Encephalitis in Infants and Children

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

Julia Granerod, Helen E Ambrose, Nicholas W S Davies, Jonathan P Clewley, Amanda L Walsh, Dilys Morgan, Richard Cunningham, Mark Zuckerman, Ken J Mutton, Tom Solomon, Katherine N Ward, Michael P T Lunn, Sarosh R Irani, Angela Vincent, David W G Brown, Natasha S Crowcroft, on behalf of the UK Health Protection Agency (HPA) Aetiology of Encephalitis Study Group

Summary

Background Encephalitis has many causes, but for most patients the cause is unknown. We aimed to establish the cause and identify the clinical diff erences 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 identifi ed 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 immunemediated 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 specifi c identifi ed cause.

www.thelancet.com/infection Published online October 18, 2010 DOI:10.1016/S1473-3099(10)70222-X

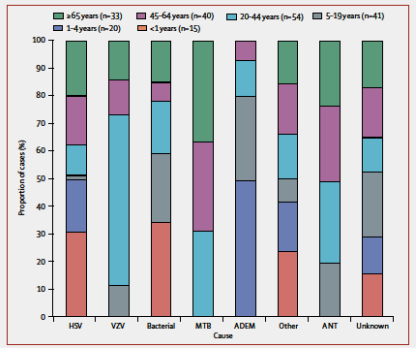

Figure 2: Age distribution of cases by cause
ADEM=acute disseminated encephalomyelitis. ANT=antibody-associated cause. HSV=herpes simplex virus. MTB=*Mycobacterium tuberculosis*. VZV=varicella zoster virus.

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	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
Mycobacterium tuberculosis	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
Toxoplasma gondii	–	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
Listeria monocytogenes	–	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

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Movement disorder after 21 days of primary intravenous aciclovir treatment for Herpes simplex encephalitis: are we making progress with this relapsing and remitting disease?

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Objectives

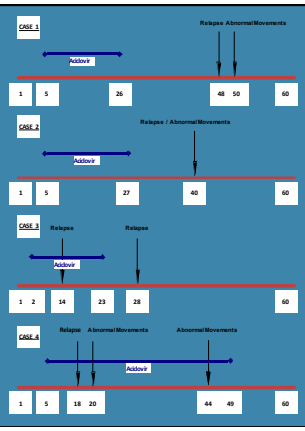
- HSV-1 Encephalitis in children is now treated with 21 days of high dose intravenous aciclovir
- Movement disorder onset after full treatment courses have been reported as consistent with relapsing disease

Cases

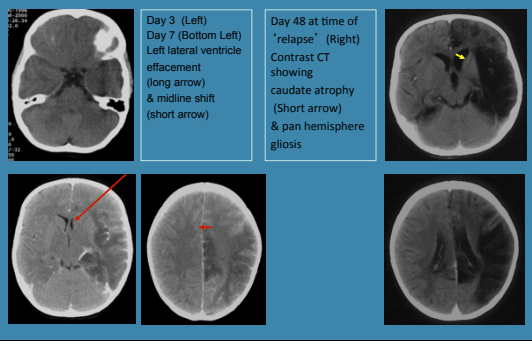
	1	2	3	4
Sex	Female	Female	Male	Male
Age (mts)	20	10	6	7
Dx	Seroconversion	HSV-1 PCR	HSV-1 PCR	HSV-1 PCR

- Between 1999 and 2007
- Classic presentations of fever, seizures requiring tertiary care including PICU at ECH
- All transferred to neurology at ECH
- All continue to be followed up by ECH

Aciclovir and Relapse



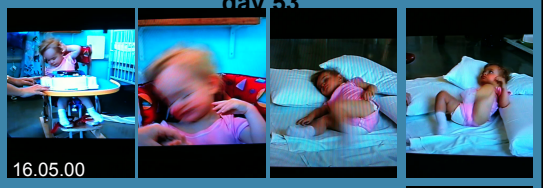
Case 1



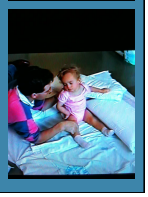
Day 3 (Left)
Day 7 (Bottom Left)
Left lateral ventricle effacement (long arrow) & midline shift (short arrow)

Day 48 at time of 'relapse' (Right)
Contrast CT showing caudate atrophy (Short arrow) & pan hemisphere gliosis

