



A NOT SO ACCIDENTAL INJURY

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Patient LM

5 month old boy



- Presented to WFH:
 - Fell from arms onto bed
 - Subsequent apnoea requiring mouth to mouth administered by father
- Preceding h/o SOB and cough 2 weeks earlier, had improved with supportive Rx

Patient LM



At WFH

- Respiratory arrest requiring intubation, BMV
- Subsequent seizure
- Glucose normal
- ?bruising noted on ankles/forehead/shoulder

Transferred to trauma RCCH

?Head injury

Patient LM

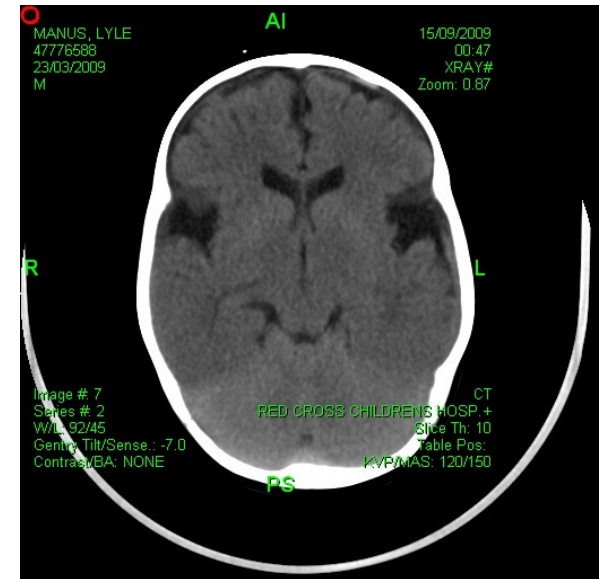
Failed trial of extubation

- *Uncontrasted CT brain:*

Reviewed by the neurosurgical registrar on call:
Atrophic brain but no evidence of fractures/SDH/intracerebral haemorrhage

- Ax: Minor closed head injury
- Consult again if deteriorates

Admitted to ICU



Patient LM

Diagnosis:

- Closed head injury
- Seizure (CHI related/sepsis/meningitis)
- Pneumonia- bilateral consolidation
- Unexplained pneumothorax/pneumomediastinum
- Bruising ?cause

***Possible case of NAI
(non-accidental injury)***

Background

- Term baby 2.87kg
- C/S for breech position
- Cord around neck
- Apgars 5 @ 1min/ 9 @ 5min
- Development normal to date
- No siblings
- No consanguinity/relevant family history



Background



- Mom's first pregnancy
- Difficulty conceiving
- No h/o prior miscarriages/SB
- Inconsistencies in the presenting history between parents
- Mom displayed blunted affect

Patient LM

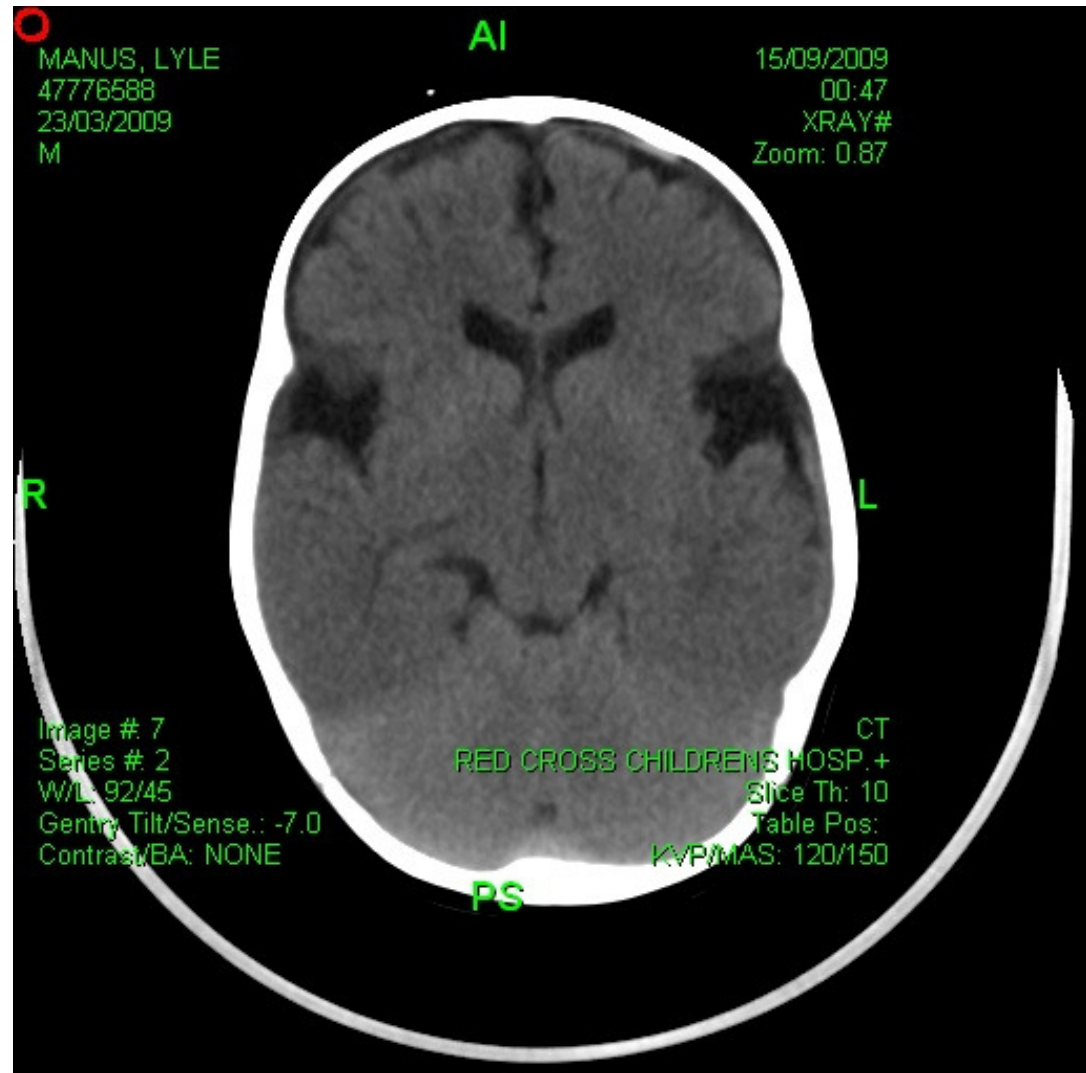
Day 2 in ICU:

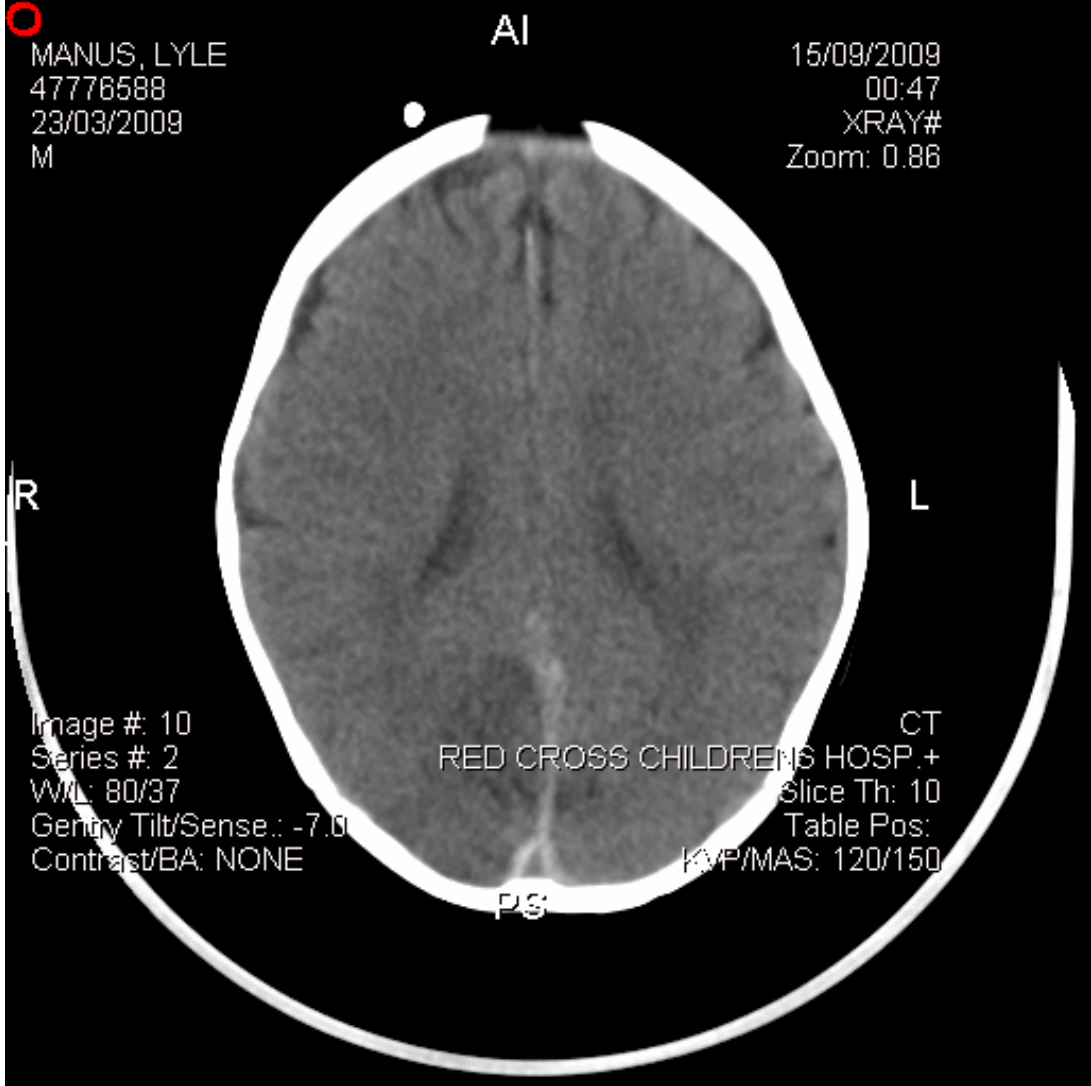
Reduced level of consciousness/bulging fontanelle

- Formal CT report
- Ophthalmology review- fundoscopy
- Skeletal survey
- EEG to exclude subclinical seizures
- Clotting profile



- No fractures
- **Subdural haemorrhages** of varying ages
- Subdural blood also **interhemispheric fissures/tentorium**
- Prominent CSF spaces in sylvian fissures
- **Bilateral hypodensities** suggestive of contusion/infarcts





