Dr Eloise Williams
Western Health
Presentation

- Female in her 20s, migrant from SE Asia 2y ago
- Unprovoked 1\textsuperscript{st} episode generalized tonic-clonic seizure
- Past medical history
  - Polycystic ovary disease
  - Typhoid fever as a child
  - Normal neurological development
  - Vaccination as a child in Philippines
  - Non smoker, non drinker, no recreational drugs
- Nil current regular medications
- Nil allergies
Over the preceding 9 months...

- 9/12 ago - myoclonic jerks of R) shoulder and arm
- Associated slowed speech
- Stereotyped movements
  - Predominantly involving R) shoulder with gasping mouth movements.
  - Partially suppressible, not occurring during sleep
- Diagnosed as tic disorder
- 4/12 ago, frequent falls due to myoclonic jerks
Over the preceding 9 months...

- Neurology review
  - MRI brain – 2 nonspecific T2 white matter foci in the R) frontal lobe, likely within normal limits.
  - EEG normal
- Referred to psychiatrist for ?conversion disorder
- 3/12 ago progressively reduced mobility
- 2/12 ago minimal speech, ‘yes/no’, able to follow commands
- Unable to feed herself resulting in 20kg loss of weight over 3/12 period
- 1/12 ago developing incontinence
Examination on admission

- Stereotyped myoclonic movements associated head turning to the R and RLL jerking
- Elicited by external stimuli
- Not present during sleep
- Bilateral hypertonia in upper and lower limbs, generalized rigidity
- Normal reflexes, plantars down-going
- Primitive reflexes present
- Occasionally following simple one-stage commands
- Responded yes/no appropriately
Investigations

- Bloods essentially normal
- CTB angiogram nil abnormalities
- CSF:
  - Normal, Gram stain negative, culture negative
  - Enterovirus, HSV, VZV, CMV PCR negative
  - Cryptococcal antigen negative
  - TB culture: no AFBs seen, culture in progress
  - Cytology negative
- CTCAP: nil abnormalities
Investigations

- MRI:
Investigations

- EEG: nonspecific focal epilepsy disorder involving bilateral frontal regions
  - Background of low amplitude, mixed frequency rhythm
  - Multiple episodes of brief jerking movement of limbs, consistent with myoclonus - not accompanied by change in the EEG
  - Multiple sharp slow waves and occasional focal slowing with delta activity seen in the frontal regions.
Investigations

- Autoimmune, metabolic and genetic causes all studies negative
- Infective causes including Treponemal and HIV serology negative
- Paraneoplastic antibodies all negative
- Protein 14-3-3 negative

- SPEP: polyclonal increase in IgG
- CSF electrophoresis: oligoclonal IgG in CSF, paired serum no oligoclonal IgG
Back to the basics...

- Repeat LP
  - Clear, glucose 2.8, protein 0.28
  - Erythrocytes 0, WCC 8, all mononuclear cells
  - Gram stain and culture negative
  - Cytology for malignancy negative
  - Polyoma virus DNA not detected
  - Treponema whipplei nucleic acid test negative
SHOW ME THE MONEY!!!!!!!
A call from the lab...

- CSF
  - Measles IgG EIA 2.4

- Paired serum
  - Measles IgG EIA 4.2
Summary

- 23 yo lady previously well, no significant past medical history and vaccinated as a child
- 9/12 rapid neurological deterioration with myoclonic jerks
- Now tonic clonic seizure and severe functional decline
- All investigations within normal limits except
  - MRI
  - Oligoclonal IgG in CSF
  - Serum Measles IgG EIA 4.2
  - CSF Measles IgG EIA 2.4
What is the diagnosis?
Subacute sclerosing panencephalitis
Clinical progress

• NGT feeding
• Non-verbal
• Temperature variability
• Compassionate access isoprinosine treatment
• Symptomatic management
• Family support and palliative care with aim to support family to take patient home
Measles Neurological Syndromes

- Measles encephalitis – occurs with onset of rash
- Acute disseminated encephalomyelitis - 0.1% of immunocompetent pts with measles
- Inclusion body encephalitis - immunocompromised pts due to persistence of virus in the CNS
- Subacute sclerosing panencephalitis
Subacute sclerosing panencephalitis (SSPE)

- SSPE is a fatal, progressive degenerative disease of the central nervous system caused by persistent infection by an altered form of the measles virus
- First described by Dawson in 1933
Dawson describes 2 cases of 'subacute inclusion body encephalitis' in 1933 & 1934

