



Causes of encephalitis and differences in their clinical presentations in England: a multicentre, population-based prospective study

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Summary

Background Encephalitis has many causes, but for most patients the cause is unknown. We aimed to establish the cause and identify the clinical differences between causes in patients with encephalitis in England.

Methods Patients of all ages and with symptoms suggestive of encephalitis were actively recruited for 2 years (staged start between October, 2005, and November, 2006) from 24 hospitals by clinical staff. Systematic laboratory testing included PCR and antibody assays for all commonly recognised causes of infectious encephalitis, investigation for less commonly recognised causes in immunocompromised patients, and testing for travel-related causes if indicated. We also tested for non-infectious causes for acute encephalitis including autoimmunity. A multidisciplinary expert team reviewed clinical presentation and hospital tests and directed further investigations. Patients were followed up for 6 months after discharge from hospital.

Findings We identified 203 patients with encephalitis. Median age was 30 years (range 0–87). 86 patients (42%, 95% CI 35–49) had infectious causes, including 38 (19%, 14–25) herpes simplex virus, ten (5%, 2–9) varicella zoster virus, and ten (5%, 2–9) *Mycobacterium tuberculosis*; 75 (37%, 30–44) had unknown causes. 42 patients (21%, 15–27) had acute immune-mediated encephalitis. 24 patients (12%, 8–17) died, with higher case fatality for infections from *M tuberculosis* (three patients; 30%, 7–65) and varicella zoster virus (two patients; 20%, 2–56). The 16 patients with antibody-associated encephalitis had the worst outcome of all groups—nine (56%, 30–80) either died or had severe disabilities. Patients who died were more likely to be immunocompromised than were those who survived (OR=3.44).

Interpretation Early diagnosis of encephalitis is crucial to ensure that the right treatment is given on time. Extensive testing substantially reduced the proportion with unknown cause, but the proportion of cases with unknown cause was higher than that for any specific identified cause.

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Introduction

Few high-quality population-based studies of encephalitis are done because the syndrome is rare. Worldwide, up to 85% of cases are of unknown cause, and there is concern about new and emerging triggers.^{1,2} Over the past decade, emerging viruses implicated in causing encephalitis include the Nipah virus, bat lyssaviruses, and avian influenza A H5N1.^{3–5} The case of West Nile virus in North America shows the potential for infections to become established in new regions if vectors are present, if avian hosts are susceptible, and if the environment is supportive.⁶ In the UK, cases of West Nile virus in human beings can pass undetected because the infection is not endemic and so clinicians might not consider this diagnosis.⁷ Furthermore, the contribution of recently described immune-mediated forms of encephalitis, such as those associated with voltage-gated potassium channels and the N-methyl-D-aspartate (NMDA) receptor antibodies,^{8–11} is unclear.

Encephalitis is associated with high morbidity and mortality. An estimated 700 cases of viral encephalitis

occur yearly in England, of which about 7% are fatal; however, both the incidence and case fatality are thought to be underestimated.¹ If infection is not fatal, individuals often have severe physical, cognitive, emotional, behavioural, and social difficulties.¹² In the USA, the yearly national costs of patients taken to hospital with encephalitis-associated illness has been estimated at US\$630 million.¹³ Effective interventions exist for some causes of encephalitis. Vaccination against mumps, measles, and rubella has substantially reduced the number of encephalitis cases associated with these diseases.¹⁴ Of the viral causes, herpes simplex virus and varicella zoster virus have well established antiviral treatments, and immunomodulation is used to treat patients with acute disseminated encephalomyelitis (ADEM) or other immune-mediated encephalitides.¹⁵ Timely and appropriate treatment is crucial for improving acute encephalitis outcome; hence, rapid identification of the cause is key.

We present the clinical and aetiological results of a prospective study of 203 patients with encephalitis in England. We aimed to establish the cause by a systematic

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Panel 1: First-line testing for cases of encephalitis***If immunocompetent***Routine CSF PCR testing*

- Herpes simplex virus 1/2
- Varicella zoster virus
- Enterovirus
- Parechovirus
- Adenovirus
- Human herpesvirus-6/7 (<30 years)
- Consider other tests depending on clinical features†

Routine serology

- If increased activity:
 - Mumps or measles
 - Influenza A or B
- Human herpesvirus-6/7 (<30 years)

If immunocompromised*CSF PCR*

As for immunocompetent, and consider:

- Cytomegalovirus
- Epstein-Barr virus
- Human herpesvirus-6/7
- JC virus
- Lymphocytic choriomeningitis virus
- HIV

Serology

- JC virus
- HIV with consent when appropriate

If travelled abroad*CSF PCR*

As for immunocompetent, and consider:

- Arboviruses (Japanese encephalitis, dengue, tickborne encephalitis, Nipah virus, Murray Valley encephalitis, St Louis encephalitis)
- Poliomyelitis
- Rabies
- West Nile virus

Serology

- Arboviruses (Japanese encephalitis, dengue, tickborne encephalitis, Nipah, Murray Valley encephalitis, St Louis encephalitis)
- Rabies
- West Nile virus

*Algorithm assumes appropriate investigations were also done when clinically indicated to exclude bacterial, fungal, and parasitic infections. †For cervical lymphadenopathy consider cytomegalovirus and Epstein-Barr virus; for respiratory illness consider influenza A and B; for parotitis and orchitis consider mumps.

diagnostic algorithm and expert review process, ascertain clinical differences between causes, document the outcome, and establish a well defined cohort for future study.

