Chronic Panencephalitis in a Patient with Progressive Dementia with Extrapyramidal Features

ANN NEUROL 2019;86:695–703

A

Clinical manifestation

Management

Travel history

- Loss of balance
- Dysarthria
- Involuntary movement of toes
- Psychomotor slowing
- Cerebellar signs
- Subcortical dementia
- Involuntary movements
- Supranuclear palsy phenotype

- Bed bound
- Mute
- Autonomic dysfunction
- Death

- Medical leave
- Glatiramer acetate
- Brain biopsy
- "Immunomodulatory therapies"
- "Chelation therapy"
- Hospice

- Immigrated to USA
- Multiple trips to India
- Trip to India

Undiagnosed Diseases Program; NIH
Dengue antibodies are enriched in the CSF

Extensive work up for infections including PCR for arboviruses in CSF was negative

Johnson et al., Ann Neurology Nov 2019
Immunostaining with antibody to Flaviviruses

4G2 in the cortex

Myounghwa Lee; NINDS
RNA Insitu hybridization for Dengue virus (types 1, 3, 4)

Cortex

Hippocampus

Cerebellum

Myounghwa Lee; NINDS
Dengue virus 1 isolate NIV_K130706770_India, complete genome
Sequence ID: KJ755855.1 Length: 10727 Number of Matches: 1
Related Information
Range 1: 10630 to 10693 GenBank Graphics Next Match Previous Match First Match

Alignment statistics for match #1

<table>
<thead>
<tr>
<th>Score</th>
<th>Expect</th>
<th>Identities</th>
<th>Gaps</th>
<th>Strand</th>
<th>Frame</th>
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<tbody>
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<td>119 bits(64)</td>
<td>2e-25()</td>
<td>64/64(100%)</td>
<td>0/64(0%)</td>
<td>Plus/Plus</td>
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Features:
Query  6       GCATATTGACGCTGGGAGAGACCAGAGATCCTGCTGTCTCTACAGCATCATTCCAGGCAC
65
Sbjct   10630   GCATATTGACGCTGGGAGAGACCAGAGATCCTGCTGTCTCTACAGCATCATTCCAGGCAC
10689

Query  66     AGAA  69
              ||||
Sbjct  10690  AGAA  10693

DENV 1 outbreak in Tamil Nadu 2012; Asian Strain
Cecilia et al., Virology Oct 2017
PCR confirmed DENV1 at autopsy and biopsy

<table>
<thead>
<tr>
<th>PCR primers:</th>
<th>Dengue 1</th>
<th>Dengue 4</th>
<th>Dengue 1</th>
<th>Dengue 4</th>
<th>Dengue 1</th>
<th>Dengue 4</th>
<th>Dengue 1</th>
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<tbody>
<tr>
<td>Autopsy</td>
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<td>Biopsy</td>
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<td>Positive control</td>
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<td>Negative control</td>
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</tbody>
</table>

Johnson et al., Ann Neurology Nov 2019
Antibody titers to Dengue virus

- Clinical assay (Quest):
  - IgM – not detected
  - IgG – 10.32 (very high, out of range of assay)
  - RNA not detected
  - NS1 antigen not detected

- NIH subtyping:
  - DENV1 – 1450
  - DENV2 – 1977
  - DENV3 – 4181
  - DENV4 – <10

Johnson et al., Ann Neurology Nov 2019
The patient was infected with three different serotypes but only one was present in the brain.

Should infection with one serotype protect against the others?
Intermediate antibody levels from previous Dengue infection cause severe complications with reinfection

Katzelnick et al., Science 2017
Tetravalent vaccine used in Philippines but poor immune response against Serotype 2

Increased cases of dengue encephalitis in vaccinated children
Why was the virus not detected in CSF despite extensive infection of the brain?

Is the brain a unique reservoir?

How does the virus spread in the brain?

Can the virus mutate and adapt to survive in the brain?
Pathway for JC virus entry into the brain

Gene rearrangement in B cells

Progressive multifocal leukoencephalopathy
16 yrs female with refractory aplastic anemia

3/2015: Allogeneic stem cell transplant
5/2016: Graft vs Host disease
   multiple immunosuppressive treatments

11/2016: ruxolitinib
1/2017: fever, seizure like episode
   IL-2R (3,230pg/ml),
   elevated ferritin (59,326 mcg/L),
   Diagnosis: Hemophagocytic Histiocytosis

CSF: 1 WBC
   Protein: 98 313 mg/dL
   JCV: 445K/ml 1.8 Million/ml

EEG: Normal Progressive slowing
2/2017: Cerebral edema and Herniation
Fatal encephalopathy with wild-type JC virus and ruxolitinib therapy