Van Bogaert in 1945, names a characteristic similar syndrome ‘subacute sclerosing leucoencephalitis’

In 1965, Bouteille identifies particles on electron microscopy that resemble nucleocapsids of paramyxovirus in brains of cases

Greenfield suggests similar etiology for both, called ‘subacute sclerosing panencephalitis’ in 1950

Connolly et al discover increased titers of measles antibody in blood and CSF in 1967

Measles virus recovered from brain of a patient in 1969 by Horta-Barbosa et al
SSPE Epidemiology

- Age of onset 5-15 years old,
- Male/female ratio 3:1
- Most contract measles early in life
- Incidence of SSPE reported as 1-11 cases/1 million measles cases, varies worldwide
- Higher incidence if infection acquired <1 yo
- Interval quiescence of 6-15 years after measles
- >90% reduction in the incidence of SSPE in developed nations since immunization introduced
- 60-80% of patients die 1-3 years after onset of illness
SSPE Pathogenesis
SSPE Natural History

Jabbour’s staging system

- **Stage I**: insidious neurolpsychological symptoms
  *Weeks to years*

- **Stage II**: myoclonus, worsening dementia
  *1-12 months*

- **Stage III**: rigidity with extrapyramidal features and unresponsiveness.
  *3-18 months*

- **Stage IV**: minimal conscious state, akinetic mutism, signs of autonomic dysfunction.
  *1-6 years*


Risk’s staging system

- **Stage 0**: subtle psychointellectual symptoms, 2 years

- **Stage 1**: obvious psychointellectual and neurological changes, 2.5 months

- **Stage 2**: stereotyped attacks, 7.5 months

- **Stage 3**: vegetative psychomotor condition, 5.5 months

- **Stage 4**: improvement, 3.5 years

- **Stage 5**: relapse: minimal conscious state, akinetic mutism, with signs of autonomic dysfunction. 1.5 years

Risk & Haddad. Archives of Neurology, 1979

SSPE Diagnosis

Dyken’s criteria

1. Clinical
   • Progressive, subacute mental deterioration with typical signs like myoclonus

2. EEG
   • Periodic, stereotyped, high voltage discharges

3. CSF
   • Raised gammaglobulin or oligoclonal pattern

4. Measles antibodies
   • Raised titre in serum $\geq 1:256$ and/or CSF $\geq 1:4$

5. Brain biopsy or post-mortem
   • showing typical pathology and/or culturing the altered measles virus
     *and/or detection of measles RNA PCR
   • Definitive = criteria 5+three other
   • Probable = 3\5 criteria
Pathology

Fabian et al. Journal of Clinical Neuroscience, 2010
SSPE Investigations

- CSF and EEG
- MRI
  - increased T2 signal intensity in the corona radiata, then the occipital white matter, brain stem, +/—cerebellum;
  - Leucoencephalopathy; central atrophy

SSPE and immunization

- No association with attenuated vaccine
- In previously vaccinated patients—thought to result from a subclinical measles infection
- No vaccine strains have been recovered from tissue specimens of patients with SSPE

Table 2. Patients with subacute sclerosing panencephalitis who were referred to the Centers for Disease Control and Prevention (CDC) and who had measles virus of the wild-type genotype identified in brain tissue samples, although the genotype or patient location ruled out an association with measles acquired in the United States during 1969–1991.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Year^ of referral to the CDC</th>
<th>Patient’s year of birth, sex</th>
<th>History of measles or rash, year of occurrence</th>
<th>Patient location^b</th>
<th>History of vaccination, if known</th>
<th>Genotype of measles virus identified</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>1992 (16)</td>
<td>1976, M</td>
<td>Measles, 1977 (12 months)</td>
<td>Wisconsin</td>
<td>No</td>
<td>C1</td>
</tr>
<tr>
<td>7</td>
<td>1993 (28)</td>
<td>1965, M</td>
<td>Measles, 1968 (3 years)</td>
<td>Wisconsin</td>
<td>Yes (12 years)</td>
<td>E</td>
</tr>
<tr>
<td>8</td>
<td>1995 (5)</td>
<td>1990, M</td>
<td>Rash, 1991 (15 months)</td>
<td>Ohio^c</td>
<td>Yes (17 months)</td>
<td>D5</td>
</tr>
<tr>
<td>10</td>
<td>2001 (16)</td>
<td>1985, M</td>
<td>NR</td>
<td>Nicaragua^d</td>
<td>Yes (15 years)</td>
<td>D3</td>
</tr>
<tr>
<td>11</td>
<td>2003 (36)</td>
<td>1967, M</td>
<td>NR</td>
<td>Illinois</td>
<td>Yes</td>
<td>E</td>
</tr>
</tbody>
</table>

**NOTE.** NR, not reported.

^a The year of onset of symptoms of subacute sclerosing panencephalitis was not available for all patients and may not be the same as the year of referral given here.