Methods**Patients**

We recruited patients for 2 years (staged start between October, 2005, and November, 2006) from 24 hospitals in three regions of England: London, the southwest, and the

Panel 2: Rare causes of encephalitis in England (not included in first-line testing)**Viral**

Cytomegalovirus, Epstein-Barr virus, flaviviruses, hepatitis viruses, human T-cell lymphotropic virus, lymphocytic choriomeningitis virus, parainfluenza virus, parvovirus B19, poliovirus, rabies virus, respiratory syncytial virus

Bacterial

Bacillus anthracis, *Bartonella henselae*, *Chlamydia psittaci*, *Chlamydia trachomatis*, *Legionella pneumophila*, *Leptospira* spp, *Listeria monocytogenes*, *Borrelia burgdorferi*, *Mycoplasma pneumoniae*, *Mycobacterium tuberculosis*, *Salmonella* spp, *Streptococcus pneumoniae*, *Streptococcus pyogenes*

Rickettsial

Coxiella burnetii, *Rickettsia rickettsii*

Parasitic

Toxoplasma gondii

Fungal

Histoplasma capsulatum

northwest of England.¹⁶ These regions differ in socio-economic and urban–rural characteristics, and comprise an estimated 11% (5 million people) of the English population. Patients were recruited by active promotion and through review of cerebrospinal fluid (CSF) analysis requests to pathology departments. We interviewed patients or next-of-kin about specific exposures, contact with any individuals with infection, risk factors, and travel or illnesses before symptom onset.

The case definition included any person of any age admitted to hospital with encephalopathy (altered consciousness that persisted for longer than 24 h, including lethargy, irritability, or a change in personality and behaviour) and with two or more of the following: fever or history of fever ($\geq 38^{\circ}\text{C}$) during the presenting illness; seizures and/or focal neurological findings (with evidence of brain parenchyma involvement); CSF pleocytosis (more than four white blood cells per μL); electroencephalographic (EEG) findings indicative of encephalitis; and abnormal results of neuroimaging (CT or MRI) suggestive of encephalitis.

The North and East Devon Multicentre Research Ethics Committee granted approval for the study (05/Q2102/22). We also obtained local research ethics committee approval and Research and Development approval from all participating centres. We obtained written informed consent from all patients or from their next of kin.

Procedures

Data recorded included demographic information, clinical findings at presentation and discharge, immune status (eg, whether an individual was HIV positive or

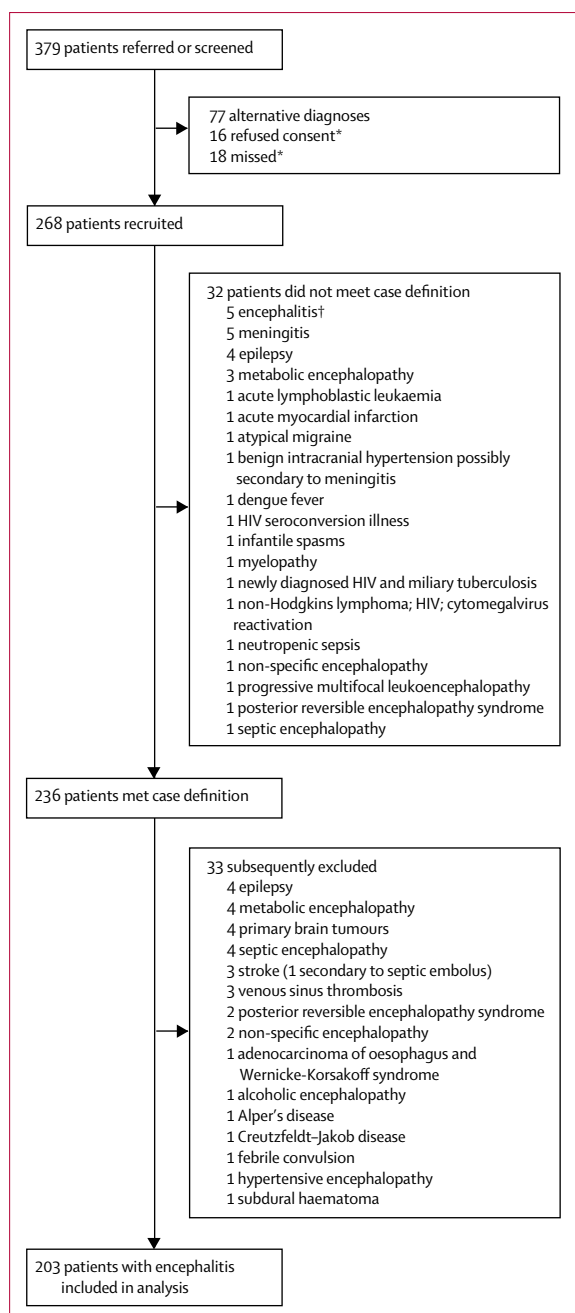


Figure 1: Study profile

*These patients might or might not have fulfilled the inclusion criteria; those who were missed either died or were transferred out of hospital before further investigation could be done to fully assess eligibility or before consent could be obtained. †These patients were ineligible for case definition because of lack of imaging or EEG results.

on immunosuppressive treatment), and results of laboratory, EEG, and neuroimaging testing. Samples obtained were from the CSF, blood, urine, stool, swabs from various sites (eg, throat or rectal), or from post-mortem examination. We followed up patients at 6 months after discharge from hospital; outcome was

