
Epilepsy in Rett syndrome

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Seizures in Rett syndrome

- ◆ Overall seen in >90% of children with RS
- ◆ Usually begin after 2 years of age
 - Mean age of onset 4 yrs , range 4m-28y
- ◆ Mixed seizure disorders relatively common
- ◆ Variable semiology
 - Generalised tonic-clonic: 70%
 - Partial: 60%
 - Tonic
 - Myoclonic jerks
 - Absence
 - Atonic

Temporal course of epilepsy in RS

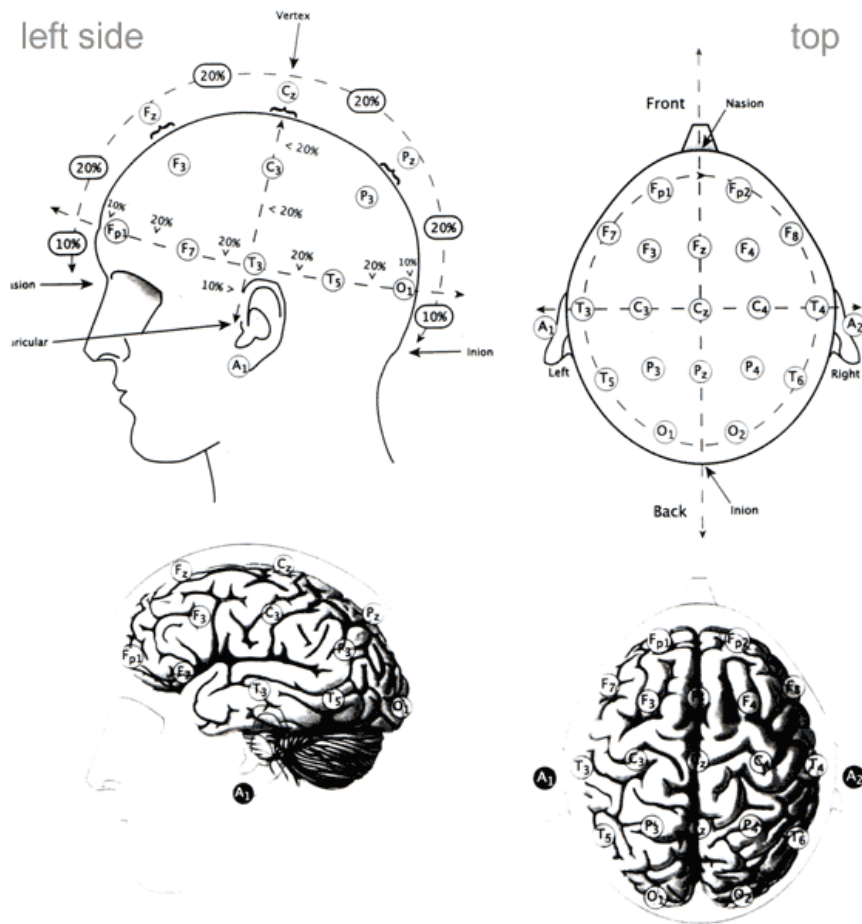
- ◆ **Seizures worst in childhood**
 - As many as 40% have episodes of status epilepticus
- ◆ **Onset < 1yr: seizures tend to be more problematic**
 - More seizure types including infantile spasms
 - More frequent sz
 - Greater risk of SE
 - Higher risk of atypical/ RS variant
- ◆ **After adolescence: partial > generalised seizures**
- ◆ **Occasional reports of deaths during seizures**
 - Aspiration, status epilepticus

The EEG in RS

- ◆ Invariably abnormal at some point in the illness
 - But EEG may be normal to 3-4 years
- ◆ The changes seen are sensitive but not specific
- ◆ In some cases EEG abnormalities antedate clinical diagnosis
 - EEG changes may *suggest* clinical diagnosis

left side

top



Relationship between brain and electrode positions

ELECTRODE PLACEMENT

International 10-20 System

Alpha: 8-13 Hz



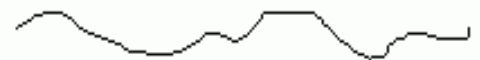
Beta: 14-30 Hz



Theta: 4-7 hz



Delta: <3.5



1 sec

Classic EEG changes in RS

- ◆ **1. Loss of normal EEG maturational changes**
 - ❖ Generalised slowing
 - ❖ Awake: loss of posterior dominant rhythm
 - ❖ Sleep: loss of normal NREM rhythms
 - ❖ Background possibly normal to 2-3 yrs
- ◆ **2. Frequent epileptiform abnormalities**
 - Almost universal after 3yrs of age
 - Centro-temporal spikes +/- sharp waves
 - ❖ Seen in 50% < 3 yrs
 - Focal sz in RS most commonly arise from central or occipital regions
 - Multifocal spikes, generalised slow spike and wave discharges
- ◆ **3. Rhythmic theta slowing: central, fronto-central regions**
 - 3-5 Hz, paroxysmal or constant, 'monorhythmic', unreactive
- ◆ **Less common: periodic patterns, hypsarrhythmia**

Activation methods

- ◆ Hyperventilation usually slows the EEG
 - This change is not seen in RS
- ◆ Apnea maybe associated with slow waves in RS
- ◆ Normal ventilation or HV may be associated with **faster** rhythms in RS
 - → Apnea or HV may pseudonormalise the EEG in RS, reversing the slowing seen at baseline
- ◆ EEG abnormalities become more prominent in sleep

EEG abnormalities correlate with clinical stage in RS

Table 1 Number of patients, number reporting seizures and EEG characteristics in different phases (*note: several patients were recorded in more than one group*).