<table>
<thead>
<tr>
<th>Autopsy Tissue</th>
<th>JCV Copies/mL</th>
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<tbody>
<tr>
<td>Frontal</td>
<td>4,735,242,050</td>
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<tr>
<td>Parietal</td>
<td>4,781,155,650</td>
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<tr>
<td>Temporal</td>
<td>6,354,835,000</td>
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<tr>
<td>Occipital</td>
<td>9,000,000,000</td>
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<td>Basal Ganglia</td>
<td>1,573,875,150</td>
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<tr>
<td>Pons</td>
<td>2,255,356,400</td>
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<tr>
<td>Cerebellum</td>
<td>2,474,767,200</td>
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</table>

12 basepair insertion in T protein of JC virus leads to expansion of transcription binding sites

<table>
<thead>
<tr>
<th>TF_Matrix_Family</th>
<th>TF_Matrix_Family_Description</th>
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<tr>
<td>O$INRE</td>
<td>Core promoter initiator elements</td>
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<tr>
<td>V$BRN5</td>
<td>Brm-5 POU domain factors</td>
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<tr>
<td>V$CIZF</td>
<td>CAS interacting zinc finger protein</td>
</tr>
<tr>
<td>V$EV11</td>
<td>EVI1-myleoid transforming protein</td>
</tr>
<tr>
<td>V$FKHD</td>
<td>Fork head domain factors</td>
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<tr>
<td>V$GATA</td>
<td>GATA binding factors</td>
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<tr>
<td>V$PLZF</td>
<td>C2H2 zinc finger protein PLZF</td>
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<tr>
<td>V$PRDF</td>
<td>Positive regulatory domain I binding factor</td>
</tr>
<tr>
<td>V$RUSH</td>
<td>SWI/SNF related nucleophosphoproteins with a RING finger DNA binding domain</td>
</tr>
</tbody>
</table>
Key Points

Shows that the virus mutated to be able to replicate efficiently in brain and spread throughout the brain.

Here the critical mutations were in regulatory region to efficiently use transcription factors in brain cells.

How does the virus spread within the brain?
HIV Dementia
Restricted viral replication in astrocytes

Productive infection in perivascular macrophages

Jones et al., 2000; Kruman et al., 1998

Ranki et al., 1995
HIV env gene is maximally diverse in HIV dementia (van Marle, 2002)
HIV transmission from lymphocytes to astrocytes by viral synapse

Do et al, J Virol 2015
Interactions between processes of astrocytes and lymphocytes
GuanHan Li et al., AIDS 2015
Transmission occurs by cell to cell contact between Lymphocytes and astrocytes

Evades neutralizing antibodies

Restricted viral replication in long lived cells in the brain leads to persistent viral reservoirs
How can viruses transmit within the brain without releasing viral particles into the CSF?
Subacute Sclerosing Panencephalitis due to Measles infection

Several years after acute measles infection

Subacute progressive mental deterioration with myoclonus

CSF: Raised IgG; oligoclonal bands and measles antibody >1:4

EEG: Periodic spikes and sharp waves

Silva–Júnior FP et al., 2013
Lymphocytic meningitis

Neuronal loss

White matter pallor

astrocytosis

Measles antigen in oligos and neuronal axons

Mahadevan et al., Neuropathology 2008
Hyperfusogenic F Proteins in Measles virus are neuropathogenic

Angius et al., J Virol 2019
Cell to cell spread in neurons of Measles virus mediated by Fusion protein

Sato et al., J Virol 2018
Mechanism of viral spread in SSPE

Mutations in M protein: Lack of viral particle formation
Mutations in F protein: Enhance Cell to Cell fusion

Watanabe et al., Trends in Microbiology 2019
Ferren et al., Viruses 2019
Mechanism of viral spread in SSPE

Mutations in M protein: Lack of viral particle formation
Mutations in F protein: Enhance Cell to Cell fusion

-> Hypermutated
-> No budding

-> Hyper fusogenic F
Mutations in HRN, in HRC, between HRN and HRC
-> Elongated intracytoplasmic tail

-> Some mutations but not well documented

Viral RNA nucleoprotein complex transmits at synapses without causing syncytia
Cell to cell spread evades neutralizing antibodies

Watanabe et al., Trends in Microbiology 2019
Ferren et al., Viruses 2019
Mechanisms of transneuronal spread of viruses

**c. Retrograde spread**
Trans-synaptic (rabies virus, PRV, HSV-1)

**Microfusion** (measles virus)

Dendrite  Axon
CONCLUSIONS

The brain is a unique reservoir for the virus.

Those viruses that can mutate and adapt to environment in the brain will be able to establish a reservoir in the brain

• mutations aid cell to cell spread
• leads to efficient replication by use of new transcription factors
• evade the immune system
• infect long lived cells (astrocytes, oligodendrocytes and neurons)
• establish latency or restricted viral replication