	Confirmed	Probable	Total (%)
Infectious cause (n=86 [42%; 95% CI 35–49%])			
Herpes simplex virus	36	2	38* (19)
<i>Mycobacterium tuberculosis</i>	1	9	10 (5)
Varicella zoster virus	9	1	10 (5)
Streptococci	2	2	4† (2)
Enteroviruses	3	..	3 (1)
Dual infection	3	..	3‡ (1)
<i>Streptococcus pneumoniae</i>	3	..	3 (1)
Influenza A	..	2	2 (1)
<i>Neisseria meningitidis</i>	2	..	2 (1)
<i>Toxoplasma gondii</i>	2	..	2 (1)
<i>Coxiella burnetii</i>	..	1	1 (0.5)
Epstein-Barr virus	..	1	1 (0.5)
<i>Enterococcus faecium</i>	1	..	1 (0.5)
Human herpesvirus-6	..	1	1 (0.5)
HIV	1	..	1 (0.5)
JC virus	1	..	1 (0.5)
<i>Listeria monocytogenes</i>	1	..	1 (0.5)
<i>Pseudomonas</i> spp	1	..	1 (0.5)
Sclerosing subacute panencephalitis (measles)	1	..	1 (0.5)
Immune-mediated cause (n=42 [21%; 95% CI 15–27%])			
Acute disseminated encephalomyelitis	23	..	23 (11)
NMDA receptor antibodies	9	..	9 (4)
VGKC antibodies	7	..	7 (3)
Secondary to systemic vasculitis	1	..	1 (0.5)
Multiple sclerosis	1	..	1 (0.5)
Paraneoplastic	1	..	1 (0.5)
Unknown cause (n=75 [37%; 95% CI 30–44%])			
Unknown	75 (37)
Total			203

NMDA=N-methyl-D-aspartate. VGKC=voltage-gated potassium channel.
 *28 herpes simplex virus-1; three herpes simplex virus-2; seven herpes simplex virus untyped. †Three group A streptococci; one group B streptococci. ‡Dual findings: one *Cryptococcus* spp and varicella zoster virus, one *Mycobacterium tuberculosis* and *Toxoplasma gondii*; one *Mycobacterium tuberculosis* and HIV.

Table 1: Classification and cause of encephalitis

scored according to the Glasgow outcome scale.¹⁷ Poor outcome was defined as death or severe disability.

First-line testing (panel 1) included all commonly recognised causes of encephalitis, less commonly recognised causes in immunocompromised patients, and travel-related causes where appropriate. To obtain maximum diagnostic sensitivity, we used DNA or RNA and antibody assays. A multidisciplinary expert review of the clinical presentation, the results of tests, and the available samples from patients directed further investigation of undiagnosed patients, which included assays for second-line infectious causes, including those thought to be rare causes of encephalitis in the UK (panel 2) and screening of CSF samples for the presence of intrathecal production of antibodies.¹⁸ Cases of

unknown cause were tested retrospectively for antibodies against voltage-gated potassium channels (n=62) and the NMDA receptor (n=48).^{8,11} All patients older than 50 years

of age were tested for antibodies to West Nile virus. All patients who died and for whom the cause was unknown were tested for lyssaviruses.

We classified cases as confirmed, probable, possible, or non-encephalitis with a definite alternative diagnosis, on the basis of aetiological case definitions.¹⁹ We divided causes into the following categories: ADEM, antibody-associated encephalitis (voltage-gated potassium channel and NMDA receptor), *Mycobacterium tuberculosis*, other bacterial encephalitis, herpes simplex virus; varicella zoster virus, and encephalitis of unknown cause.

Statistical analyses

We investigated differences in demographic and clinical variables and differences in laboratory and imaging results with Fisher's exact test. Factors associated with an infectious or immune-mediated cause, an unknown cause, death, and extended duration of hospital stay were studied in univariable and multivariable analyses. All variables with p of 0.2 or less in the univariable analyses were included in the multivariable regression models. Variables were added in a backwards stepwise procedure. A p value of less than 0.05 was deemed significant. For all outcomes, apart from duration of hospital stay, logistic regression was used with associations assessed by odds ratios (OR) and their Wald CIs. For duration of hospital stay, a log transformation was used to correct bias; normal error regression was then used to adjust for any patients who died in hospital.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

We recruited 203 patients with encephalitis (figure 1), with a median age of 30 years (range 0–87); 109 (54%, 95% CI 47–61) were male. We identified a cause for 128 cases (63%, 56–70). Specific triggers that caused most cases were herpes simplex virus, ADEM, antibody-associated causes (NMDA receptor antibodies and voltage-gated potassium channel antibodies), varicella zoster virus, and *M tuberculosis* (table 1). There was strong evidence of variation in causes of encephalitis by age (p<0.001; figure 2) but not by sex (p=0.96).

No patient had indigenously acquired West Nile virus or lyssaviruses in the study—one patient who tested positive for herpes simplex virus by PCR while on holiday from Canada had West Nile virus IgM and IgG antibodies. Eight (35%) patients with ADEM had serological evidence of recent infection: four from *Mycoplasma pneumoniae*, one from influenza A, one from influenza B, one from group A streptococcus, and one from *Campylobacter jejuni*. One patient with ADEM

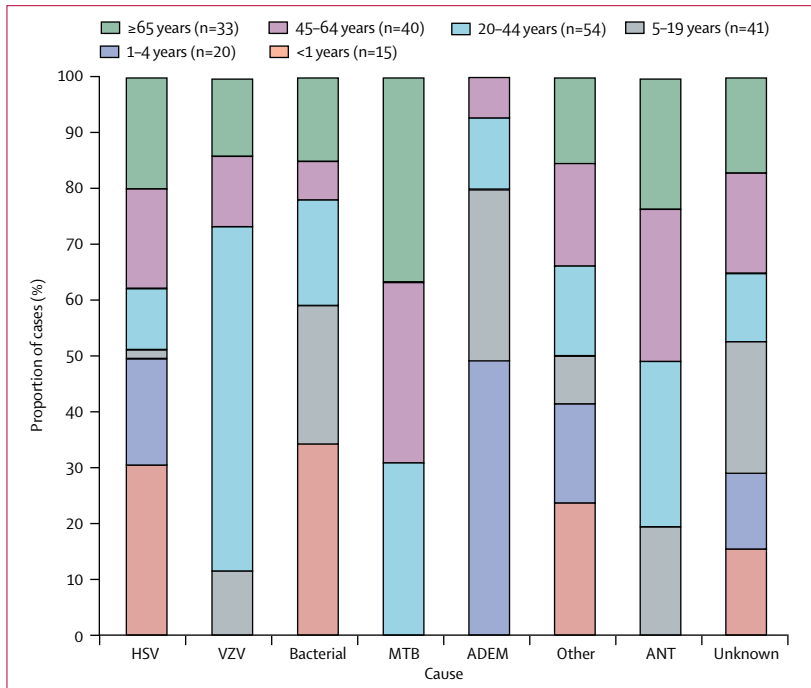


Figure 2: Age distribution of cases by cause
ADEM=acute disseminated encephalomyelitis. ANT=antibody-associated cause. HSV=herpes simplex virus. MTB=*Mycobacterium tuberculosis*. VZV=varicella zoster virus.

