6 (20.7)
Enterovirus	21 (18.4)	1 (7.1)	3 (4.2)	18 (60)
Varicella zoster virus	14 (12.3)	2 (14.2)	7 (9.9)	5 (17.2)
Herpes Simplex virus 1	9 (7.9)	8 (57.1)	1 (1.4)	0 (0)
Herpes Simplex virus 2	2 (1.8)	0 (0)	1 (1.4)	1 (3.4)
Epstein-Barr-Virus	2 (1.8)	1 (7.1)	1 (1.4)	0 (0)
Influenza virus A/B	1 (0.9)	1 (7.1)	0 (0)	0 (0)
Bacterial	**33 (22.3)**	**0 (0)**	**18 (20.2)**	**15 (34.1)**
Streptococcus pneumoniae	16 (48.5)		9 (50)	7 (46.7)
Neisseria meningitidis	4 (12.1)		3 (16.7)	1 (6.7)
Streptococcus ssp.	4 (12.1)		2 (11.1)	2 (13.3)
Haemophilus influenzae	2 (6.1)		1 (5.6)	1 (6.7)
Listeria monocytogenes	1 (3)		0 (0)	1 (6.7)
Staphylococcus aureus	1 (3)		0 (0)	1 (6.7)
Tuberculosis	3 (9.1)		2 (11.1)	1 (6.7)
Borrelia burgdorferi	2 (6.1)		1 (5.6)	1 (6.7)
Treponema pallidum	**1 (0.7)**	**1 (6.7)**	**0 (0)**	**0 (0)**
Immune-mediated cause	13 (5)	13 (28.3)	0 (0)	0 (0)
NMDA-Receptor-Antibody	4 (30.7)	4 (30.7)		
LGI1 Antibody	4 (30.7)	4 (30.7)		
Caspr2	2 (15.4)	2 (15.4)		
Anti-Hu	1 (7.7)	1 (7.7)		
GAD	1 (7.7)	1 (7.7)		
SREAT	1 (7.7)	1 (7.7)		
Aseptic	5 (1.9)	0 (0)	0 (0)	5 (5.9)
Intravenous Immunoglobuline	3 (60)			3 (60)
Craniopharyngeoma	1 (20)			1 (20)
Autoimmune Disease	1 (20)			1 (20)
Unknown cause	92 (35.7)	18 (39.1)	38 (29.9)	35 (41.2)

Figures

Figure 1

Flow chart of patient recruitment and data acquisition. E/ME/M encephalitis, meningoencephalitis or meningitis
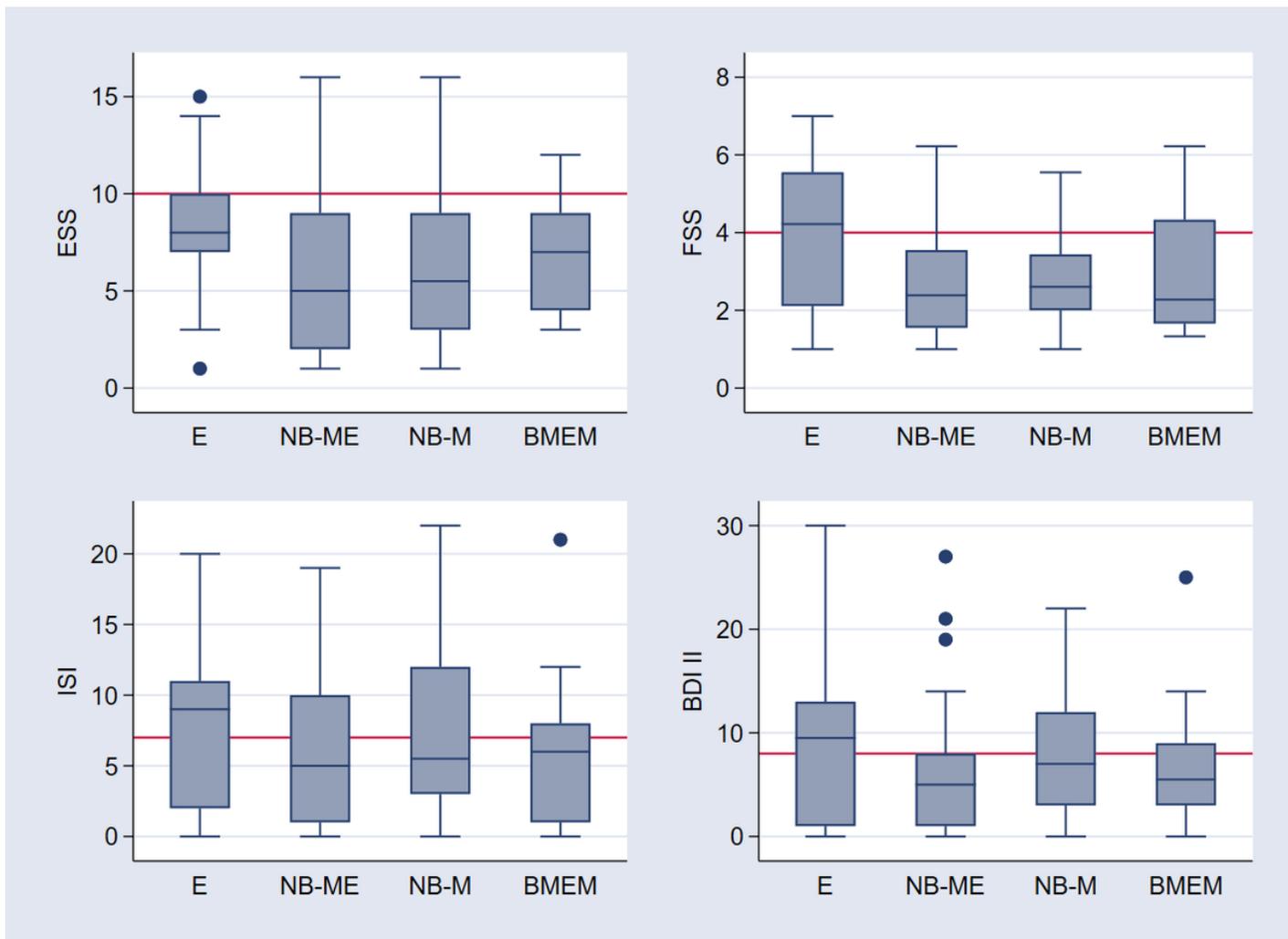
Figure 2

Questionnaire Scores at follow up. ESS Epworth Sleepiness Score, FSS Fatigue Severity Scale, ISI Insomnia Severity Index, BDI II Beck Depression Inventory II; E Encephalitis, NB-ME Non-bacterial Meningoencephalitis, NB-M Non-bacterial Meningitis, BMEM Bacterial Meningoencephalitis/Meningitis, boxes medians and interquartile ranges, red line indicates cut off for pathological scores.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryData.docx