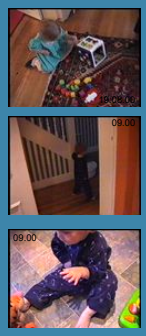
Video of hemiballismus at clinical relapse on day 53



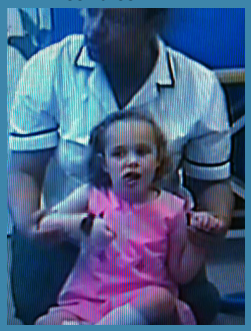
Lt hemiballismus onset day 50:
abolished by sleep
Corksrewing awake: 'candyfloss hair'
Most settled if nestled tightly in chair
Glazed look
Irritable++++++
NG feeding: can drink from spout
Rx: haloperidol 12.5microg/kg bd



2 years old

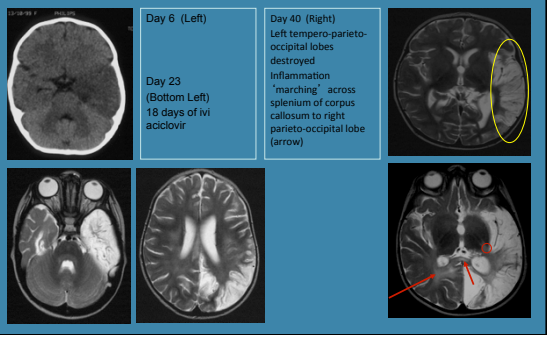


Tongue dyskinesia
+ seizures +++



6 years old

Case 2

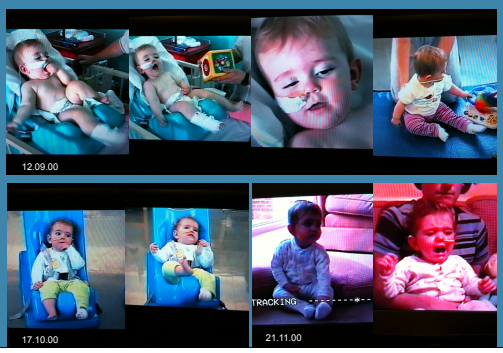


Day 6 (Left)

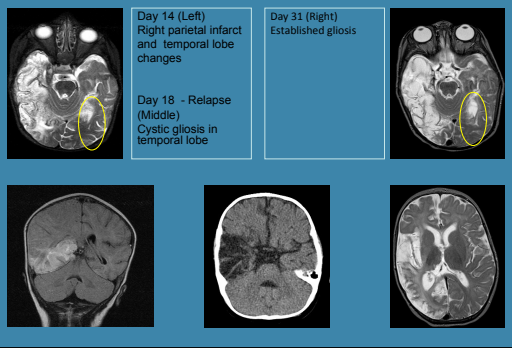
Day 23
(Bottom Left)
18 days of ivi aciclovir

Day 40 (Right)
Left tempero-parieto-occipital lobes destroyed
Inflammation 'marching' across splenium of corpus callosum to right parieto-occipital lobe (arrow)

Video of choreiform movements at clinical relapse on day 40



Case 4



Long-term Follow-up

- Case 1-3 are ambulant but have been left with severe cognitive and behavioural impairment.
- Case 4, still in primary phase at day 18 with fever and positive PCR.

  He completed 44 days of uninterrupted intravenous aciclovir and 13 months of oral valaciclovir.
- Better outcome with a mild left hemiplegia, well controlled seizures and minimal/no cognitive impairment

Conclusions

- All cases received haloperidol and swaddling acutely for the movement disorder (we would now probably use clonidine)
- A movement disorder may represent active HSV-1 disease even after 21 days of intravenous aciclovir treatment
- Possibly immune activated process
- Longer term treatment may improve

RESEARCH ARTICLE

N-Methyl-*D*-Aspartate Receptor Antibodies in Post–Herpes Simplex Virus Encephalitis Neurological Relapse