	Immunocompetent patients* (n=172)	Immunocompromised patients† (n=31)	Total
Herpes simplex virus	37 (22%, 16–28)	1 (3%, 0.1–17)	38
Acute disseminated encephalomyelitis	23 (14%, 9–19)	..	23
Antibody-associated encephalitis	15 (9%, 5–14)	1 (3%, 0.1–17)	16
<i>Mycobacterium tuberculosis</i>	9 (5%, 2–10)	1 (3%, 0.1–17)	10
Varicella zoster virus	4 (2%, 0.6–6)	6 (19%, 7–37)	10
Streptococci	4 (2%, 0.6–6)	..	4
Enterovirus	3 (2%, 0.4–5)	..	3
Dual finding	..	3 (10%, 2–26)	3
<i>Toxoplasma gondii</i>	..	2 (6%, 1–21)	2
Epstein-Barr virus	..	1 (3%, 0.1–17)	1
Human herpesvirus-6	..	1 (3%, 0.1–17)	1
HIV	..	1 (3%, 0.1–17)	1
JC virus	..	1 (3%, 0.1–17)	1
<i>Listeria monocytogenes</i>	..	1 (3%, 0.1–17)	1
Pneumococcus	..	1 (3%, 0.1–17)	1
Other‡	13 (8%, 4–13)	..	13
Unknown	64 (37%, 30–45)	11 (35%, 19–55)	75

Data are number (%; 95% CI). The dual findings are the same as for table 2. *Includes cases for whom immune status was unknown. †Reasons for immunocompromised status: 18 HIV positive; three on chemotherapy; ten with other reasons or exact reason unknown. ‡Other causes include *Pseudomonas* spp, *Coxiella burnetii*, *Enterococcus faecium*, meningococcus, pneumococcus, influenza A, sclerosing subacute panencephalitis, paraneoplastic encephalitis, multiple sclerosis, and encephalitis secondary to systemic vasculitis.

Table 2: Causes of encephalitis in immunocompetent versus immunocompromised patients

also had evidence of intrathecal antibodies against *M pneumoniae*, but of ten patients with encephalitis who were tested, none was identified to be positive for *M pneumoniae* by PCR of CSF samples.

Of 172 (85%) immunocompetent individuals with encephalitis, 94 (55%, 95% CI 47–62) were male; median age was 25 years (range 0–87). Of 31 (15%) immunocompromised individuals with encephalitis, 15 (48%; 30–67) were male; median age was 38 years (range 7–77). 58% (95% CI 39–75) of the immunocompromised patients were HIV positive. The pattern of causes was different in these two groups of patients (table 2). ADEM and enteroviral encephalitis occurred only in

immunocompetent patients, as did most cases of antibody-associated encephalitis. By contrast, varicella zoster virus was more common in immunocompromised patients than in immunocompetent patients. The proportion of cases of unknown cause was similar in the two groups (table 2).

Most patients with encephalitis had fever during the presenting illness (table 3). More than 50% of patients had headache, seizures, lethargy, and personality or behavioural changes. Irritability, neck stiffness, focal neurology, and coma were also recorded (table 3). The proportion of patients with seizures and irritability varied significantly by cause. Most patients with

