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Neurological manifestations of dengue: a comparative study of viral, clinical, pathophysiological and genetic factors

Submission date	Recruitment status	[X] Prospectively registered
16/07/2008	No longer recruiting	[_] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
17/07/2008	Completed	[_] Results
Last Edited	**Condition category**	[_] Individual participant data
26/01/2009	Infections and Infestations	[_] Record updated in last year

Plain English summary of protocol
Not provided at time of registration

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers

ctu01dxdec07

Study information

Scientific Title

Study objectives
The aim of the current study is to gain more insight into the pathogenesis of dengue-associated neurological manifestations by detailed virological analyses, radiological assessments and analyses of the host response and genetics in dengue patients with central nervous system (CNS) symptoms.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Ethics approval pending as of 16/07/2008 from:
1. Oxford Tropical Medicine Research Ethics Committee (OXTREC) (UK)
2. Hospital for Tropical Diseases (Viet Nam)
2. Childrens Hospital No. 1 (Viet Nam)

Study design
A descriptive, prospective, case-control study

Primary study design
Observational

Secondary study design
Case-control study

Study setting(s)
Hospital

Study type(s)
Diagnostic

Participant information sheet
Not available in web format, please use the contact details below to request a patient information sheet

Health condition(s) or problem(s) studied
Dengue fever (neurological)

Interventions
Blood tests:
At day of inclusion and at day 6 (or at discharge if patients are discharged before day 6), 4 ml of ethylenediaminetetraacetic acid (EDTA) blood will be drawn. The following blood tests will be done at childrens Hospital No. 1:
1. Routine tests (complete blood count [CBC], ureas and electrolytes [U&E], liver function tests

[LFTs], glucose, albumin, ammonia)
2. Dengue NS1 rapid test

The remainder of the sample will be used at HTD/OUCRU for:
3. Dengue NS1 ELISA
4. Anti-dengue virus (DENV) and anti-Japanese encephalitis virus (JEV) IgM/immunoglobulin G (IgG) detection
5. RT-PCR for DENV
6. DENV viral load assessment
7. DENV whole genome sequencing
8. Immunological testing (chemokines/cytokines)
9. Cell pellets obtained after separation of plasma from blood will be stored for future host genetic analyses. The specific analyses will in part depend on the preliminary results of an ongoing project at OUCRU/HTD which looks at possible host-genetic factors in dengue haemorrhagic fever (DHF)/dengue shock syndrome (DSS).

Also, at day of inclusion and at day 6 (or at discharge if patients are discharged before day 6) a lumbar puncture will be performed and 4 ml and 2 ml of CSF will be drawn, respectively. A magnetic resonance imaging (MRI) scan will be performed on all patients in group A when they are stable enough to endure such a scan. In case of fatal outcomes, after consent has been given by parents/legal guardians, post-mortem biopsies will be obtained from brain and liver and stored.

Intervention Type
Other

Phase
Not Specified

Primary outcome measure
1. To compare the clinical, radiological and laboratory findings in paediatric dengue patients with and without neurological manifestations and in children with Japanese encephalitis or other viral encephalitides and relate this to outcome

Secondary outcome measures
1. To evaluate antigen detection-based assays for the diagnosis of DENV and JEV infection in children with neurological manifestations. We will use currently available, or if necessary, re-configured NS1 Ag detection assays as a diagnostic tool, and compare sensitivity and specificity with serology.
2. To measure virological parameters in paediatric dengue patients with and without neurological manifestations, and in patients with JE (or other viral encephalitides) and study the genome of these viruses. We will compare plasma viral loads and NS1 concentrations at baseline in dengue cases with and without CNS involvement. We will sequence the complete genomes of viruses isolated from the CSF and plasma of all dengue and JE cases.
3. To define and characterise the CSF pleiocytosis resulting from DENV or JEV infection by flow cytometry and relate this to outcome. Potential qualitative and quantitative differences in the CSF cellular response between patients with true encephalitis (e.g. JE) and patients with dengue-associated neurological symptoms may provide insight into the pathogenesis of dengue-associated neurological disease.
4. To define the inflammatory response, including cytokines, chemokines and their receptors in plasma and CSF, as well as soluble markers of neuronal damage and macrophage activation in