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ABSTRACT: Herpes simplex virus encephalitis (HSVE) is a devastating condition that relapses, often with a chorea in children, despite adequate antiviral treatment. At relapse, evidence of viral replication is frequently absent, suggesting that the relapse may be immune-mediated. Seven children who had a neurological relapse following their initial encephalitis, identified from 20 cases of pediatric HSVE, were studied. Serum and/or cerebrospinal fluid (CSF) were tested for *N*-methyl-*D*-aspartate receptor (NMDAR) and other antibodies previously reported in central nervous system autoimmunity. Five of the 7 relapsing children had choreoathetosis; 2 of these were NMDAR antibody–positive, 2 were negative (1 with HSV-positive CSF), and 1 was not available for testing. An additional patient, who relapsed with cognitive regression but with no movement disorder, was also NMDAR antibody–positive. In 2 of the NMDAR antibody–positive patients who were treated at relapse and in 1 who was treated following only after 10 years of having a relapsing encephalopathy, a beneficial response was observed. Neurological relapses after HSVE may frequently be immune-mediated, particularly in children with chorea. NMDAR antibodies are common, and immunotherapy may be beneficial. © 2013 *Movement* Disorder Society

Key Words: herpes simplex virus; encephalitis; *N*-methyl-*D*-aspartate (NMDA) receptor; choreoathetosis; movement disorder; relapsing

RESEARCH ARTICLE

N-Methyl-*D*-Aspartate Receptor Antibodies in Post–Herpes Simplex Virus Encephalitis Neurological Relapse

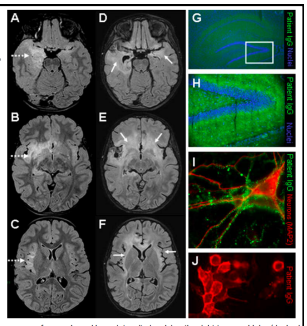

FIG. 1. Neuroimaging of BH case 2 (**A**–**F**). Axial FLAIR images showing an area of parenchymal hyperintensity involving the right temporal lobe (dashed arrow, **A**) extending into the adjacent frontoparietal regions (dashed arrow, **B**) and insula (dashed arrow, **C**), with some early involvement in the contralateral temporal lobe. Repeat MRI on day 30 demonstrates progression of hyperintensity to involve larger regions of the left and right temporal lobes (white solid arrows, **D**), frontoparietal white matter (white arrows, **E**), and insula (white arrows, **F**) with ex vacuo enlargement of the left lateral ventricle and less marked encephalomalacia of the mesial temporal lobe (**D**, **E**). This characteristic limbic involvement with apparently unilateral onset and subsequent less marked contralateral limbic involvement ("sequential bilaterality") is consistent with HSVE. Detection and characterization of NMDAR antibodies in BH case 2 (**G**-**I**). Hippocampal "neuropil" binding pattern on sagittal rat brain sections (**G**, ×10) and the dentate gyrus shown in higher magnification (**H**, ×20). IgG NMDAR-antibody-positive serum (green) showing surface binding to two superimposed neurons and their processes in primary cultures of live hippocampal neurons identified by the neuronal marker microtubule–associated protein 2 (MAP2, in red) (**I**, ×100). Cell-based assay for NR1/NR2B (NMDAR) antibodies using transfected human embryonic kidney (HEK293) cells shows surface binding (red) (**J**, ×40).

BFMDRS 120:
How cliniacally severe is this dystonia?

On lap | In seating | NG feeding

NMDA receptor antibody positive encephalitis: diagnosed 10 years later on stored serum!

Influenza Encephalitis ECH 2011

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Marilyn MacDougall
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Differences of Clinical Manifestations According to the Patterns of Brain Lesions in Acute Encephalopathy with Reduced Diffusion in the Bilateral Hemispheres

ORIGINAL RESEARCH

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T. Tsuji
M. Suzuki
T. Kubota
T. Kato
M. Komatsu
T. Shono
F. Hayakawa
T. Shimizu
T. Morishima

BACKGROUND AND PURPOSE: The precise clinical characteristics of acute encephalopathy with bilateral reduced diffusion are not fully understood. We compared clinical, laboratory, and neuroimaging findings according to the patterns of brain lesions among children with reduced diffusion in the bilateral hemispheres.

MATERIALS AND METHODS: Nine patients were analyzed. The patterns of brain lesions were divided into diffuse lesions and central-sparing lesions. Diffuse lesions were defined as reduced diffusion in the whole cortex and/or subcortical white matter. Central-sparing lesions were defined as the lack of reduced diffusion in the areas around the bilateral Sylvian fissures. Clinical, laboratory, and neuroimaging findings were compared between groups.