	All encephalitis* (n=203)	HSV (n=38)	VZV (n=10)	Bacterial† (n=13)	MTB (n=10)	ADEM (n=23)	Antibody-associated cause‡ (n=16)	Unknown (n=75)	p value§
Symptoms or clinical signs									
Fever¶	147 (72, 66–78)	29 (76, 60–89)	5 (50, 19–81)	11 (85, 54–98)	10 (100, 69–100)	18 (78, 56–92)	9 (56, 30–80)	54 (72, 60–82)	0.12
Headache	122 (60, 53–67)	16 (42, 26–59)	7 (70, 35–93)	8 (61, 31–86)	9 (90, 55–100)	17 (74, 51–90)	8 (50, 25–75)	46 (61, 49–72)	0.07
Seizures	105 (52, 45–59)	24 (63, 46–78)	1 (10, 0.2–44)	7 (54, 25–81)	0 (0, 0–31)	7 (30, 13–53)	14 (88, 62–98)	42 (56, 44–67)	<0.001
Lethargy	111 (55, 48–62)	16 (42, 26–59)	8 (80, 44–97)	9 (69, 38–91)	3 (30, 7–65)	15 (65, 43–84)	7 (44, 20–70)	45 (60, 48–71)	0.09
Irritability	75 (37, 30–44)	11 (29, 15–46)	4 (40, 12–74)	8 (62, 31–86)	0 (0, 0–31)	10 (43, 23–65)	3 (19, 4–46)	34 (45, 34–57)	0.01
PB change	131 (64, 57–71)	24 (63, 46–78)	7 (70, 35–93)	9 (69, 38–91)	7 (70, 35–93)	10 (43, 23–65)	11 (69, 41–89)	51 (68, 56–78)	0.53
Stiff neck	46 (23, 17–29)	5 (13, 4–28)	3 (30, 7–65)	2 (15, 2–45)	3 (30, 7–65)	10 (43, 23–65)	1 (6, 0.1–30)	17 (23, 14–34)	0.08
Focal neurology	73 (36, 29–43)	16 (42, 26–59)	6 (60, 26–88)	2 (15, 2–45)	2 (20, 2–56)	10 (43, 23–65)	8 (50, 25–75)	21 (28, 18–40)	0.10
Coma	37 (18, 13–24)	9 (24, 11–40)	2 (20, 2–56)	0 (0, 0–25)	1 (10, 0.2–44)	1 (4, 0.1–22)	2 (12, 1–38)	19 (25, 16–37)	0.20
Neurological signs**	61 (30, 24–37)	9 (24, 11–40)	4 (40, 12–74)	2 (15, 2–45)	2 (20, 2–56)	8 (35, 16–57)	4 (25, 7–52)	24 (32, 22–44)	0.77
Gastrointestinal symptoms**††	98 (48, 41–55)	13 (34, 20–51)	3 (30, 7–65)	9 (69, 38–91)	4 (40, 12–74)	15 (65, 43–84)	4 (25, 7–52)	44 (59, 47–70)	0.01
Respiratory symptoms**††	41 (20, 15–26)	5 (13, 4–28)	1 (10, 0.2–44)	1 (8, 0.2–36)	1 (10, 0.2–44)	14 (61, 38–80)	1 (6, 0.1–30)	15 (20, 12–31)	<0.001
Rash**	23 (11, 7–16)	2 (5, 0.6–18)	5 (50, 19–81)	2 (15, 2–45)	1 (10, 0.2–44)	0 (0, 0–15)	1 (6, 0.1–30)	10 (13, 7–23)	0.01
Photophobia**	16 (8, 5–12)	3 (8, 2–21)	0 (0, 0–31)	1 (8, 0.2–36)	0 (0, 0–31)	1 (4, 0.1–22)	1 (6, 0.1–30)	10 (13, 7–23)	0.84
Urinary symptoms**††	21 (10, 6–15)	1 (3, 0.1–14)	0 (0, 0–31)	0 (0, 0–25)	6 (60, 26–88)	7 (30, 13–53)	0 (0, 0–21)	5 (7, 2–15)	<0.001
CSF results									
CSF pleocytosis‡‡	159/198 (80, 74–86)	33/37 (89, 74–97)	9 (90, 55–100)	12 (92, 64–100)	10 (100, 69–100)	17/20 (85, 62–97)	11 (69, 41–89)	53/74 (72, 60–81)	0.1
CSF protein§§	120/191 (63, 55–70)	24/34 (71, 52–85)	7 (70, 35–93)	7/11 (64, 31–89)	10 (100, 69–100)	11/20 (55, 31–77)	7 (44, 20–70)	41/72 (57, 45–69)	0.06
CSF: blood glucose ratio¶¶	45/129 (35, 27–44)	5/18 (28, 10–53)	2/6 (33, 4–78)	5/8 (63, 24–91)	8/9 (89, 52–100)	4/13 (31, 9–61)	4/15 (27, 8–55)	13/48 (27, 15–42)	0.01
Neuroimaging or neurophysiology									
CT	51/170 (30, 23–37)	18/32 (56, 38–74)	3/7 (43, 10–82)	2/12 (17, 2–48)	3 (30, 7–65)	6/16 (38, 15–65)	2/12 (17, 2–48)	13/67 (19, 11–31)	0.01
MRI	102/169 (60, 53–68)	25/28 (89, 71–98)	3/7 (43, 10–82)	1/9 (11, 0.3–48)	3/7 (43, 10–81)	22/22 (100, 85–100)	4 (25, 7–52)	34/65 (52, 39–65)	<0.001
EEG	100/120 (83, 75–89)	22/27 (81, 62–94)	2/4 (50, 7–93)	4/6 (67, 22–96)	3/3 (100, 29–100)	10/10 (100, 69–100)	13 (81, 54–96)	38/44 (86, 73–95)	0.26

Data are number (%; 95% CI). ADEM=acute disseminated encephalomyelitis. CSF=cerebrospinal fluid. HSV=herpes simplex virus. MTB=Mycobacterium tuberculosis. PB=personality and/or behavioural. VZV=varicella zoster virus. *All encephalitis includes those from other causes (not shown). †Includes *Neisseria meningitidis*, *Streptococcus pneumoniae*, *Listeria* spp, *Enterococcus faecium*, *Pseudomonas* spp, and group A or B streptococci. ‡Includes voltage-gated potassium channel antibodies and anti-NMDA receptor antibodies. §Fisher's exact test, comparing aetiological categories (except all encephalitis). ¶Fever at time of admission. ||Coma was defined as a Glasgow outcome scale admission score of ≤ 8 . **These symptoms were not actively sought in every case but documented if they were included in the "other" box of our questionnaire; thus, this represents the minimum proportion of patients with these symptoms or clinical signs because we only know if they were present or not known. ††Gastrointestinal symptoms were predominantly vomiting and diarrhoea; respiratory symptoms included cough, sore throat, sinusitis, runny nose, upper respiratory tract infection, and dyspnoea; and urinary symptoms included urinary tract infection, dysuria, urinary retention, and incontinence. ‡‡Pleocytosis was recorded if white-blood cell counts were $>14 \mu\text{L}$ in neonates, $>10 \mu\text{L}$ in infants (aged 1 month to 12 months), and $>4 \mu\text{L}$ in all others. §§Abnormal protein defined as greater than 0.5 g/L. ¶¶Abnormal ratio defined as CSF: blood glucose less than 0.50.