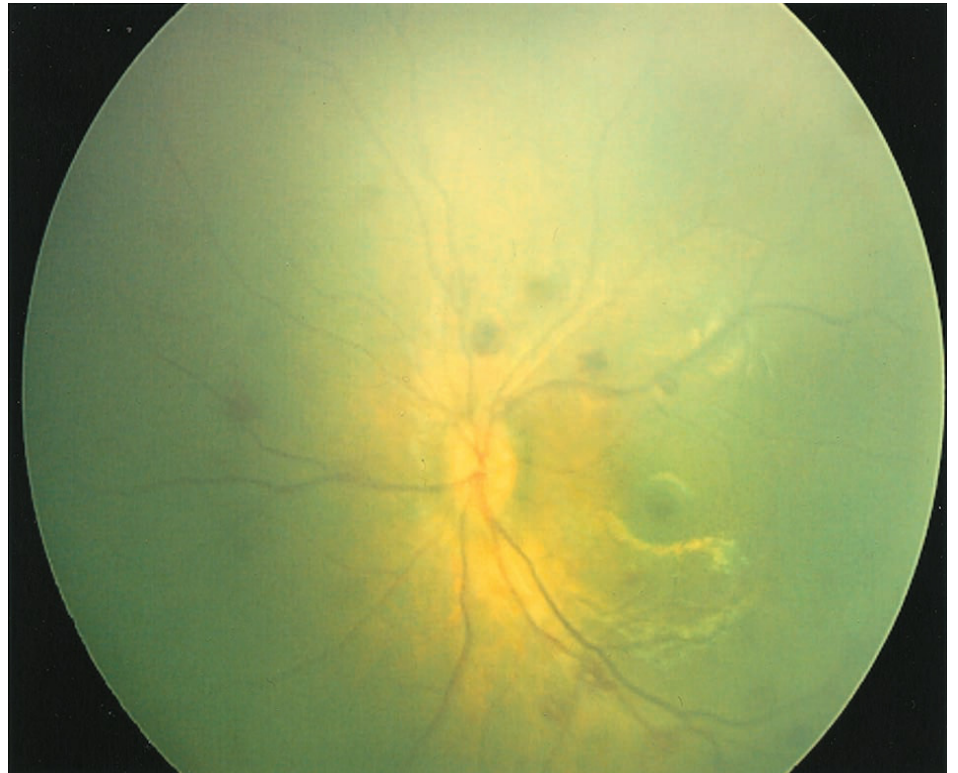
Highly suggestive of non-accidental injury

NAI

Further investigations

- Clotting profile: normal
- Skeletal survey: normal
- Fundoscopy:

***bilateral retinal
haemorrhages***



Open and shut case...

Must be NAI!

NAI?



- Standard NAI management protocol
- Family informed
- S/W involved
- Case opened



- Neurology consulted

Given overall findings- NAI

Urine sample for completeness

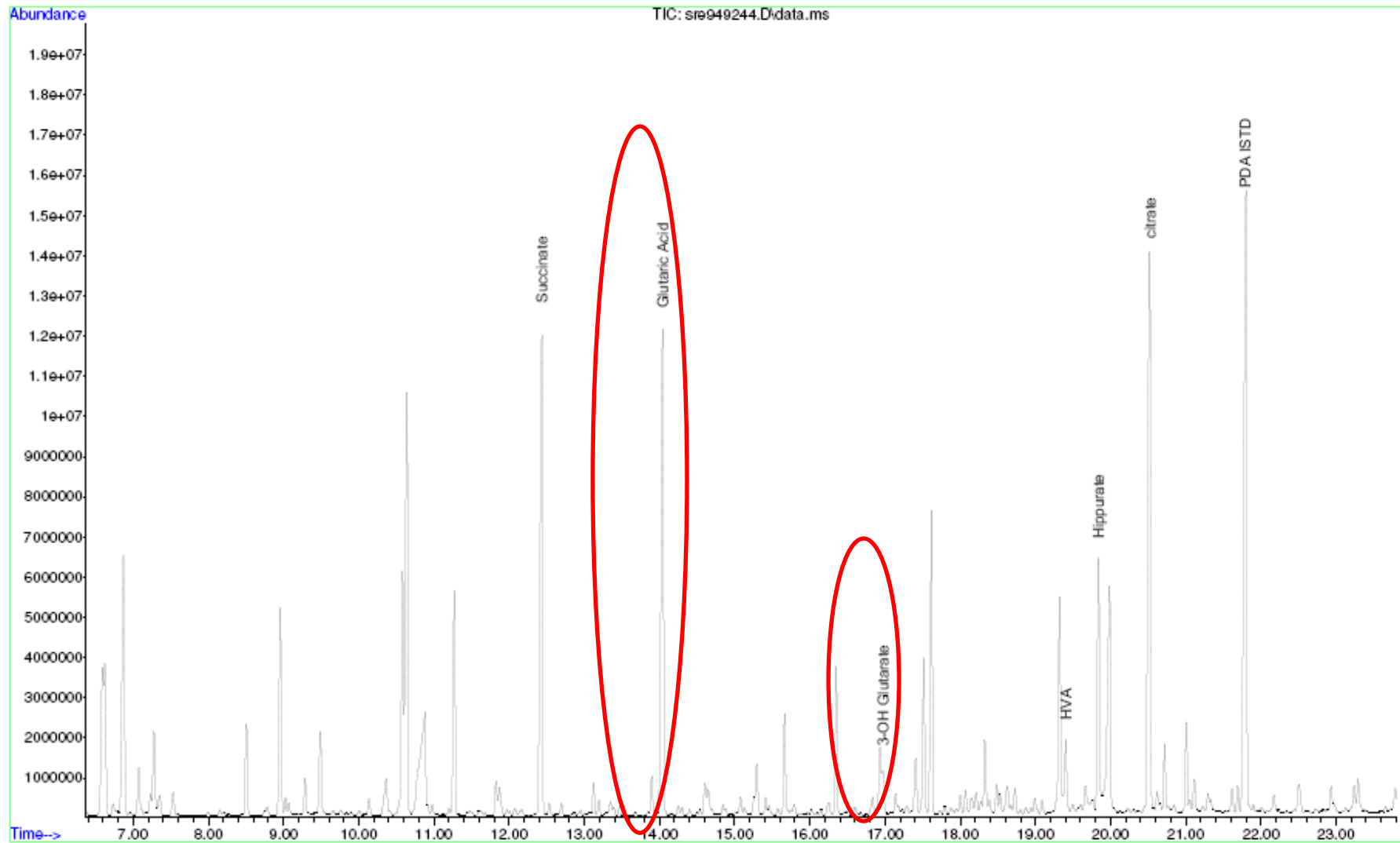
- Pneumonia resolved
- No further seizures/gradual improvement in level of consciousness
- Successfully weaned off ventilator
- Discharged from ICU

- Urinary profile:

Raised **urine glutaric acid**

Associated peak of **3-OH glutarate**





Must be NAI!