RESULTS: Five patients showed diffuse lesions and 4 showed central-sparing lesions. Coma was significantly more common in patients with diffuse lesions, whereas a biphasic clinical course was more common in those with central-sparing lesions. Outcome was worse in patients with diffuse lesions. Maximal aspartate aminotransferase, alanine aminotransferase, and kinase levels were also significantly higher in patients with diffuse lesions. In 2 patients with diffuse lesions, diffusion-weighted images during the acute phase revealed reduced diffusion in the bilateral frontal and occipital areas, followed by diffuse lesions. No patient with central-sparing lesions showed MR imaging abnormalities during the acute phase.

CONCLUSIONS: Clinical manifestations in patients with diffuse lesions were severe, whereas those in patients with central-sparing lesions were relatively mild.

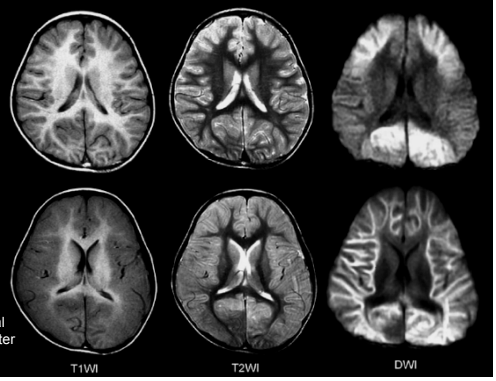
MRI in 65/79 cases
DWI in37/65
Widespread reduced diffusion in 9/37

MRI Diffuse reduced diffusion over 5 days in severe 'flu encepahalitis

N=5/37

Day one
Fronto-Occipital Cortical Reduced diffusion

Day 5
Diffuse cortical Swelling Reduced Subcortical White matter diffusion

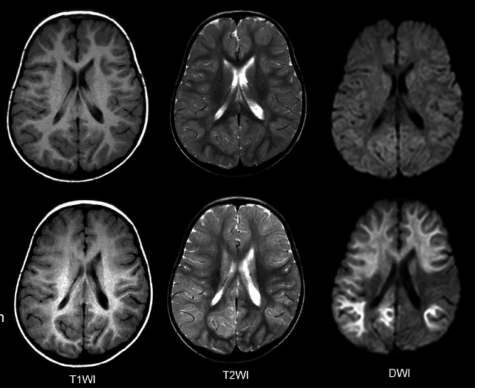


MRI central sparing diffusion over 5 days in severe 'flu encepahalitis

N=4/37

Day 2
Normal MRI

Day 4
Thickening & Reduced Diffusion of Frontal region & caudate



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T. Morishima

Table 1: Patients' characteristics, neurologic symptoms, and outcome

	Diffuse Lesions (n = 5)	Central-Sparing Lesions (n = 4)	P Value
Age (months)*	18 (3–52)	15 (10–66)	NS
Sex (M-F)	3:2	2:2	NS
Prodromal illness			Not done
Influenza	2	1	
Subitum	0	1	
Gastroenteritis	2	0	
NSFI	1	2	
Coma	5	1	.048
Biphasic clinical course	1	4	.048
Seizure at onset	3	4	NS
Prolonged seizure at onset	1	1	NS
Seizure after the first 24 hours	2	4	NS
Outcome			.056
Death	3	0	
Severe cognitive impairment	1	1	
Mild cognitive impairment	1	2	
Healthy	0	1	

Note:—NSFI indicates nonspecific febrile illness; NS, not significant.
* Data are shown as median (range).

Case presentation

13 yr EW

Presentation to Epsom A&E

- 12/12/10 with prolonged GTC
- 24hr Hx of non specific chest pain,fever, URTI
- Ambulance called 2 x 10mg rectal diazepam
- In A&E had 0.1mg/kg lorazepam IV then phenytoin → decision to intubate
- Intubated with propafol, sux and atrocurium
- Profound hypotension, ECG showed ST depression → started dopamine, noradrenaline and milrinone
- Transferred to PICU

Past Medical History

- SVD, Term, uneventful postnatal
- Developmentally normal
- Febrile convulsions (had >12 before age 2 yrs)
- Admitted to PICU 7yrs for prolonged seizure- intubated and ventilated for 48hrs
- CT head and EEG reported normal

Family History

- Strong family history of febrile convulsions up to age 7 yrs in father and in half brother
- Mother has schizophrenia

Multiorgan failure

- 1. CV- Myocarditis, hypotension
- 2. Respiratory- pulmonary oedema,
- 3. Neurology- obtunded
- 4. Renal- ARF multifactorial
- 5. GI and Liver- derranged LFTs, abnormal clotting
- 6. Sepsis