Phase ^a	Cases	Patients reporting past seizures No. (%)	No. of records	EEGs			
				Abnormal records		Sleep records	
				Total No. (%)	With epileptogenic activity No. (%)	Total No. (%)	Abnormal increase in sleep No. (%)
Pre-regression	1	1	1 ^b	1	1	1	1
Early regression	18	2	18	6	6	4	1
Late regression/ early post-regression	37	24(65)	59	44 (75)	37(84)	20 (34)	16(80)
Late post-regression	49	38(76)	72	66 (92)	47(71)	30 (42)	22(73)

^a see text; ^b febrile convulsion

Cooper et al Eur J Paed Neurol 1998

Centro-temporal spikes in RS

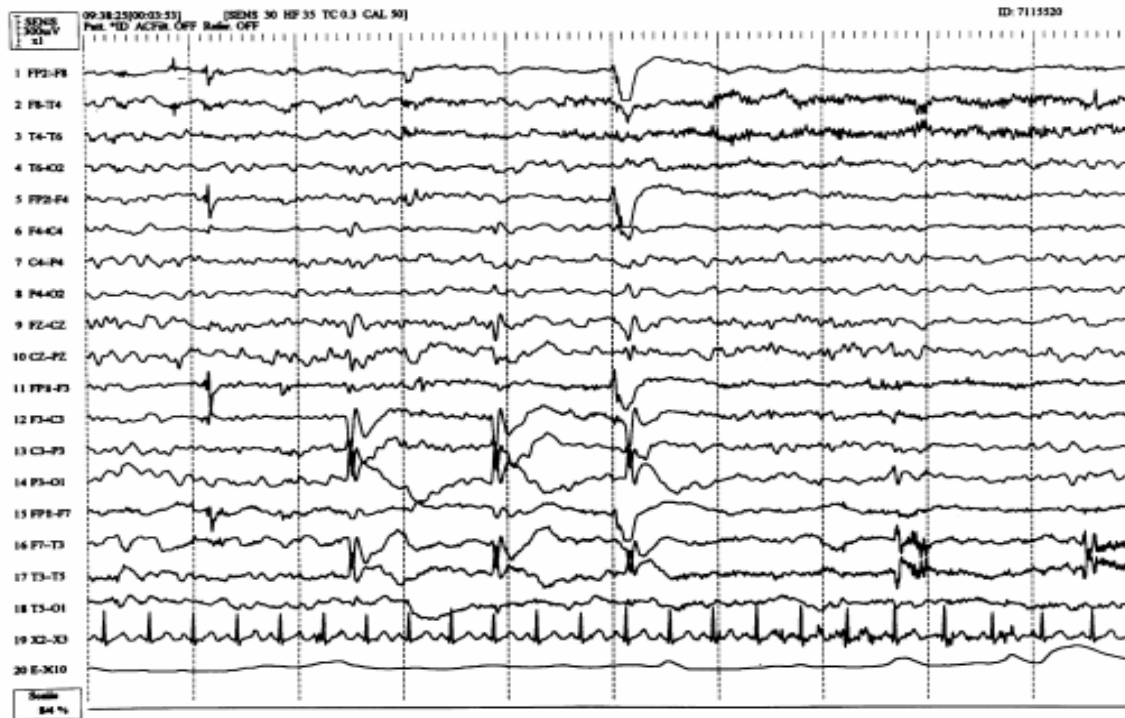


Fig. 2. Centrotemporal spike-wave complexes in a 2 year old girl with RS.

Monorhythmic theta in RS

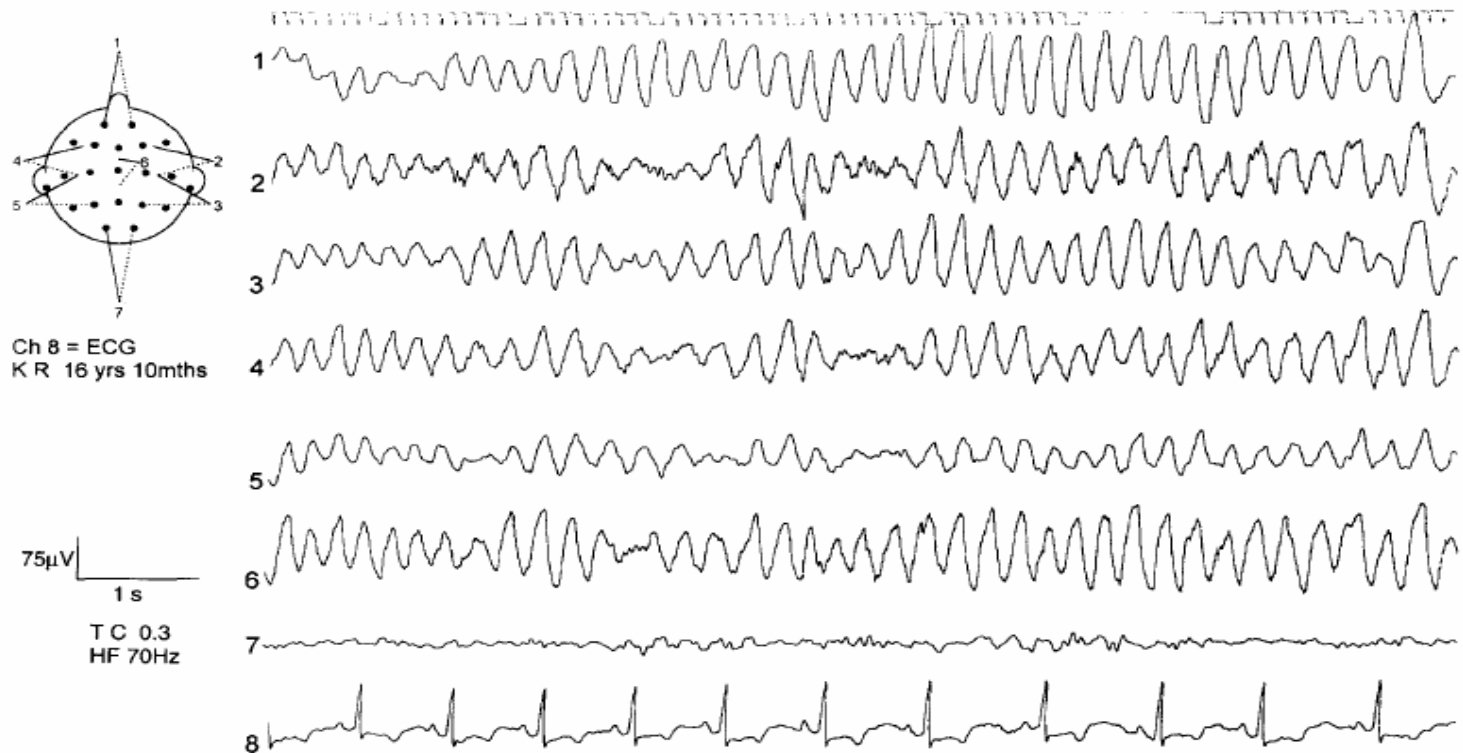


Fig. 1. EEG in classic Rett girl aged 16 years 10 months showing persistent 'monorhythmic' unreactive theta activity.