Table 3: Summary of clinical findings for patients with encephalitis, by cause

antibody-associated encephalitis had seizures, as did more than half of those with herpes simplex virus and unknown cause (table 3). By contrast, few patients with ADEM, varicella zoster virus, and *M tuberculosis* had seizures. The presence of respiratory symptoms, urinary symptoms, rash, and gastrointestinal symptoms also varied significantly by cause. Respiratory symptoms were more common in patients with ADEM than in any other group. Higher proportions of patients with ADEM or *M tuberculosis* had urinary symptoms, which were rare in any other group. Rash was most common in patients with varicella zoster virus. Gastrointestinal symptoms (predominantly vomiting) were present in nearly half of all patients with encephalitis and were most common in patients with bacterial or unknown causes and ADEM (table 3). Although evidence of aetiological variation was weaker for other clinical symptoms or signs, there were notable differences. Although fever was present in most patients with encephalitis, five with varicella zoster virus and seven with antibody-associated causes were afebrile. Focal neurological symptoms were most common in cases of varicella zoster virus (table 3).

The presence of pleocytosis and abnormal protein in the CSF did not vary significantly between patients with different causes of encephalitis; however, the proportion of patients with an abnormal ratio of CSF to blood glucose did vary significantly (table 3). About 30% of patients with viral or immune-mediated encephalitis and an unknown cause had an abnormal ratio (table 3). Many patients with bacterial causes of encephalitis had an abnormal glucose ratio (table 3). Bacterial causes were also associated with increased white-cell counts (table 4).

170 patients (84%) had CT, 169 (83%) MRI, and 120 (59%) EEG (table 3). There was strong evidence of variation by cause in patients with abnormal CT and abnormal MRI findings, but not with an abnormal EEG finding (table 3). Patients with herpes simplex virus were most likely to have abnormal CT, whereas patients with antibody-associated and bacterial encephalitis were least likely to have abnormal CT. CT scans were abnormal in nearly a fifth of patients with unknown cause. MRI was most likely to be abnormal in patients with ADEM and herpes simplex virus and least likely to be abnormal in patients with antibody-associated encephalitis and patients with bacterial causes. MRI

	Median white blood-cell count per μL in CSF (IQR)	Proportion of white blood cells that are lymphocytes (%; IQR)	Median protein concentration in CSF (g/L; IQR)	Median glucose concentration in CSF (mmol/L; IQR)
All encephalitis* (n=203)	47 (16-130)	95 (80-100)	0.6 (0.35-1.2)	3.3 (2.7-3.9)
Herpes simplex virus (n=38)	43 (14-140)	92 (77.5-100)	0.6 (0.4-1)	3.3 (2.7-3.7)
Varicella zoster virus (n=10)	54 (23-146)	95 (89-99)	1.1 (0.6-1.8)	4.3 (3.5-5)
Bacterial cause† (n=13)	126 (30-575)	73 (50.5-95)	0.8 (0.4-3.7)	2.6 (1.8-3.8)
<i>Mycobacterium tuberculosis</i> (n=10)	84 (36-216)	99 (88-100)	1.4 (0.8-2.1)	2 (1.6-2.7)
Acute disseminated encephalomyelitis (n=23)	43 (22-115)	100 (95-100)	0.5 (0.4-0.8)	2.9 (2.6-3.4)
Antibody-associated encephalomyelitis ‡ (n=16)	22 (6.5-60)	98 (93-100)	0.3 (0.2-0.5)	3.7 (3.3-4.3)
Unknown (n=75)	47 (16-118.5)	95 (70-100)	0.5 (0.3-1.1)	3.4 (2.9-4)

CSF=cerebrospinal fluid. *All encephalitis includes those from other causes (not shown as separate category). †Includes *Neisseria meningitidis*, *Streptococcus pneumoniae*, *Listeria* spp, *Enterococcus faecium*, *Pseudomonas* spp, and group A/B streptococci. ‡Includes voltage-gated potassium channel antibodies and anti-NMDA receptor antibodies.

Table 4: Summary of CSF investigations for patients with encephalitis

	ENC* (n=198)	HSV (n=38)	VZV (n=10)	Bacterial† (n=13)	MTB (n=10)	ADEM (n=23)	ANT‡ (n=16)	Unknown (n=70)	p value¶
Glasgow outcome scale									
Fatalities	24 (12; 8-17)	4 (11; 3-25)	2 (20; 2-56)	1 (8; 0.2-36)	3 (30; 7-65)	1 (4; 0.1-22)	3 (19; 4-46)	6 (9; 3-18)	0.26
Vegetative state	0 (0; 0-2)	0 (0; 0-9)	0 (0; 0-31)	0 (0; 0-25)	0 (0; 0-31)	0 (0; 0-15)	0 (0; 0-21)	0 (0; 0-5)	..
Severe disability	45 (23; 17-29)	11 (29; 15-46)	2 (20; 2-56)	2 (15; 2-45)	2 (20; 2-56)	3 (13; 3-34)	6 (38; 15-65)	16 (23; 14-34)	0.66
Moderate disability	43 (22; 16-28)	8 (21; 9-37)	2 (20; 2-56)	4 (31; 9-61)	2 (20; 2-56)	3 (13; 3-34)	6 (38; 15-65)	11 (16; 8-26)	0.46
Good recovery	86 (43; 36-51)	15 (39; 24-57)	4 (40; 12-74)	6 (46; 19-75)	3 (30; 7-65)	16 (70; 47-87)	1 (6; 0.1-30)	37 (53; 40-65)	0.02
Admission details									
Median length (range) of stay (days)§	28 (2-521) (n=200)	30 (5-521)	30 (10-248)	22 (8-128)	87 (26-201)	17 (6-137)	89 (14-407)	24 (2-225) (n=72)	

Data are n (%; 95% CI). According to the Glasgow outcome scale, good recovery is defined as resumption of normal activities even though there might be minor neurological or psychological deficits. ADEM=acute disseminated encephalomyelitis. ANT=antibody-associated. ENC=all encephalitis. HSV=herpes simplex virus. MTB=*Mycobacterium tuberculosis*. VZV=varicella zoster virus. *All encephalitis includes "other causes" group not displayed as separate aetiological category. †Includes *Neisseria meningitidis*, *Streptococcus pneumoniae*, *Listeria* spp, *Enterococcus faecium*, *Pseudomonas* spp, and group A/B streptococci. ‡Includes voltage-gated potassium channel antibodies and anti-NMDA receptor antibodies. §Only including cases where admission history clear. ¶Fisher's exact test comparing aetiological categories (except all encephalitis).