How did we nearly miss it and how do we explain the rest..?

- Clinical presentation- suspicious
- Bruising
- Pneumothorax/pneumomediastinum
- History inconsistencies
- Maternal affect
- Neuroimaging
- Retinal haemorrhages

Glutaric Aciduria type 1

- First described 1975 by Goodman et al
- 1991 Morton et al identified GA1 as cause of familial “Amish cerebral palsy” among the conservative Plain sect in Lancaster County, Pennsylvania
- Found over 80% of retrospectively identified patients had remained severely disabled by dystonia following abrupt neurological deterioration at ages ranging from 3 to 18 months, often in association with an infectious illness

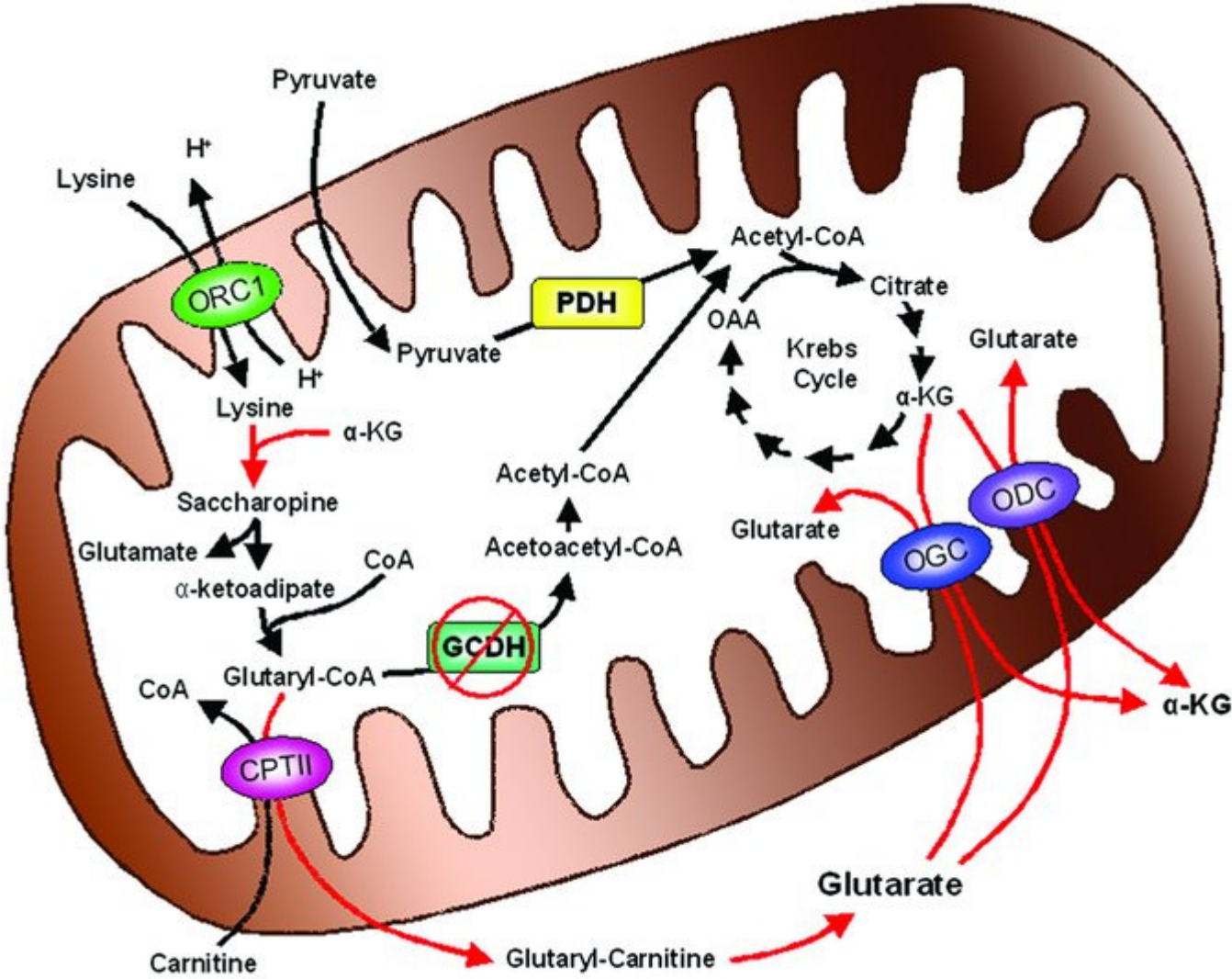
Pathogenesis

Glutaryl coA dehydrogenase deficiency



- Disorder of mitochondrial lysine and tryptophan degradation
- Glutaryl-CoA is proximal to the enzyme block
- Glutarate, 3-hydroxyglutarate and glutarylcarnitine accumulation in tissues- interfere with energy metabolism
- Riboflavin dependent
- Biochemical toxicity thought to trigger stroke-like striatal degeneration in susceptible children

Pathogenesis



Genetics



- Estimated prevalence of 1 in 100 000 newborns
- Autosomal recessive inheritance
- *Glutaryl coA dehydrogenase* gene mapped to **chromosome 19p13.2** which codes for precursor protein of 438 amino acids
- Single point mutation
- >150 GCDH gene mutations known

Genetics



- Worldwide: R402W most frequent mutation reported
- In SA: A293T mutation (null mutation): 293 alanine to threonine: homozygous mutation with undetectable GCDH activity
- Our patient: heterozygous mutation
A293T/R402W

Biochemical phenotype



- Two categories depending on metabolite excretion:

High excretors

-High excretion of GA and 3-OH-GA, ratio >1

-Undetectable GCDH activity

Low excretors

-May show normal excretion of GA, slightly raised 3-OH-GA and ratio <1

-Associated with residual GCDH activity

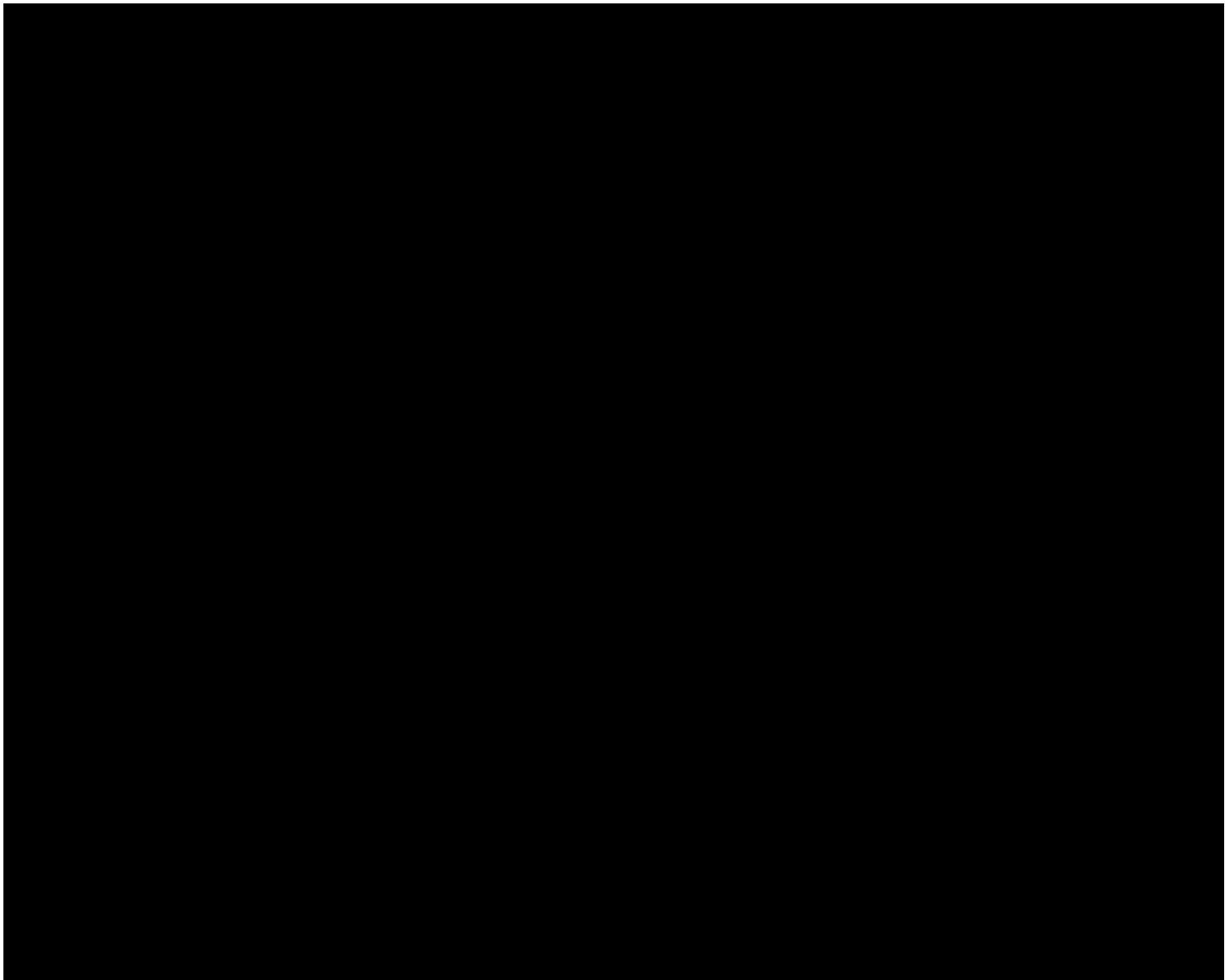
Clinical phenotype is variable with no established correlation between biochemical phenotype or genotype

Clinical phenotype

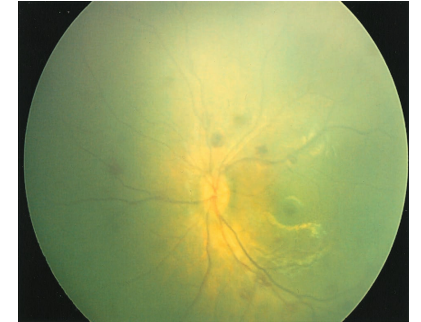
- Macrocephaly at birth is the earliest presenting sign
- Hallmark of the disease:

*Acute focal striatal necrosis in infancy
causing dystonia*

- Acute neurological crisis between 3-18 months typically precipitated by a common childhood infection
- Profound hypotonia, dystonia or choreoathetosis
- May be accompanied by encephalopathy +/- seizures



Ocular findings

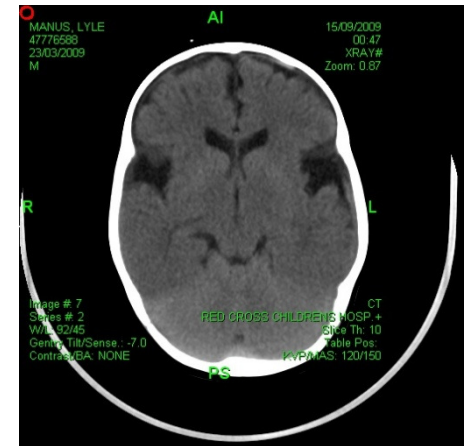


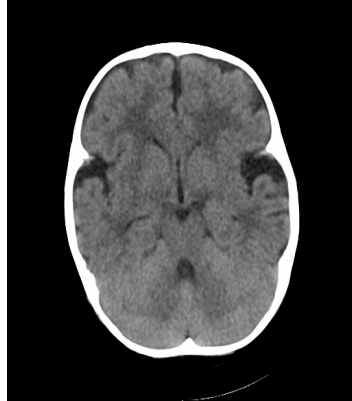
- Retinal haemorrhages in 20-30% of patients with chronic subdural effusions and haematomas
- Cataracts
- Gaze palsies, strabismus
- Pigmentary retinopathy
- Limited data re: the persistence or resolution of these findings
- One case study reports resolution of haemorrhages at 4 month follow up