Cooper et al Eur J Paed Neurol 1998

Periodic complexes in RS

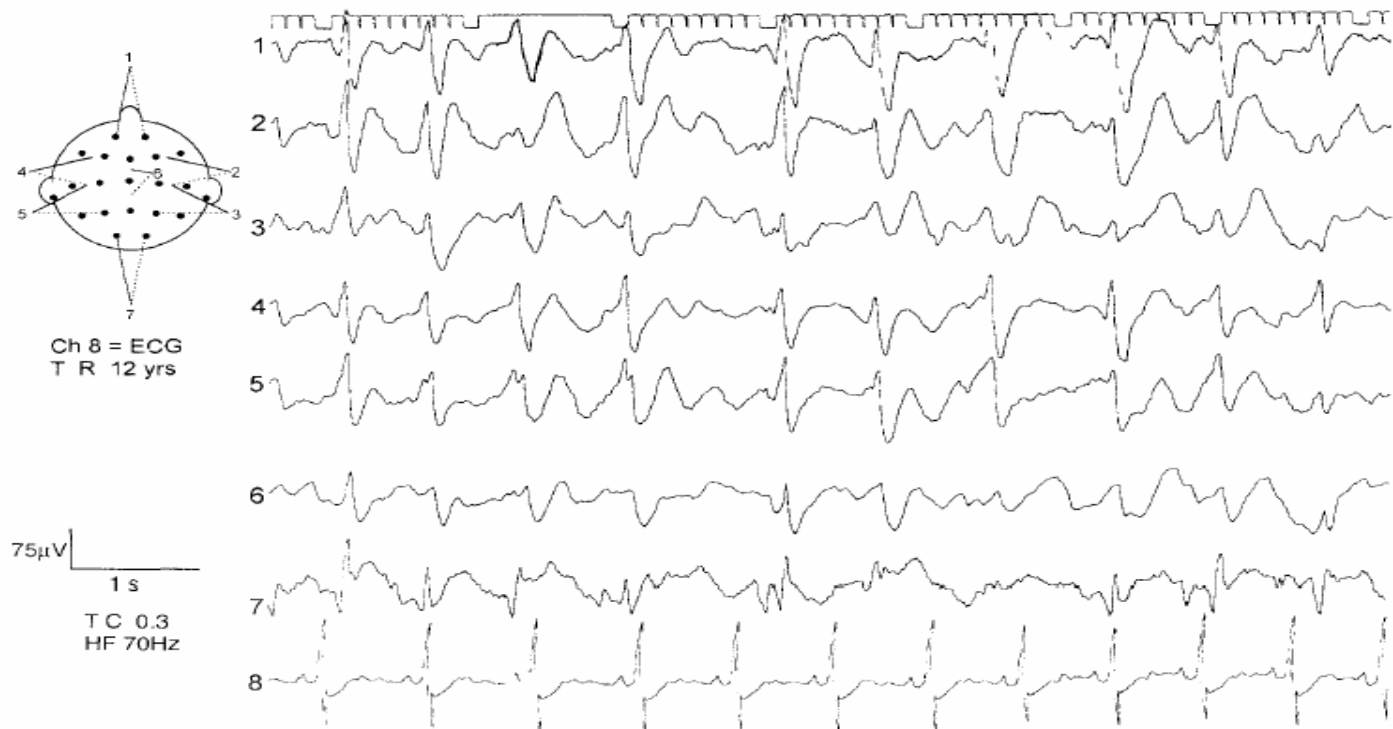
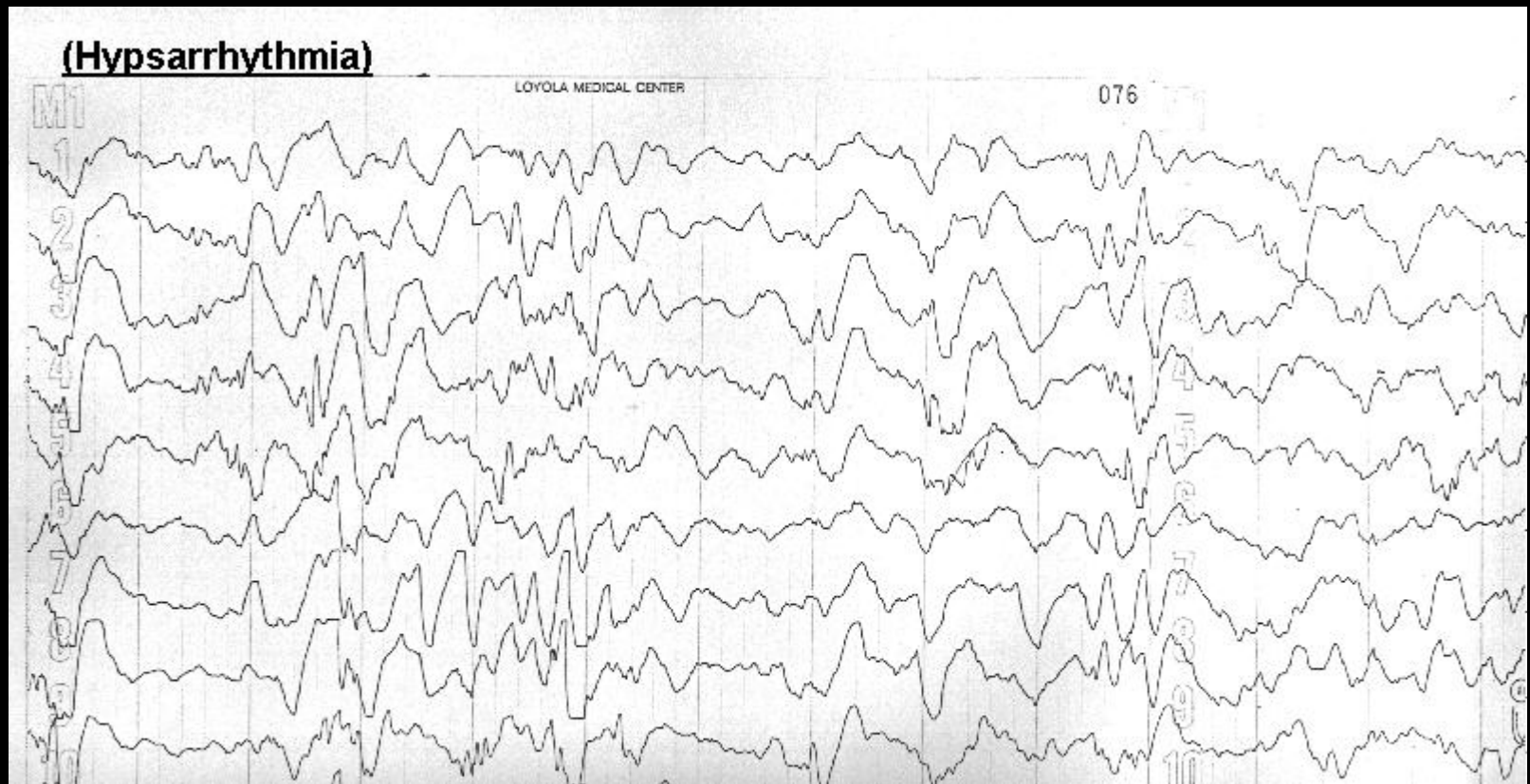


Fig. 2. EEG in Rett patient aged 12 years. Note widespread repetitive spike discharges similar in pattern to those seen in spongiform encephalopathy.

Hypsarrhythmia



Rett vs Angelman



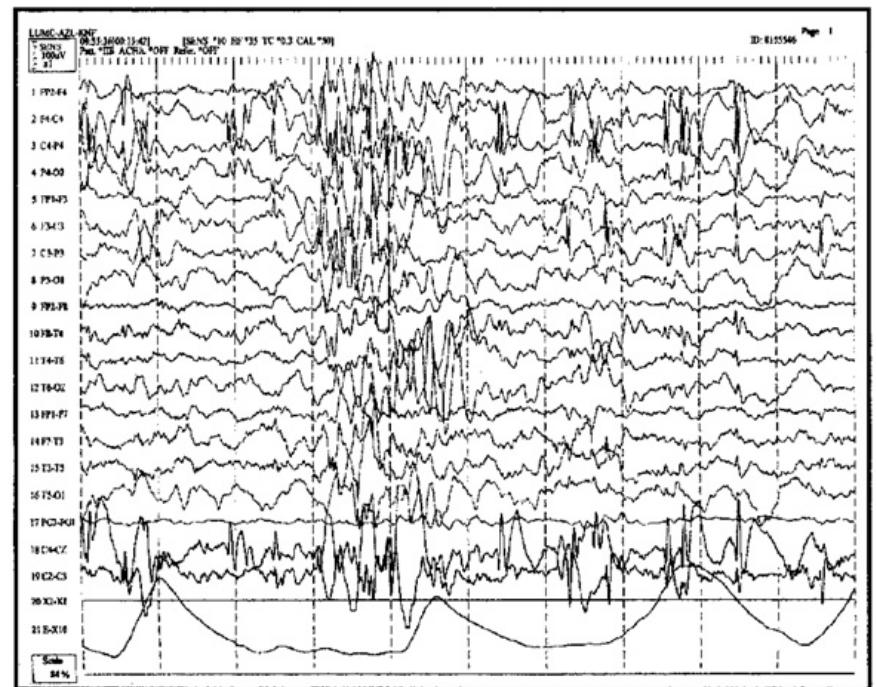
Rett vs Angelman

- ◆ EEG features compatible in very young children
 - Angelman syndrome tends to be associated with
 - ❖ High-amplitude frontal slowing
 - ❖ Triphasic waves
 - ❖ High amplitude 4-6 Hz activity
 - These changes not invariable <2 years

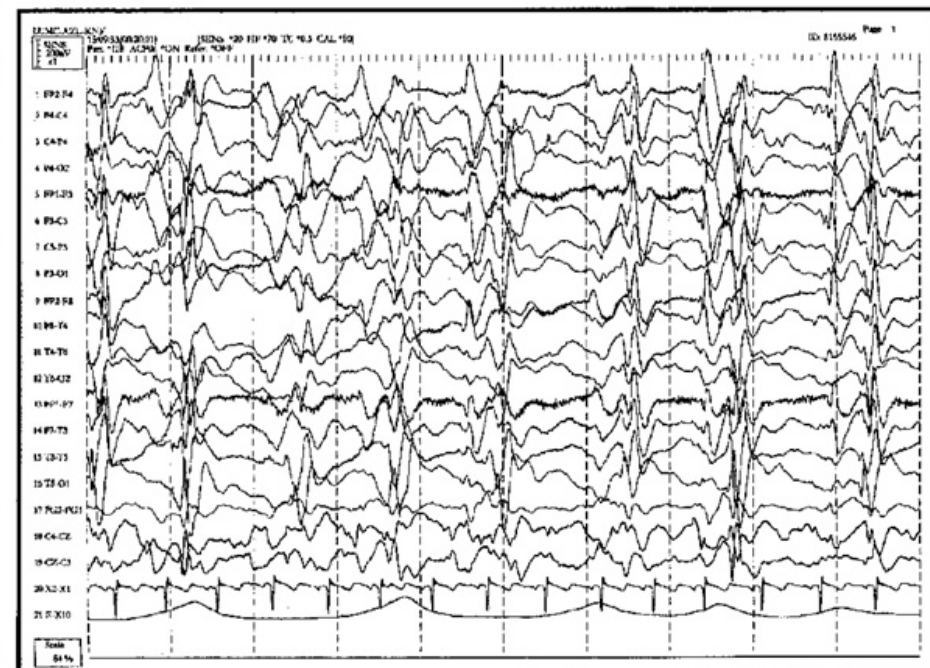
Rett vs Angelman



A



B



Lann and Vein Epilepsia 2002

Treatment of seizures in RS

- ◆ Difficult and often 'unsuccessful'
- ◆ Anticonvulsant polypharmacy may be required
- ◆ 1st line agents: VPA, CBZ, LTG
 - Concerns re ↑ NH₃ probably unfounded
- ◆ 2nd line:
 - Benzodiazepines
 - Topiramate
 - ❖ ? Risk of exacerbation of autonomic abnormalities
 - Ketogenic diet
- ◆ * risk of exacerbating osteopenia
 - Worst with CBZ, VPA, clonazepam, Pb (Vestergaard et al 2004)

Natural history of epilepsy in RS

- ◆ **Severity of epilepsy decreases after adolescence**
 - Seizures may cease altogether
 - Early onset does not adversely affect prognosis for remission of epilepsy
 - Severe early seizures may adversely affect head growth
- ◆ **After adolescence: partial > generalised seizures**
- ◆ **Seizure free rate for 1 yr:**
 - After 10 yr: 8%
 - After 27 yr: 40%

Not all 'seizures' in RS are epileptic

- ◆ 82 females with RS aged 2-30 yrs
 - 55 (67%) history of sz, 43 (52%) on AEDs
- ◆ VideoEEG monitoring up to 130 hours
- ◆ EEGs abnormal in all
 - Epileptiform abnormalities: stage III 60%, stage IV 97%
 - **Electrographic** seizures reported in 13 patients : partial +/- generalised
 - Clinical events correlating with electrographic seizures noted in 5 of these 13 patients: 8 no clinical correlate
 - 23/55 with history of 'seizures' had episodes during monitoring which parents felt were sz but which were **not** associated with EEG changes
- ◆ **Conclusions:**
 - 1. Seizures are under-recognised in RS
 - 2. Seizures are over-recognised in RS

Clues to nature of ?seizures

- ◆ **Most focal seizures in RS derive from central or occipital regions**
- ◆ **Clinical correlates:**
 - Focal clonic activity
 - Head or eye deviation
 - Apnea
- ◆ **Less likely to be associated with epileptiform discharges:**
 - Motor arrests
 - Respiratory abnormalities
 - Dystonic posuring
 - Bilaterally symmetrical stereotypies

Motor abnormalities in RS

- ◆ Head turning, dystonic posturing
- ◆ Twitching
- ◆ Jerking
- ◆ Falling forward
- ◆ Trembling
- ◆ Staring
 - ‘Vacant spells’
- ◆ Crying
- ◆ Laughing
 - Including ‘night laughter’

These are not seizures or seizure equivalents



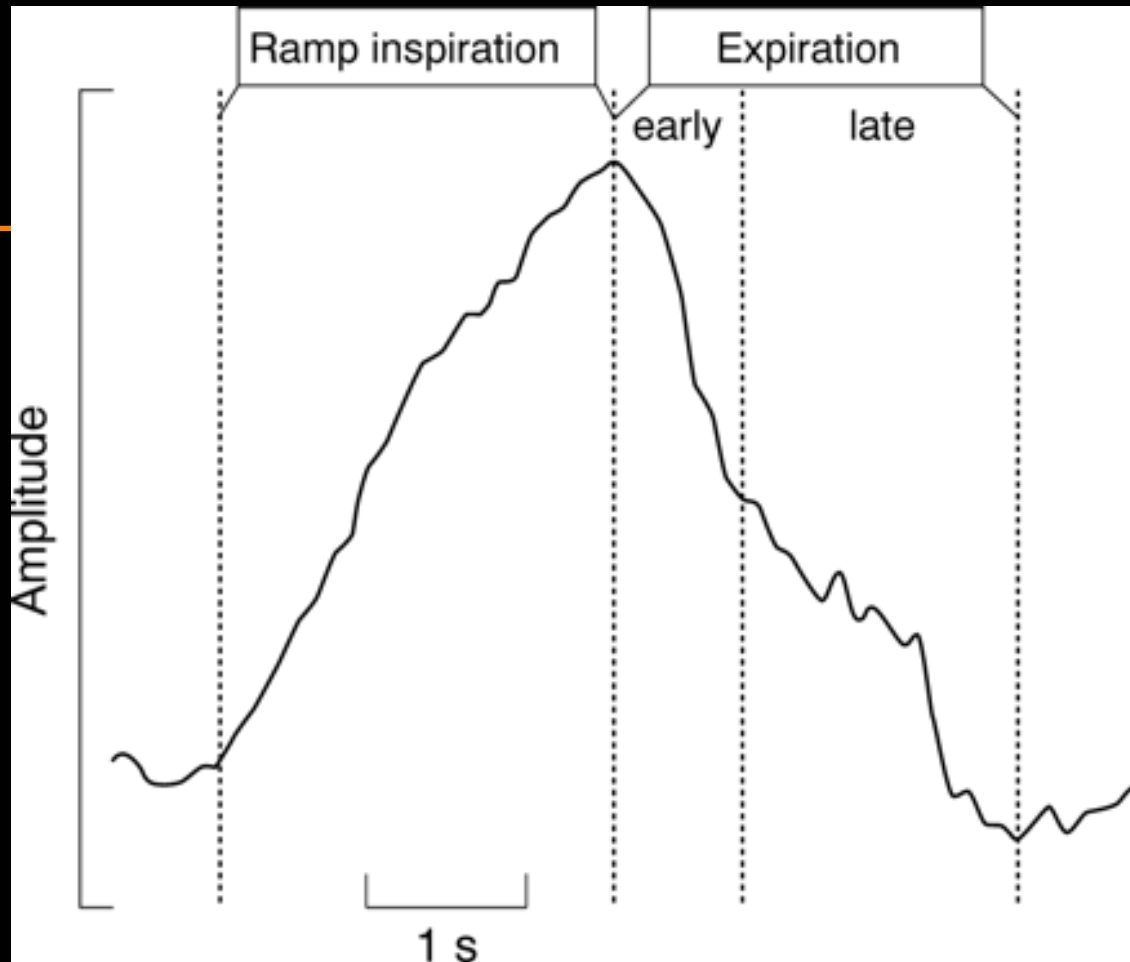
Autonomic abnormalities in RS

◆ Respiratory

- Hyperventilation
- Breath-holding
- Alternative hyperventilation and apnea
 - ❖ +/- Valsalva manoeuvre
- Aerophagia + bloating
- Usually occur only in wakefulness
- Mechanism unclear: ? Epileptiform discharges from limbic structures alter autonomic NS function

These are not seizures or seizure equivalents

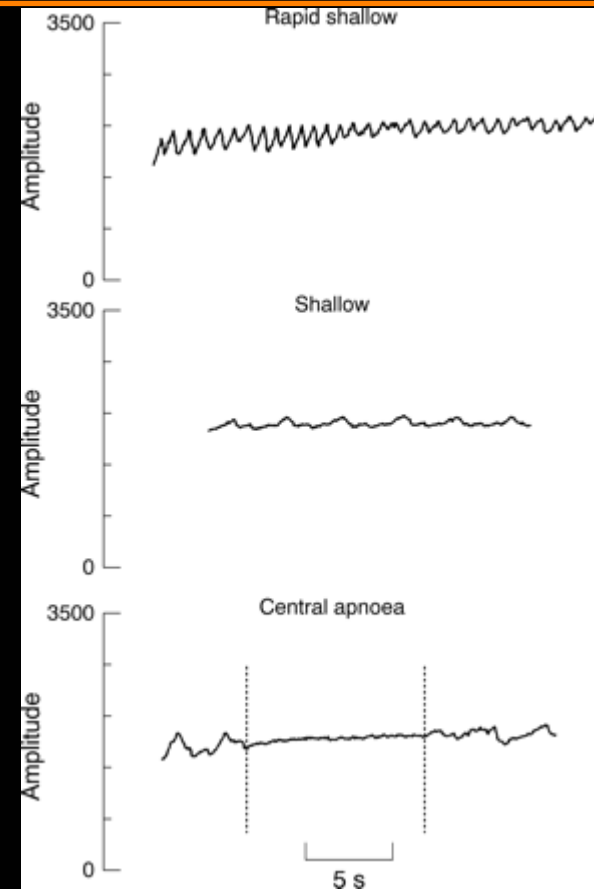
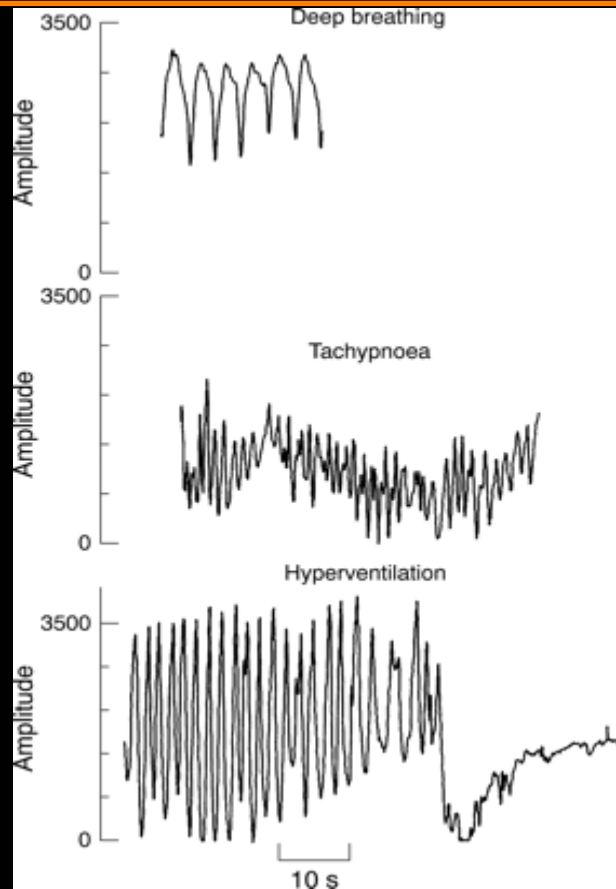
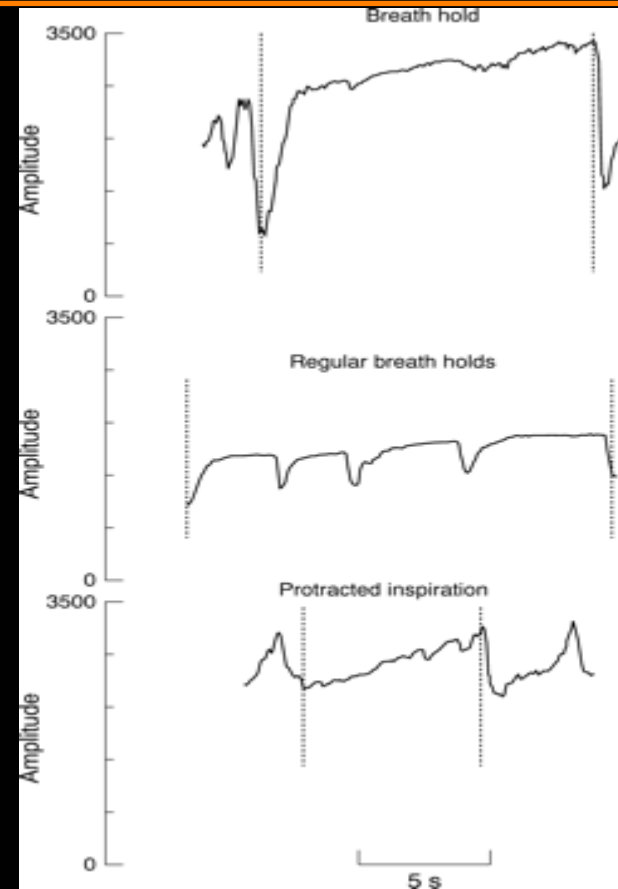


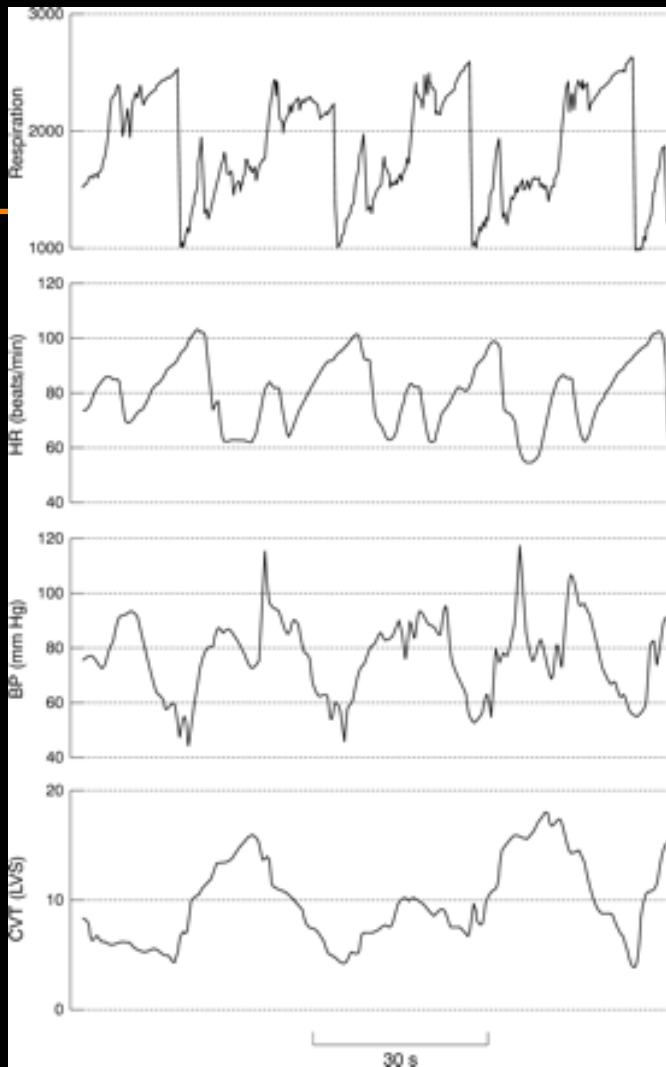


Normal breathing. Ramp inspiration terminated immediately by double phased expiration. Rate 35 breath/min, amp in arbitrary units.

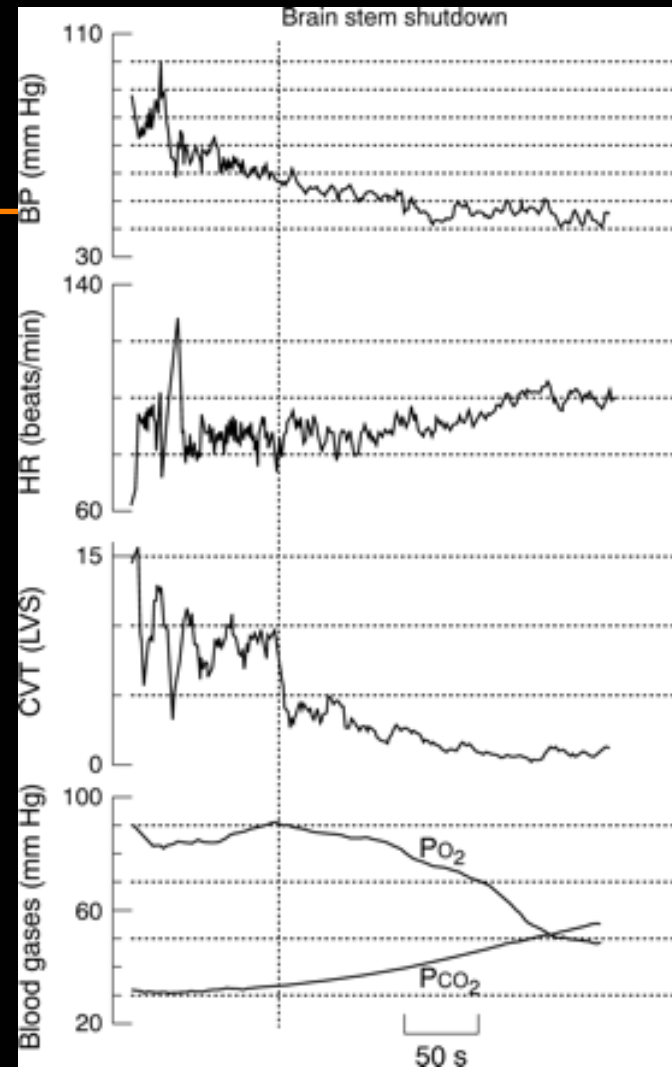
Julu et al Arch Dis Child 2001

Abnormal breathing patterns in RS





Valsalva manoeuvre



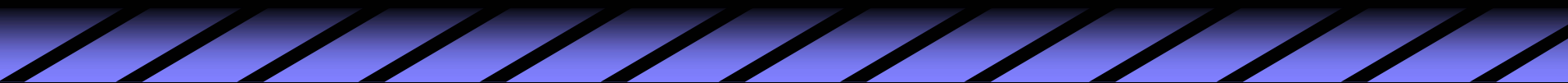
Episode of collapse

Autonomic abnormalities in RS

◆ Altered sensation

- Decreased nociception
- Length-dependent
- Always incomplete
- ? Insensitivity or indifference to pain