Table 5: Outcome of 198 patients with encephalitis

	Infectious versus immune-mediated		Known versus unknown		Outcome-death	
	Odds ratio (95% CI)	p value	Odds ratio (95% CI)	p value	Odds ratio (95% CI)	p value
Immunocompromised	3.44 (1.28–9.27)	0.01
Focal neurological symptoms	0.51 (0.26–0.98)	0.003
Respiratory symptoms	0.19 (0.07–0.53)	0.002
Photophobia	3.86 (1.3–11.49)	0.01
CSF pleocytosis	0.38 (0.18–0.8)	0.01
Abnormal CSF protein	3.49 (1.46–8.32)	0.005

CSF=cerebrospinal fluid. Age, sex, cause, fever, headache, seizures, lethargy, irritability, personality or behavioural change, stiff neck, coma, neurological signs (non-focal), gastrointestinal symptoms, rash, urinary symptoms, abnormal CSF: blood glucose ratio, abnormal CT, abnormal MRI, and abnormal EEG were additional variables included in the models and had no significant association. To minimise loss of data and increase power, abnormal CSF: blood glucose ratio and coma were excluded from the infectious versus immune-mediated model; abnormal CSF: blood glucose ratio, coma, abnormal CT, and abnormal MRI were excluded from the known versus unknown model; abnormal CSF: blood glucose ratio and abnormal CT were excluded from the outcome model.

Table 6: Summary of final regression models, by variable

scans were abnormal in about a third of patients with unknown cause.

Outcome data were available for 198 patients (97%); five patients were lost to follow-up. 24 patients died; death was most common in patients with *M tuberculosis*, varicella zoster virus, and antibody-associated encephalitis (table 5). The worst outcome was seen in patients with antibody-associated encephalitis or *M tuberculosis* (table 5). The median length of hospital stay for these two groups was nearly three times longer than that for all cases. The outcome was poor in 15 (39%, 24–57) patients with herpes simplex virus and in 22 (31, 21–44) cases of unknown cause. The proportion of patients with poor outcome was higher in those with antibody-associated encephalitis than in those with bacterial encephalitis ($p=0.05$), ADEM ($p=0.01$), or encephalitis of unknown cause ($p=0.03$). Patients with ADEM had the best outcome ($p=0.02$), with more than two-thirds making a good recovery (table 5). 158 patients (78%, 71–83) of all those with encephalitis received aciclovir; the median time from hospital admission to initiation of aciclovir was 1 day (range 0–93).

Patients with infectious causes were less likely to have respiratory symptoms but were more likely to have abnormal CSF protein concentrations than were patients with immune-mediated causes (table 3). Patients with encephalitis of unknown cause were more likely to have photophobia but were less likely to have an abnormal CSF white cell count and focal neurological symptoms than were all cases of known cause (table 3 and table 6).

In logistic regression analyses for which death was an outcome, patients who died were more likely to be immunocompromised than were patients who did not die (table 6). Similar findings were reported when the length of hospital stay was used as the outcome measure after adjustment for potential confounders (data not shown).

Discussion

Less than half of patients presenting with encephalitis had a proven infectious cause in this study. Herpes simplex virus was the most common infectious cause,

followed by varicella zoster virus and *M tuberculosis*. Thus, more than a quarter of patients were potentially treatable with aciclovir. This result confirms previous reports of the important role of herpes simplex virus as a cause for sporadic acute infectious encephalitis, and of the increasing recognition of the role of varicella zoster virus, particularly in immunocompromised individuals.^{20,21}

The identification of *M tuberculosis* is clinically important because not only do these patients need specific treatment, but this cause is also associated with high mortality and poor outcome. Although most of these patients had fever, headache, and personality or behavioural changes, only a third had neck stiffness. Most cases of *M tuberculosis* in this study were classified as probable rather than confirmed cases, indicating the difficulty of detection of *M tuberculosis* in the CNS.^{19,22}

1% of cases were caused by enteroviruses, similar to the results of a study in France,²³ but lower than that reported in a study in California.²⁴ Enterovirus encephalitis is more prevalent in children than in adults and is often mild, although disease associated with enterovirus 71 has high morbidity.²⁵ Differences in the proportion of children recruited or in the severity of illness might explain the difference between studies; in the California cohort, 45% were children, whereas 10% were children in the French study and 34% were children in this study. Fewer children than expected were recruited, perhaps because children are less likely than adults to have a lumbar puncture in the UK, one of our main methods of case ascertainment.²⁶ In view of the importance of accurate diagnosis to establish appropriate treatment, lumbar punctures in children with encephalitis are indicated.

About a fifth of patients had immune-mediated encephalitis—mostly ADEM. Most studies of encephalitis have not distinguished ADEM from other acute encephalitides. However, identification of such patients is important as treatment strategies involve immunomodulation. Patients with ADEM seem to meet the same case definition and present in similar ways to acute

infectious encephalitis. Although most patients with ADEM were children, 20% were aged 20 years or older. In 35% of patients with ADEM, there was serological evidence of an infection, commonly *M pneumoniae*, which is increasingly but controversially linked to ADEM.²⁷ 61% of patients with ADEM had a preceding respiratory illness, consistent with *M pneumoniae* and other respiratory pathogens as precipitants.