Neuroimaging

Pre-symptomatic changes:

- The combination of **fronto-operculo-temporal hypoplasia** and
- **Widened anterior temporal and sylvian CSF spaces** most common MRI abnormality found
- Virtually pathognomonic



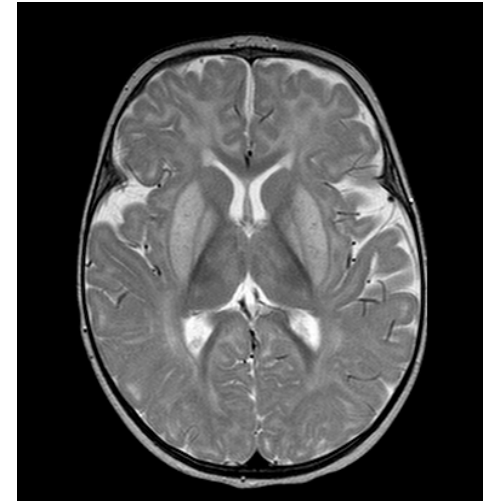


- Micrencephalic macrocephaly and large fluid collections within middle cranial fossae:
associated with stretched bridging veins that can be a cause of **subdural haematoma and acute retinal haemorrhage** *after minor head trauma*

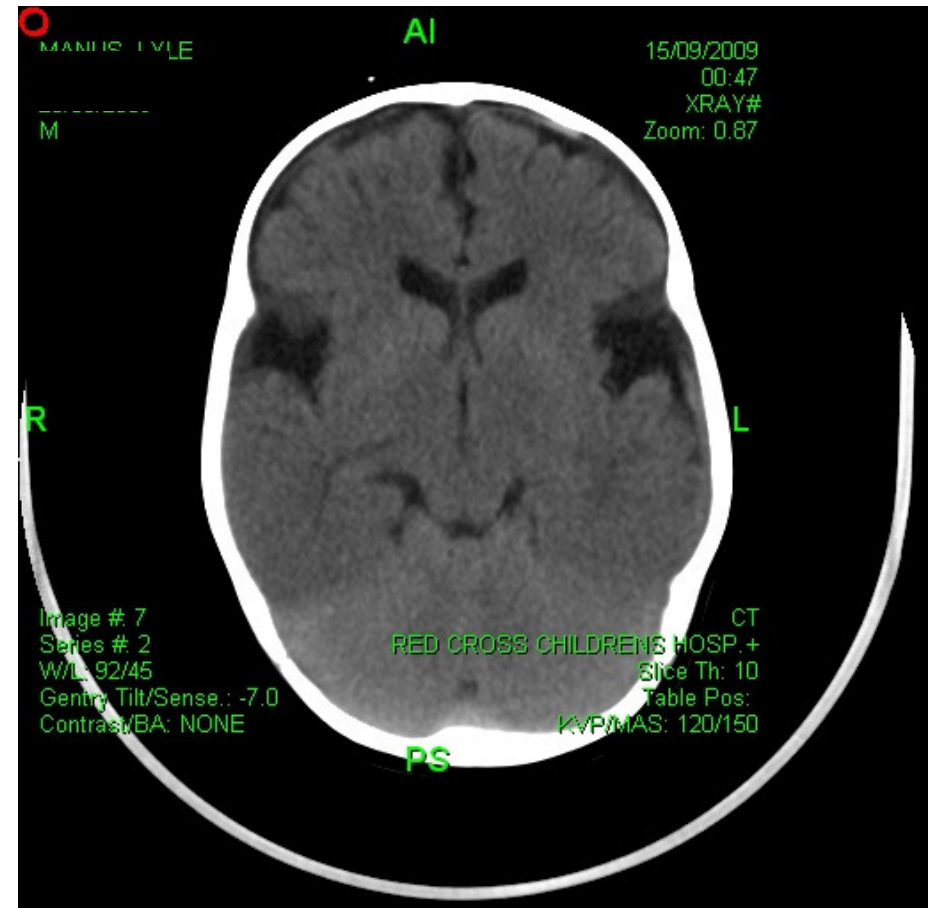
Neuroimaging

Major changes after crises:

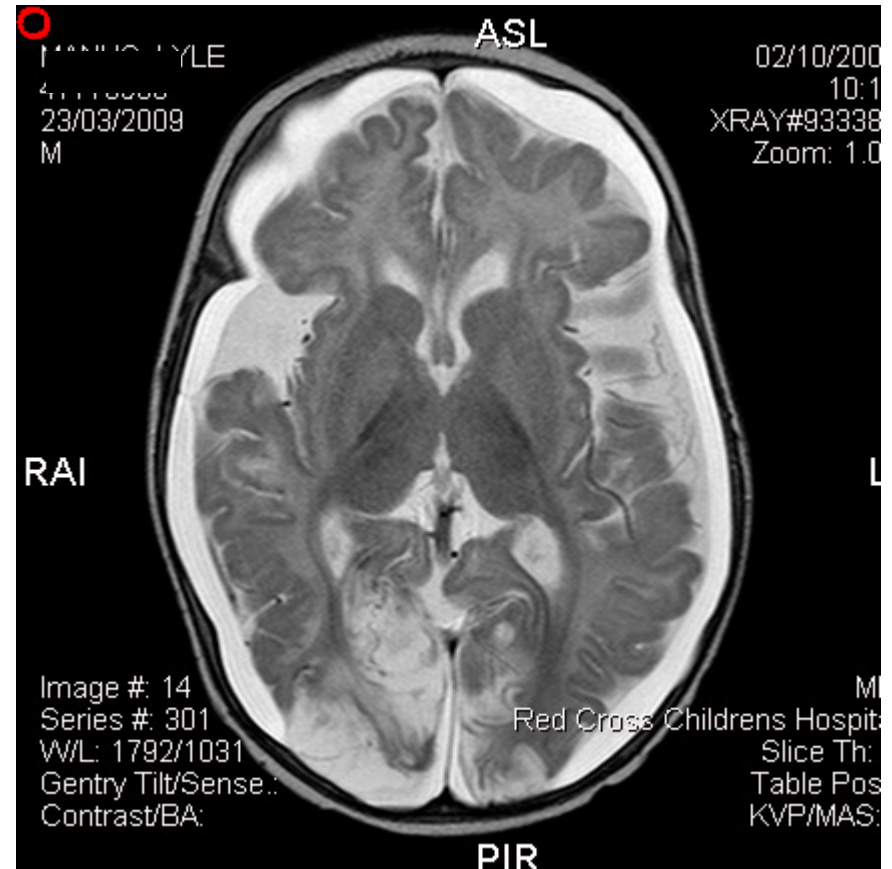
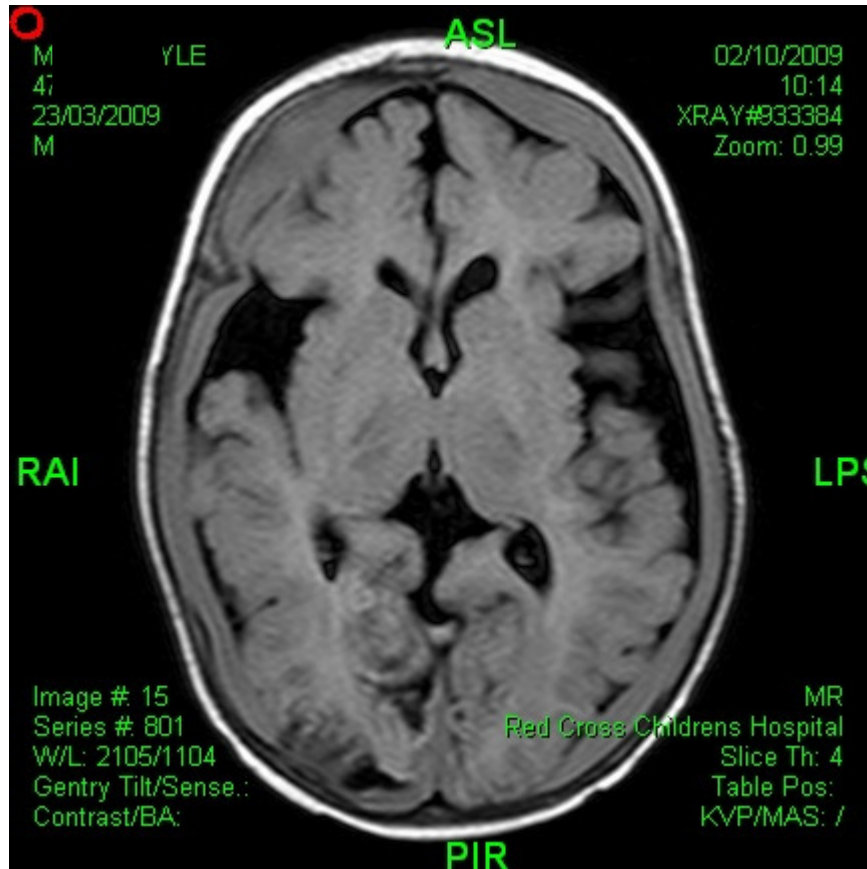
- ***Acute striatal necrosis***
- Initial swelling and necrosis
- Putamen & caudate heads (less frequently pallidum) restricted diffusion/T2 hyperintensity
- Later replaced by thin gliotic strip
- Subgroup of patients develop necrosis without crisis 'insidious onset disease'