Cardiovascular

- Post intubation hypotension → inotropes for 5 days
- Cardiology team – Myocarditis
- Serial ECGs showed resolving ST changes
- Echo 12/12/10 " Normal structural heart, mildly impaired LV function due to septal dyskinesia"
- Trop T raised 9.8
- Received immunoglobulin
- Repeat echo "LV function slightly impaired" No f/u. Haemodynamically stable

Respiratory

- Arrived to PICU ventilated
- SIMV pressures 23/11 with poor respiratory effort
- CXR showed pulmonary oedema
- Weaned to PS mode
- Intubated for 14 days
- Unsafe to extubate → Tracheostomy 24/12/10
- Now self ventilating
- Decannulation of tracheostomy started

Renal

- Acute renal failure secondary to hypotension- very poor u/o
- Day 1 Cr 114, Ur 21, Na 146, K 3
- Day 5 Cr >500 anuric→ haemofiltration
- Renal USS "Bilateral echobright cortices in keeping with ARF"
- Hypertensive→ Amlodipine
- PD catheter inserted 24/12/10→ PD for 4 days.
- Now U&Es normalised
- Renal team r/v Amlodipine

GI and liver

- Acute liver dysfunction Day 1- ALT 4393 on 15/12/10
- INR 3.3 and thrombocytopenia
- Severe rhabdomyolysis (CPK 5093)
- received FFP+ Blood products

- Initially on TPN→ NJ feeds → NG feeds
- NG removed yest, eating and drinking well with assistance

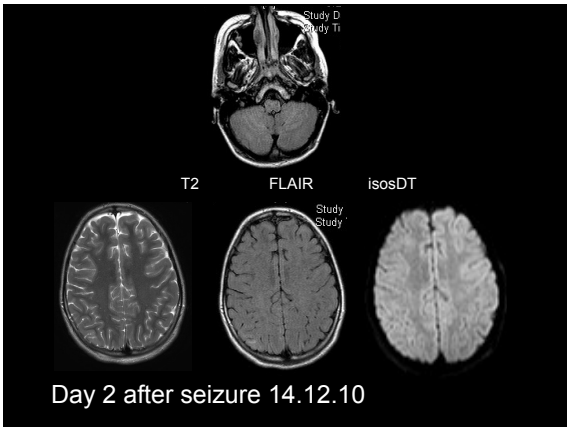
Other

- **Ophthalmology review-** bilateral subconjunctival haemorrhages
- "Blurred discs" will f/u

- **Sepsis**
- Influenza B virus on BAL on 13/12/10
- Blood cultures and CSF cultures NAD
- 10 day course of Tamiflu advised by ID
- 7 days Ceftriaxone and acyclovir

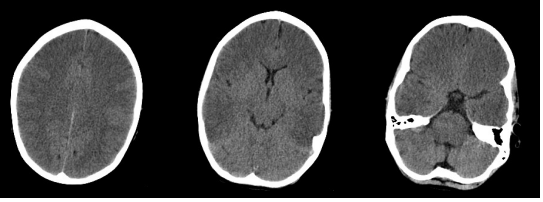
Neurology

- Day 1- obtunded GCS 3/15
- Day 2-MRI brain "Bilateral symmetrical cerebellar signal changes of uncertain aetiology." EEG showed features in keeping with an encephalopathy.

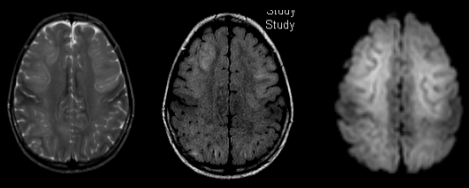


→ pred

ventilation requirements → IV phenytoin.
Urgent CT head " generalised cerebral oedema" EEG showed encephalopathy



Day 9 – MRI "extensive cortical swelling, oedematous change and diffuse white matter changes"

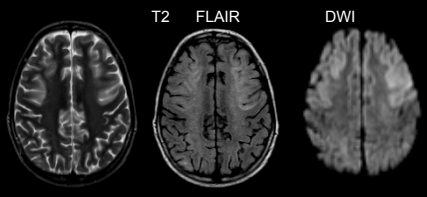


What is the prognosis based on these scans?