We found 16 patients with antibody-associated encephalitis in otherwise unexplained cases. The results of this study highlights the epidemiological importance of these antibodies in a population-based cohort of patients; previous studies report case series,^{9,10,28} although ten patients with NMDA receptor antibodies possibly associated with mycoplasma infections were identified in the California Encephalitis Project.²⁸ Our detection of antibodies to both NMDA receptors and voltage-gated potassium channels in patients with suspected acute encephalitis—especially when associated with features of limbic encephalitis, prominent seizures, normal CT scans, absence of fever, and only mild CSF pleocytosis—suggests that serological testing is important so that immunomodulation is instituted promptly, as this approach seems to be effective if given early.⁸ Furthermore, underlying tumours should be sought because these encephalitides can be paraneoplastic. Although obtained prospectively, most cases of antibody-associated encephalitis in our study were diagnosed at the conclusion of the study when the samples received further testing. Therefore, the delay to diagnosis could account for the poor outcome observed in this group. We are now testing all patients, including those for whom a viral cause was identified, to study whether antibodies could also have a role in infections. We did not detect any evidence of indigenous human West Nile virus infection in patients aged older than 50 years—the age-group most at risk for neuroinvasive disease.⁶ Although no indigenous cases of West Nile virus have been detected in the UK, this virus remains a concern because of climate change and vectors being present in the UK.

Prompt distinction between causes of acute encephalitis is essential to direct appropriate management. We confirmed the well described clinical findings for viral, bacterial, and mycobacterial causes. However, no single presenting symptom, sign, or CSF measurement could alone or in combination accurately separate one group from another. At presentation, only a few patients with proven infectious causes had neither fever nor CSF pleocytosis (24% and 11%, respectively, for herpes simplex virus); encephalitides cannot be excluded because patients are afebrile with normal CSF.

Seizures, especially in the absence of fever, should alert clinicians to antibody-associated encephalitis because this symptom commonly occurs in NMDA receptor and voltage-gated potassium channel encephalitides.^{8,9} Gastrointestinal symptoms were common in patients with bacterial encephalitides and might be associated with

systemic infection, and in the ADEM group, these symptoms could be a manifestation of the precipitant infection. Similarly, the high rates of urinary symptoms noted in patients with ADEM or *M tuberculosis* infection might be associated with the tendency of these diseases to involve the spinal cord. The high rate of EEG abnormalities across the cohort is indicative of encephalopathy, a key requirement for recruitment into this study; but EEG did not help with distinction between causes. Our data provide further evidence that MRI is more sensitive than CT in revealing parenchymal change in encephalitis. However, we did not investigate the patterns or timings of appearance of MRI abnormalities within the different groups. In keeping with most results from encephalitis studies, we detected slightly more male than female patients—whether men and boys are more susceptible to encephalitis, or indeed whether they have greater exposure to causative agents, needs to be established.

The number of deaths (12%) in this study was higher than that previously described in England for cases of viral encephalitis (7%).¹ This rate was also higher than the 2% and 7% rates described in North America,^{13,20} but was similar to those reported in a recent French study (10%).²³ We reported deaths in the community because patients were followed up 6 months after discharge from hospital. Although the study might have been biased towards more severe cases, the 10% mortality in those with encephalitis from herpes simplex virus was substantially lower than that reported in the aciclovir treatment trials (19–28%).^{29,30} Surprisingly, the outcome of cases of unknown cause was similar to those with herpes simplex virus—results from earlier studies have associated failure to identify a cause with a better outcome.^{13,31} Logistic regression analyses indicated that patients who died were more likely to be immunocompromised than were those who survived.²³ In addition to the substantial long-term morbidity present in many patients, their median hospital stay in this study was 28 days (IQR 15–62), indicating an important economic burden.¹³

Systematic use of molecular diagnostics coupled with investigation for non-infectious causes might explain the low proportion of cases of unknown cause (37%) compared with the 60% previously described¹—a lower proportion than that reported in most other studies.² Despite this finding, the proportion of cases with unknown cause was higher than that for any specific identified cause. Explanations include the failure to identify non-encephalitic syndromic mimics, inadequate case investigation, and the presence of novel infectious or non-infectious encephalitis causes.

Although the three geographical areas encompassed both rural and urban communities, as well as areas of different socioeconomic means, the age, sex, and ethnic origin of this cohort did not differ from the general population in England. Bias towards ascertainment of severe encephalitis cases might be present because more

than 60% of patients were transferred from a first hospital of admission to more specialised units. Both mild and severe cases in study hospitals and severe cases transferred from other hospitals were studied; however, non-referred mild cases might not have been ascertained. Bias towards mild cases might also have occurred because of challenges in recruiting patients who died soon after admission, although we were only notified of few such cases. Of all patients initially screened, about a third had proven non-encephalitis illnesses, which presented as mimics of encephalitis, as described in other studies.³²

Timing of sample acquisition during CNS infections affects test positivity and this factor might have contributed to failure to identify organisms.³³ The largest proportion of unknown causes was seen in children compared with older adults, as reported in other studies.¹³ Cases of ADEM were unlikely to be among the group with unknown cause because most had ADEM excluded after MRI head scans. Although undescribed microbes or novel immune-mediated causes might contribute to cases classified as unknown, non-encephalitic causes should also be considered. The poor outcome we report in those for whom a cause could not be identified emphasises the importance of further research to define causality in these patients.

Contributors

JG and NSC led the study design, recruitment of hospitals to the study, epidemiological analysis, and writing the paper; ALW, DM, KJM, MZ, and RC were involved in recruitment of hospitals to the study and epidemiological and clinical analyses; HEA and JPC did the laboratory studies and writing of the paper; RC, MZ, KJM, KNW, TS, and MPTL contributed to the writing of the paper and did the clinical diagnostics; SRI and AV did the auto-antibody assays and contributed to the relevant part of the manuscript; and NSC, JG, NWSD, DM, and DWGB initiated the study, contributed to the clinical and epidemiological analyses, and were involved in writing the report.

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Conflicts of interest

AV and the Department of Clinical Neurology in Oxford receive royalties from Euroimmun AG and Athena Diagnostic, and payments for antibody assays. All other authors declare that they have no conflicts of interest.

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