◆ Peripheral perfusion

- Deceleration in foot growth
 - Blueish-red discoloration of feet
 - Trophic changes- skin and nails
 - Abnormal distal sweating patterns
- 

Autonomic abnormalities in RS

◆ Gastro-intestinal

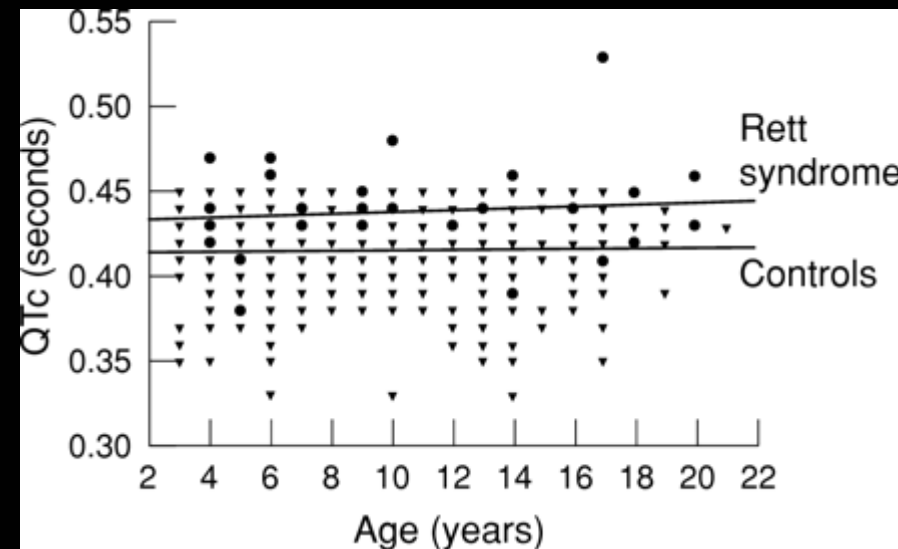
- Swallow dysfunction, GOR, constipation

◆ Cardiovascular

- Decreased heart rate variability
- Increased QTc

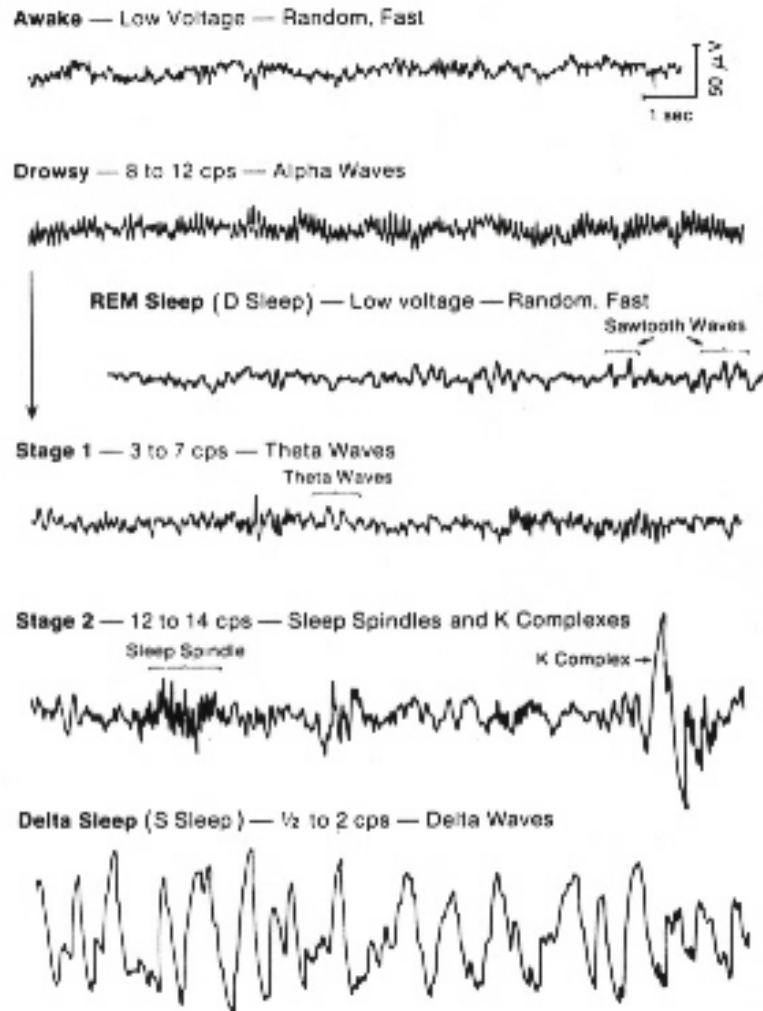
◆ Ocular

- Pupillary dilatation



Ellaway et al Arch Dis Child 1999

Sleep in RS



Sleep in RS

- ◆ **Derangement of daytime and/or nighttime sleep virtually universal**
 - Disturbance possibly limited to daytime or nighttime sleep
 - Increased sleep latency
- ◆ **EEG : epileptiform changes increased in sleep**
- ◆ **EEG stages of sleep lost**
 - Spindles, VSW, K complexes present in stage II (regression), lost by stage IV
 - High-voltage delta persists, makes staging of sleep impossible
 - Sleep studies: fragmented/ disrupted sleep patterns
 - REM sleep may or may not be recorded
 - HV not seen in sleep

Take home messages

- ◆ All anticonvulsants have side-effects
- ◆ Most children with RS will require anticonvulsants
- ◆ These seizures are likely to be required long term
 - One medication is always better than two
 - Two medications are better than three
- ◆ EEG abnormalities do **not** → children are having sz
- ◆ All that shakes is not a seizure
- ◆ Epilepsy is an age-dependent phenomenon in RS and is often outgrown