- Day 15 transferred to Savannah
- reacted to father's voice some voluntary movements
- O/E hypertonic R>L
- reflexes brisks, plantars equivocal
- fixing and following
- MRI 29.12.10

"diffuse white matter loss, swelling improved"

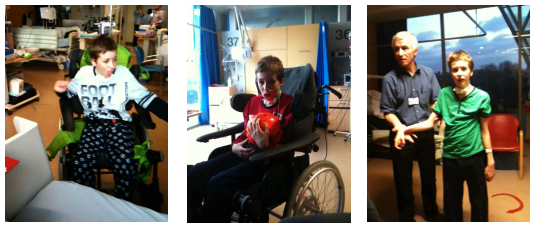
MRI 29.12.10



On prednisolone 20mg/day

- Rehab on Savannah
- 1. Physio
- 2. OT
- 3. SLT
- 4. Tracheostomy Nurses
- 5. Outstanding investigations

Rapid motor and emotional recovery



04.01.11 08.01.11 19.01.11

R C

Born May1999

Admitted ECH 05/01/2011

History

Flu-like symptoms
- 21-25 Dec High fever, vomiting, aching (famiy)
- 02/01 cough, feverishness

Treated by GP with amoxil on 02/01/11, seen at DGH for anaphylactic reaction

Re-presented & admitted 03/01/2011

On ward:
- Cold (temp 35)
- Sats 93% in air
- Tachycardic HR 120-130
- BP 100/60

PMH:
- Asthma
- Ventolin inhaler
- Flu vaccine Sept 2010
- Brother

PICU referral

05/01at 23:00
- ↑ Temp 37.5
- ↑ Respiratory distress : 6/ O2, sat 86%
- agitated and restless
- Persistent tachycardia, mottled , BP 114/68
- GCS 15/15 PEARL co-operative

Acute deterioration at 03:00
- anaesthetic team for help
- IV line sited: fluid bolus (5ml/kg)
- Patient less responsive

Resuscitation

- Acute respiratory arrest
  - Bag & mask ventilated
  - Recovered ?
  - Sedated with thiopentone & rocuronium
  - BP unrecordable
  - Bradycardia :PEA
  - Total of 4 minutes of CPR before output recovered
  - Required inotrope infusions to maintain BP

Retrieval

- Febrile 39^{o}C
- Gradual response to inotrope therapy
  - 04:00 BP 70/30 → 05:00 Bp 95/55
- High pressure to ventilate and oxygenate
- Pupils unequal Left >right
  - Responded to single dose 3% saline

Admission to PICU 07:30 05/1/11

Clinical signs:

Respiratory failure:
- FiO2 60%

Circulatory failure
- 4 inotropes

Renal impairment
- CVVH

CNS
- 4 limb shaking movement
- ? Waking up
- but pupils not reacting

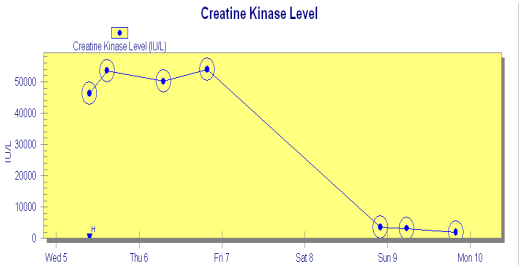
Results:

ECHO ↓ function

Deranged liver and renal function
- Urea 13, Creatinine 93
- ALT 231
- CPK 46 250

Metabolic acidosis
- pH 7.21 BE -11 lactate 4.5

RC CK levels Jan 2011



Initial treatment

Cefuroxime, Clarithromycin, Aciclovir, Tamiflu

IVIG 1g/kg/day

CVVH: high CK, fluid and temperature control

Day 2 : 06/01/2011

06:00 generalized tonic clonic seizure
- Duration 10 minutes
- Treated with IV diazepam & loading dose of phenytoin 3ml/kg 3% saline

Muscle relaxed &sedated, PEARL

H1N1 positive: zanamivir added

EEG report :
- background markedly abnormal, diffusely attenuated & slowed
- No electrographic response to stimulation
- No epileptiform activity / sub-clinical seizure activity seen