^b Location where patient resided during childhood or state of residence at the time of referral.

^d Patient 10 lived in Florida after 15 years of age.
SSPE in adults

- More difficult diagnosis later in life
- Adult onset cases present at a mean age of 25.4 years
- Longer latency between measles infection and onset of SSPE
- Higher proportion undocumented history of prior measles infection in childhood
- Visual manifestations are commonest clinical presentation
- More aggressive course
SSPE Treatment

• There is no cure for SSPE
• At best, 30-35% of individuals benefit from therapy
• 5% spontaneous remission rate reported in the literature
• Daily oral isoprinosine combined with weekly intrathecal interferon treatment has most evidence
Treatment outcomes

Gascon et al, Brain and Development, 1993

- 18 pts with stage I-III SSPE disease treated with combination therapy
- Compared with 11 historical controls treated with isoprinosine or no treatment
- 8/18 improved or arrested in combination group
- 1/11 remission in control group
- 44% rate of remission/ stabilization in combination treatment group vs 9% in control group
- 6 episodes of serious adverse reactions
  - 3 neurotoxicity
  - 1 thrombocytopenia
  - 2 ventriculitis-meningitis

Eroglu et al, Journal of Neurological Sciences, 2009

Fig. 1. Survival of patients with treated isoprinosine alone, α-interferon + isoprinosine alpha-interferon plus oral isoprinosine and all patients.
Treatment

- Other drugs trialled
  - Ribavirin
  - Amantadine
  - Steroids
  - Cimetidine
  - Plasmapheresis
- Potential hope for the future…
  - Recombinant adenovirus
- Prevention: vaccination (95-98% effective)
Measles Prevention

First live attenuated monovalent measles vaccine licenced in Australia in 1968

Measles vaccine incorporated into national immunization schedule in 1975 – single dose age 12 months

1965
146 measles deaths

1975
1975
62 measles deaths

1993: Large epidemic with >10 000 cases

1993: 2nd dose of MMR for all 10-16 year olds recommended

1995

In 1985, the Australian Measles Control Campaign launched, create new targets, re-schedule 2nd dose MMR to age 4, catch-up vacc of primary school children

In 2014, the WHO declares that measles elimination has been achieved

2013 - MMR dose re-schedule d to 18 months

2015

In 1998, the Australian Measles Control Campaign launched, create new targets, re-schedule 2nd dose MMR to age 4, catch-up vacc of primary school children

2005

1995

1985

1975

1965

146 measles deaths

62 measles deaths
Measles Prevention

- Measles vaccine incorporated into national immunization schedule in 1975 – single dose age 12

1993:
- Large epidemic with >10,000

In 2014, the WHO declares that measles elimination has been achieved

**Fig. 1. Measles notification rates per million population, Australia, 1991–2007**

<table>
<thead>
<tr>
<th>Year</th>
<th>Cases per million population</th>
</tr>
</thead>
<tbody>
<tr>
<td>1991</td>
<td>75</td>
</tr>
<tr>
<td>1992</td>
<td>53</td>
</tr>
<tr>
<td>1993</td>
<td>351</td>
</tr>
<tr>
<td>1994</td>
<td>265</td>
</tr>
<tr>
<td>1995</td>
<td>19</td>
</tr>
<tr>
<td>1996</td>
<td>36</td>
</tr>
<tr>
<td>1997</td>
<td>45</td>
</tr>
<tr>
<td>1998</td>
<td>13</td>
</tr>
<tr>
<td>1999</td>
<td>2</td>
</tr>
<tr>
<td>2000</td>
<td>5</td>
</tr>
<tr>
<td>2001</td>
<td>2</td>
</tr>
<tr>
<td>2002</td>
<td>0.5</td>
</tr>
<tr>
<td>2003</td>
<td>2</td>
</tr>
<tr>
<td>2004</td>
<td>0.5</td>
</tr>
<tr>
<td>2005</td>
<td>6</td>
</tr>
<tr>
<td>2006</td>
<td>0.5</td>
</tr>
<tr>
<td>2007</td>
<td>6</td>
</tr>
</tbody>
</table>

- Measles vaccine incorporated into national immunization schedule in 1975 – single dose age 12