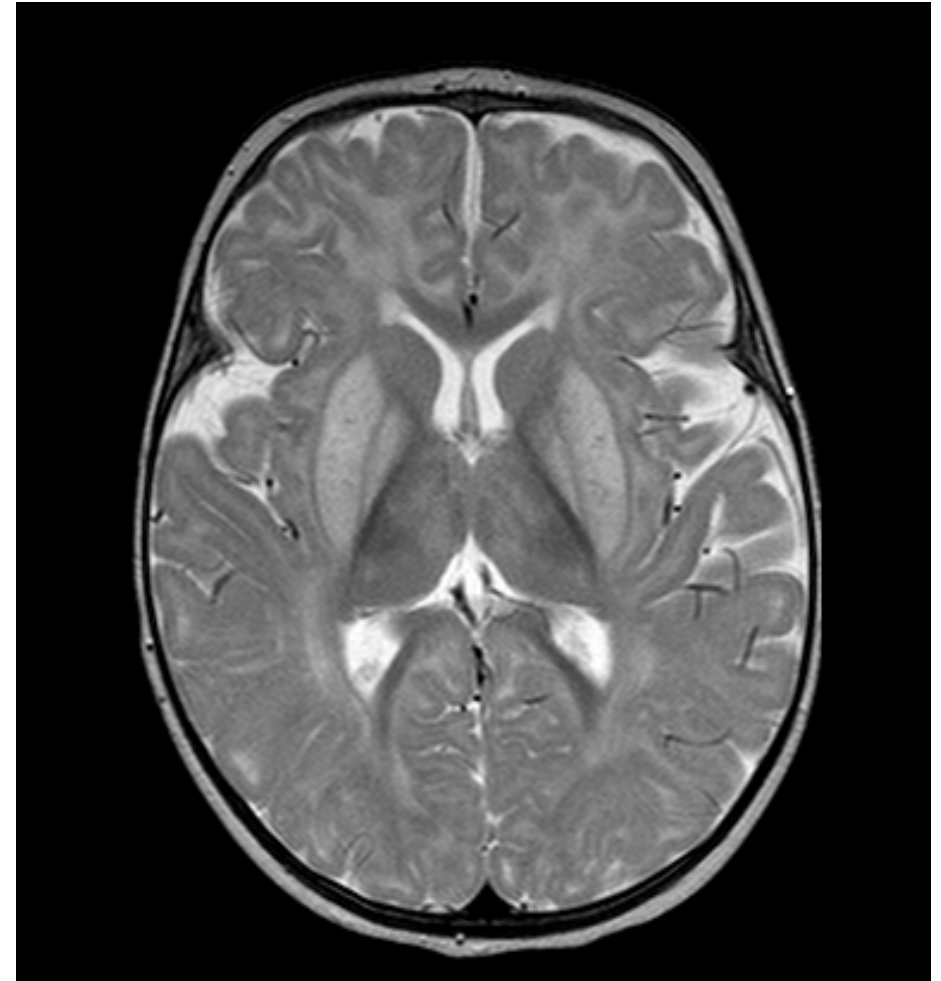
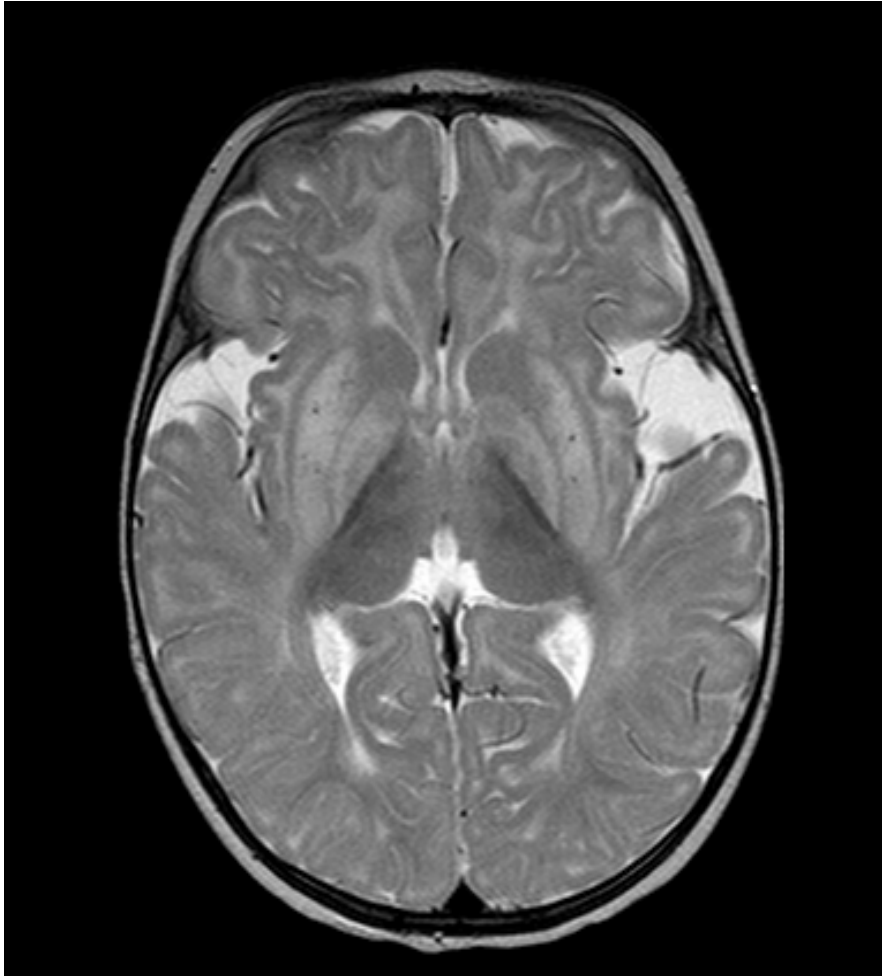
Patient LM CT brain

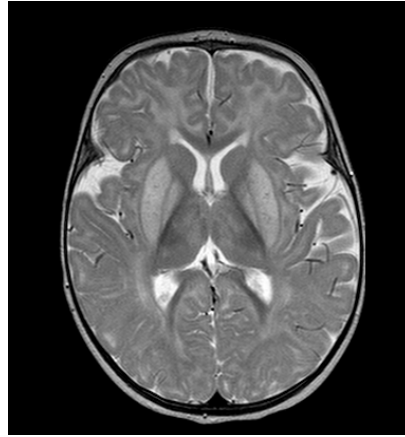


Patient LM MRI



Typical MRI findings





- **A single crisis during infancy or childhood determines the functional outcome by determining the degree of striatal damage**
- Extent of striatal necrosis is unpredictable and unrelated to severity of precipitating illness
- Principal cause of subsequent morbidity and mortality

Diagnosis

- Clinical presentation
- Typical neuroimaging
- Urinary OA profile
- Determination of GCDH activity in fibroblasts and leucocytes-confirmation of the diagnosis
- Genetic mutation

Treatment



- Lysine restricted diet / Carnitine supplementation
 - better than protein restriction alone in pre-symptomatic patients
 - No difference in symptomatic patients
 - Prevents damage in approx. 75% enzyme def individuals if pre-symptomatic
 - *Can significantly improve outcome BUT does not reverse striatal damage*
- Riboflavin -not clearly beneficial
- Multidisciplinary Approach -dietician

Prognosis

***Depends on when diagnosis is made
and access to care***



- The later the insult the less the damage
- Unusual to have acute crisis beyond 2 years
- Mostly die in first decade of life
- Frequently during acute episode
- Targeted screening siblings/dyskinetic CP/populations
- Newborn screening

Take home message



- **High index of suspicion in typical presentations and *always* in suspected cases of NAI**
- Incorrect diagnosis may have significant social ramifications and clinical course
- Well documented- subdural haematomas varying ages
+/- retinal haemorrhages
- Still the possibility of coexisting GA I and nonaccidental injury...

Our patient..?