Day 3

Stable cardiac and respiratory function:
- no escalation of inotropes

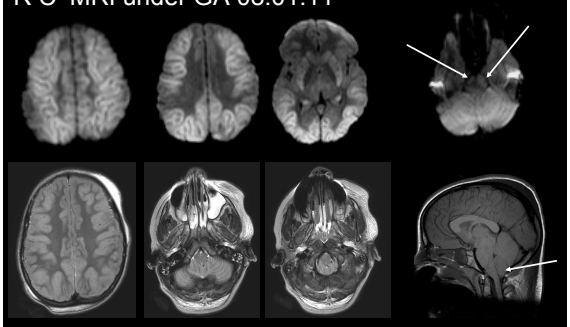
Still CVVH dependent, 5litres positive fluid balance

CNS: opens eyes to voice
- ongoing 'shivering' movements
- No purposeful movement seen
- Reflexes brisk
- Morphine 20mcg/kg/hr, clonidine 0.3mcg/kg/hr

Day 4

- Slight improvement in cardiovascular and respiratory status
- Decision to perform MRI: 08/01/2011
  - Necrotising encephaphalitis (extensive) impending tonsillar herniation
  - PICU discussion with mother & neurology team
- Started high dose Methyprednisolone
  - Single episode bradycardia & hypertension overnight

R C MRI under GA 08.01.11



What do the arrows show?

What is the prognosis based on these scans?

Next three days

- Ventilation & CVS status improved
- CVVH stopped on 10/1, PD inserted 12/1

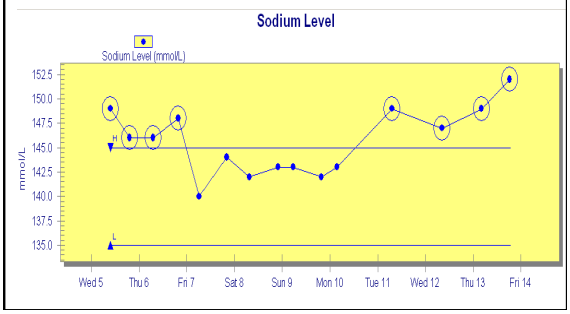
- CNS unchanged
  - Opening eyes
  - No other purposeful movements noted
  - Ongoing shivering movements
  - Brisk reflexes
  - Blinking, Cough & gag present

12/01/2011 21:00

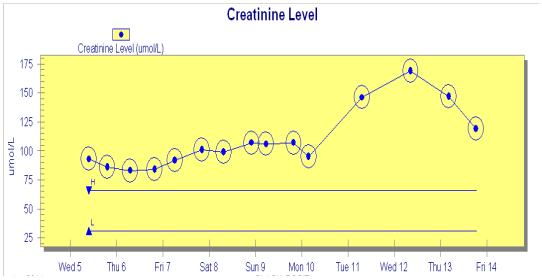
- Pupils fixed and dilated
- Large diuresis

- No response to pain
- Altered respiratory pattern
- Rx hypertonic saline
- Urgent CT scan at 22:10:
  - increased cerebellar tonsillar herniation

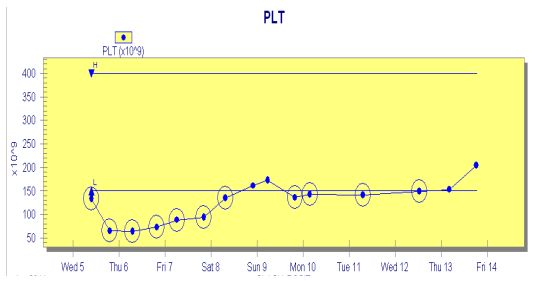
RC Sodium levels Jan 2011



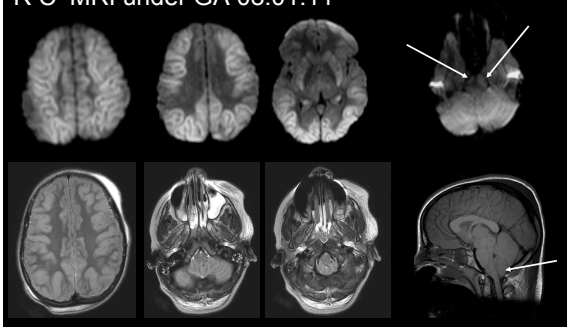
RC Creatinine Jan 2011



RC Platelet count Jan 2011



R C MRI under GA 08.01.11



What do the arrows show?

Died 13/01/2011

What is the prognosis based on these scans?

13/01/2011

- No clear improvement
- Discussion with mother
  - Extubated at 18:30
  - Deceased at 18:45