CSF, and relate these to outcome
5. To determine whether there are host genetic factors associated with the development of neurological manifestations resulting from DENV or JEV infection

Overall study start date
01/04/2009

Completion date
01/10/2011

Eligibility

Key inclusion criteria
Cases:
1. Aged between 6 months and 16 years, either sex
2. Consent given by parents or legal guardians
3. History of fever with altered or reduced conscious level (Glasgow coma scale less than or equal to 14) lasting longer than 1 hour
4. History of illness of less than 7 days
5. One or more of the following on admission:
5.1. Hepatomegaly
5.2. Skin or any organ bleeding
5.3. Platelet count less than 150,000/mm^3
5.4. Haematocrit greater than 42%
5.5. Serum glutamic oxaloacetic transaminase (SGOT)/prothrombin time (PT) greater than 100
5.6. Albumin less than 3.2 g/dL
5.7. Positive rapid test for Dengue NS1 (plasma or cerebrospinal fluid [CSF]), or any of the following at Hospital for Tropical Diseases (HTD)/Oxford University Clinical Research Unit (OUCRU):
5.7.1. Positive Dengue immunoglobulin M (IgM)/NS1 enzyme-linked immunosorbent assay (ELISA) (plasma or CSF)
5.7.2. Positive dengue reverse transcription polymerase chain reaction (RT-PCR) (plasma or CSF)

Control group 1:
1. First consecutive, age-matched hospitalised dengue patient
2. Confirmed by rapid NS1-detection
3. Parents/legal guardians give informed consent to participate in the study

Control group 2:
1. First two consecutive, age-matched patients admitted with suspected viral encephalitis
2. Parents/legal guardians give informed consent to participate in the study based on:
2.1. History of fever with altered or reduced conscious level lasting longer than 1 hour
2.2. History less than 7 days
2.3. Two or more of the following signs or symptoms:
2.3.1. Seizures*
2.3.2. Agitation/delirium/behavioural changes
2.3.3. Abnormal movements
2.3.4. Facial/limb paresis/paralysis
2.3.5. Dysconjugate gaze
2.3.6. Extrapyramidal signs/symptoms (e.g. ataxia, tremor, rigidity, masked facies)
2.3.7. Neck stiffness

2.3.8. Tense fontanel
2.3.9. CSF pleiocytosis
2.3.10. Electroencephalogram (EEG)/neuroimaging findings consistent with encephalitis, or
2.4. Laboratory evidence of viral aetiology of encephalitis

*Children between six months and five years with a single convulsion lasting less than 15 minutes who recovered consciousness within 60 minutes are considered to have had a simple febrile convulsion

Participant type(s)
Patient

Age group
Adult

Sex
Both

Target number of participants
We expect to enrol 50 study patients in a period of two years; 50 non-encephalitis dengue patients and 100 encephalitis patients will serve as control groups.

Key exclusion criteria
1. Bacterial, mycobacterial or parasitological causes as evidenced by microscopy or culture of CSF
2. Pre-existing neurological conditions, e.g. cerebral palsy, epilepsy, cerebral infarction /haemorrhage
3. Pre-existing chronic liver or renal disease

Date of first enrolment
01/04/2009

Date of final enrolment
01/10/2011

Locations

Countries of recruitment
Viet Nam

Study participating centre
The Oxford University Clinical Research Unit (OUCRU)
Ho Chi Minh City
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Sponsor type
University/education

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ROR
https://ror.org/052gg0110

Funder(s)

Funder type
Charity

Funder Name
The Wellcome Trust (UK) (grant ref: 077078)

Results and Publications

Publication and dissemination plan
Not provided at time of registration

Intention to publish date

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration