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Clinical Short Communication

First reported cases of anti-NMDA receptor encephalitis in Vietnamese adolescents and adults

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ABSTRACT

Introduction: Anti-NMDA receptor encephalitis is increasingly recognised as an important differential diagnosis in patients with encephalitis of unknown aetiology. We report the first case series of patients diagnosed in Vietnam.
Methods: Samples of CSF from patients with presumed encephalitis but negative microbiological investigations, who exhibited dyskinesia, autonomic instability or psychosis were tested for antibodies against the NR1 subunit of the glutamate (type-NMDA) receptor using an indirect immunofluorescence assay.
Results: Of 99 patients admitted with all-cause encephalitis over an 18 month period, 9.1% (n = 9 patients, 5 female, median age 28 years) had confirmed NMDAR encephalitis. All patients were admitted from one mental health hospital, and the incidence may therefore be an underestimate. Common features included reduction in speech (n = 9), catatonia (n = 9), convulsions (n = 7), dyskinesia (n = 9), rigidity (n = 9) and autonomic dysfunction (n = 7). Aside from a modest lymphocytic pleocytosis, routine CSF analysis was usually normal. No female patient had ovarian teratoma detected by abdominal ultrasound. Most patients were treated with high dose corticosteroids, and one patient received intravenous immunoglobulin. The median duration of hospitalization was 75 days and no patient died during admission.
Conclusions: Anti-NMDA receptor encephalitis is an important differential diagnosis to consider for patients presenting with acute onset psychiatric symptoms, who develop ensuing seizures, movement or autonomic disorder in Vietnam. A stronger evidence base for management and access to second line immunotherapy agents may help to reduce morbidity from this disease.

1. Introduction

Encephalitis is a condition defined by inflammation of the brain parenchyma with associated neurological dysfunction. Globally, its incidence has increased by 7.7% between 2005 and 2015 [1]. While encephalitis is most often suspected to be viral in aetiology, extensive investigation frequently fails to identify an infectious pathogen. Likewise in a recent cohort of 291 adults with presumed viral encephalitis admitted to our hospital, only 32% of patients had a microbiologically confirmed infection [2]. Patients with encephalitis of unknown aetiology often have prolonged hospital stays, and are discharged with lasting neurological impairment [2,3].

Over the past 10 years, autoimmune encephalitides, especially anti-*N*-methyl D aspartate (NMDA) receptor encephalitis, have been increasingly recognised as important differential diagnoses for viral encephalitis, particularly in young adults and children [4,5,6]. Notably, the California Encephalitis project found that the frequency of anti-NMDA receptor encephalitis surpassed that of individual viral infections to cause 41% of known-cause encephalitis in patients aged <30 years in the USA [7]. Since its first discovery in 2007 as a phenomenon associated with underlying ovarian teratoma, the epidemiology of anti-NMDA receptor encephalitis has shifted substantially; it has more often been reported in female patients without tumor, males and children in recent years [8]. There are few reports from resource-limited settings [9].

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Distinguishing between infectious and autoimmune causes of encephalitis is essential to help direct therapy, with antimicrobial agents for the former and immunosuppression for the latter. Until recently, laboratory methods to confirm the diagnosis of anti-NMDA encephalitis were not available in Vietnam, and no cases have yet been reported from the country.

At an infectious diseases referral hospital in southern Vietnam, we investigated whether anti-NMDA receptor encephalitis was prevalent in patients with suggestive clinical features, in whom conventional microbiological testing had not identified an infectious cause. Herein we report the demographic characteristics, clinical features, management and outcomes of the first case series of patients with anti-NMDA receptor encephalitis in Vietnam.

2. Methods

2.1. Setting

The study was conducted in an adult infectious diseases ward of the Hospital for Tropical Diseases in Ho Chi Minh City, Vietnam. The ward specializes in the treatment of patients with severe central nervous system infection. The hospital is a primary, secondary and tertiary referral centre for the whole of southern Vietnam, and serves a population of over 42 million people.

2.2. Inclusion criteria

Primary screening criteria included adult patients (aged ≥15 years) admitted to the ward with presumed encephalitis, who exhibited at least one of abnormal movements (orofacial, limb or trunk dyskinesia), seizures, autonomic dysfunction and/or personality change or psychosis, and whose CSF tested negative on all microbiological investigations.

Between January 2015 and February 2016, patients meeting the screening criteria were retrospectively selected from a descriptive study aimed at improving the diagnosis of CNS infections in Vietnam. Between March and September 2016 when the diagnostic test for anti-NMDA receptor encephalitis was available as part of routine care in our hospital, any patient meeting the criteria was included.

2.3. Clinical information and CSF collection

Information on demographics, clinical features and management was collected, alongside an acute CSF specimen for each patient, which was either stored at −80 °C for subsequent analysis (January 2015–February 2016) or processed immediately (March–September 2016). Routine analysis for all CSF samples included cell count, protein, lactate and glucose analysis, gram stain and bacterial culture, india ink, Ziehl-Neelson staining and real time PCR for Herpes Simplex virus 1 and 2. Additional analyses included mycobacterial culture, fungal culture, IMMY lateral Flow Assay and Japanese encephalitis virus specific IgM when clinically indicated.

2.4. Diagnosis of anti-NMDA receptor encephalitis

For patients selected from the descriptive study mentioned above, detection of antibodies (IgA, IgG or IgM) against the NR1 subunit of the glutamate (type-NMDA) receptor was done using an in-house [10] and/or a commercial indirect immunofluorescence cell-based assay (Cat. No. FB 112d-1005-51, EUROIMMUN, Luebeck, Germany). For the period from March to September 2016, the EUROIMMUN assay was used as part of routine diagnosis. All the assays were carried out as previously described [10] or according to the manufacturer's instructions (EUROIMMUN), and the results were read by fluorescence microscopy (Nikon). Auto-antibody testing was conducted on CSF samples only.

2.5. Outcome assessment and follow up

Outcomes were assessed on the basis of survival to discharge, and residual symptoms and degree of independent functioning at 8 month follow up, as reported by the patient and family members by telephone consultation.

2.6. Ethics

The study was approved by the Scientific and Ethical Committee of the Hospital for Tropical Diseases, Vietnam, and the Oxford University Tropical Research Ethics Committee, UK. Informed consent was obtained in writing from patients or from family members if the patient was unconscious.

3. Results

Of 99 patients admitted with all-cause encephalitis over the 18 month study period, 24 patients fulfilled the selection criteria. Nine patients

Table 1
Clinical features displayed by patients with confirmed anti-NMDA receptor encephalitis at any stage during their hospital admission.

Characteristic	
Female	5 (55.6)
Age	28 (15–43)^
Duration of illness prior to admission to HTD (days)	14 (14–52)^
Prior admission to Mental Health hospital	9 (100)
Symptoms	
Insomnia	2 (22.2)
Delusions	2 (22.2)
Reduction in speech/mutism	9 (100)
Irritability	4 (44.4)
Hyperactivity	4 (44.4)
Catatonia	9 (100)
Clinical signs	
Fever >38 °C	2 (22.2)
Convulsions	7 (77.8)
Movement disorder	
Chewing	8 (88.9)
Tongue biting	5 (55.6)
Dystonia	5 (55.6)
Rigidity	9 (100)
Autonomic dysfunction	
Tachycardia	7 (77.8)
Tachypnoea	7 (77.8)
Sweating	7 (77.8)
Required invasive ventilation	8 (88.9)
CSF analysis	
CSF white cell count (cells/mm^3)	16 (5–116)^
CSF protein (g/dL)	0.24 (0.2–0.6)^
CSF glucose (mmol/L)	4.1 (3.5–5.3)^
CSF glucose/blood glucose ratio >0.5	9 (100)
CSF lactate (mmol/L)	1.9 (1.7–3.3)^
Imaging	
CT	3
MRI	6
Reported as abnormal (see Fig. 1)	1
Investigation for teratoma	
Trans-abdominal ultrasound (female)	5
Management	
Methylprednisolone/prednisolone	7
Intravenous immunoglobulin	1
Dexamethasone	1
No corticosteroid therapy	1
Outcome at discharge (n = 8)	
Survival to discharge	8
Duration of hospital stay (days)	75 (35–98)^
Outcome at 8 months (n = 7)	
Returned to work/school	4
Independent with activities of daily living	7
Residual cognitive deficit	2

N (%), Median (range)^. Unless otherwise stated, n = 9.