1993:
- Large epidemic with >10,000

In 2014, the WHO declares that measles elimination has been achieved

**Fig. 1. Measles notification rates per million population, Australia, 1991–2007**

<table>
<thead>
<tr>
<th>Year</th>
<th>Cases per million population</th>
</tr>
</thead>
<tbody>
<tr>
<td>1991</td>
<td>75</td>
</tr>
<tr>
<td>1992</td>
<td>53</td>
</tr>
<tr>
<td>1993</td>
<td>351</td>
</tr>
<tr>
<td>1994</td>
<td>265</td>
</tr>
<tr>
<td>1995</td>
<td>19</td>
</tr>
<tr>
<td>1996</td>
<td>36</td>
</tr>
<tr>
<td>1997</td>
<td>45</td>
</tr>
<tr>
<td>1998</td>
<td>13</td>
</tr>
<tr>
<td>1999</td>
<td>2</td>
</tr>
<tr>
<td>2000</td>
<td>5</td>
</tr>
<tr>
<td>2001</td>
<td>2</td>
</tr>
<tr>
<td>2002</td>
<td>0.5</td>
</tr>
<tr>
<td>2003</td>
<td>2</td>
</tr>
<tr>
<td>2004</td>
<td>0.5</td>
</tr>
<tr>
<td>2005</td>
<td>6</td>
</tr>
<tr>
<td>2006</td>
<td>0.5</td>
</tr>
<tr>
<td>2007</td>
<td>6</td>
</tr>
</tbody>
</table>
Measles Prevention

- First live attenuated monovalent measles vaccine licensed in Australia in 1968.
- Measles vaccine incorporated into national immunization schedule in 1975 – single dose age 12 months.

1985-1993: Large epidemic with >10,000 cases.
1993: 2nd dose of MMR for all 10-16 year olds recommended.

In 1998, the Australian Measles Control Campaign launched, creating new targets and rescheduling the 2nd dose of MMR to age 4, catching up vaccination of primary school children.

In 2014, the WHO declares that measles elimination has been achieved.

2013-MMR dose rescheduled to 18 months.

146 measles deaths in 2018.
Public Health Significance

176 cases reported in US Jan 1-March 2015, 130 cases from Disneyland outbreak

Calculated likely vaccination rate 50-86% in this population given spread of the virus
Public Health Significance

RETRACTED: Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children

Dr AJ Wakefield, FRCS, SH Murch, MB, A Anthony, MB, J Linnell, PhD, DM Casson, MRCP, M Malik, MRCP, M Berelowitz, FRCPsych, AP Dhillon, MRCPath, MA Thomson, FRCP, P Harvey, FRCP, A Valentine, FRCR, SE Davies, MRCPath, JA Walker-Smith, FRCP

DOI: http://dx.doi.org/10.1016/S0140-6736(97)11096-0

2015 Measles Cases in the U.S.
January 1 to March 13, 2015

Cases*:
- 0
- 1-4
- 5-9
- 10-19
- 20+

* Provisional data reported to CDC's National Center for Immunization and Respiratory Diseases

† CDC will update these data weekly on Mondays.
Public Health Significance

RETRACTED: Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children

Dr AJ Wakefield, FRCS, SH Murch, MB, A Anthony, MB, J Linnell, PhD, DM Casson, MRCP, M Malik, MRCP, M Berelowitz, FRCPsych, AP Dhillon, MRCPsych, MA Thomson, FRCP, P Harvey, FRCP, A Valentine, FRCR, SE Davies, MRCPsych, JA Walker-Smith, FRCP

Altmetric 795
DOI: http://dx.doi.org/10.1016/S0140-6736(97)11096-0

RETRACTED

2015 Measles Cases in the U.S.
January 1 to March 13, 2015
Our thoughts are also with the measles-ravaged country America. I hope we are screening them before they come to Africa.

8:46 PM - 1 Feb 2015

34,472 RETWEETS 27,470 FAVORITES
SO YOU PEOPLE HAVE EASY ACCESS TO VACCINES AND YOU STILL REFUSE THEM?
Acknowledgements

- Western Neurology Unit
- VIDRL
References

- Bellini WJ, Rota JS, Lowe LE, Katz RS, Dyken PR, Zaki SR, Shieh WJ, Rota PA. Subacute sclerosing panencephalitis: more cases of this fatal disease are prevented by measles immunization than was previously recognized. The Journal of Infectious Diseases. 2005; 192(10): 1686-1693
- Gadoth N. Subacute sclerosing panencephalitis the story of a vanishing disease. Brain and Development. 2010; 34: 704-711