Workshop- Masterclass Nov 12

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Hon Consultant: Young Epilepsy
Matthew’s Friends
Case 1: James, 14

Infantile onset epilepsy - 1st seizure soon after vaccination.

Infantile spasms, treated with Vigabatrin.

AED HISTORY: SVA, TPM, LTG, LEV, CLZ, CBZ. NO STEROIDS

Current seizures:

1. Atypical absences
2. Drops with arms elevation
3. Nocturnal cluster of spasms and convulsions
4. Jerks-
Slow Spike & Wave
Intractable epilepsy - How common is it?

- Adults (>15 y): 16%  Picolet et al, 2008

- Childhood epilepsy cohorts:
  - Netherlands: DSEC: 8.5%  (Geerts et al 2010)
  - USA: Connecticut cohort 14%  (Berg AT et al, 2006)
    - 23% failed at least 2 AEDs

- Temporal lobe epilepsy:
  - 37%  (Dlugos et al, 2001)
  - 69%  (Spooner et al 2006)
ILAE task force:

Drug-resistant epilepsy: failure of adequate trials of two tolerated, appropriately chosen and administered antiepileptic drugs (monotherapy or in combination) to achieve seizure freedom.

They also recommended replacing the term “intractable” with “drug-resistant” epilepsy.
New AEDSs - no impact on DRE

Responder rates with new AEDs

Treatment goals:
- QOL
- Sz control
- Adherence, S/E profile

Responder rates in adult patients
(add-on therapy for partial refractory epilepsy)

Vagus Nerve Stimulation-what is it?

Stimulation via electrodes wrapped around the left vagus nerve (inside the carotid sheath)

Nerve is stimulated below – the superior and inferior cervical cardiac branches emerge

Stimulator inserted in the chest or axilla

Subsequently controlled by external computer via wand
Pacemaker-like pulse generator
Bipolar lead with two stimulating electrodes
Battery life of 5-10 years
Course and projections of vagus nerve

cingulate gyrus
orbitofrontal cortex
parabrachial nucleus (PB)
hypothalamus
amygdala
nucleus
locus coeruleus
thalamus
vagus nerve
nucleus track solitarius
pons
cerebellum
spinal cord
Peripheral stimulation of the vagus- may cause changes in the EEG.
Reduced frequency of spiking in cats using strychnine seizure model
Modification of EEG in electroshock models and pentylene tetrazol model

1938 Bailey and Bremer
1960’s Chase, Stoica
1980’s Zabara
Late 1980’s - early 1990’s first systematic human trials
VNS – mechanisms

**Human studies**

VNS increases blood flow to thalamus and modifies blood flow to other vagal projection centres (PET)

fMRI shows activation in response to VNS in cortical regions especially orbitofrontal, parieto-occipital, left temporal cortex and amygdala
VNS - mechanism of action

- Locus coeruleus
- Norepinephrine
- Raphe nuclei
- Serotonin
- Thalamus

Locus coeruleus
Norepinephrine

Raphe nuclei
Serotonin

Thalamus
Synchronization of spikes

Cortex
Epileptic focus

Anti-epileptic effect

Left Vagus Nerve

Desynchronization EEG rhythms

Lesions

CBF

CSF
What does VNS offer?

3 areas of benefit for seizures
  – Acute abortive
  – Acute prophylactic
  – Chronic progressive

• Other benefits?
  – Quality of life
  – Mood, behavior, alertness, memory, school
On-demand magnet stimulation is a unique benefit of VNS Therapy

- Offers more control for patients and their families\(^1,2\)
- Initiates on demand stimulation
  - May abort or decrease severity of seizures\(^1-3\)
  - May improve postictal period\(^2\)
- Stops stimulation
  - Acutely manage side effects\(^3\)

VNS – efficacy

Randomized, placebo controlled, double blind studies

E03

114 patients age > 12 years

> 6 partial szs/month; taking 1 – 3 AEDs

‘high’ stimulation (30s/5min) v low (30s/90min)

at 3 months 24.5% reduction in seizures v 6.1%

31% >50% sz reduction v 13%
199 patients age > 12 years

at 3 months 28% reduction in seizures vs 15%

23.4% >50% sz reduction vs 15.7%

10.6% >75% sz reduction vs 2.0%

3 months from end of trial - median sz reduction 34%

12 months from end of trial

median sz reduction 45%

> 50% sz reduction 34%

> 75% sz reduction 20%

side effects diminished with treatment duration
VNS Therapy in Paediatric Patients (EO1-EO5)

Medan Decrease in Seizure Frequency

(Last Visit Carried Forward/All Patients n=60)

Real-world outcomes with VNS Therapy

% of Patients with ≥50 seizure frequency reduction

- **Vonck** (n=118) MeanF/U 33 mo: 50%
- **Renfroe** (n=120) MeanF/U 3 mo: 51%
- **Labar** (n=269) MeanF/U 12 mo: 57%
- **DeHerdt** (n=138) MeanF/U 44 mo: 59%
- **Elliott** (n=436) MeanF/U 59 mo: 64%

VNS: Seizure frequency reduction over time

Seizure frequency reductions among patients with stable AED regimens for 12 months (n=269)


- 3 Months
- 12 Months

- ≥50%: 48% (3 Months), 57% (12 Months)
- ≥75%: 23% (3 Months), 35% (12 Months)
- ≥90%: 12% (3 Months), 18% (12 Months)
- 100%: 3% (3 Months), 6% (12 Months)

How poor are they that have not patience! William Shakespeare
Responser rates

Elliott Et al- 141 paed patients

Seizure free  ≥ 90% Reduction  ≥ 75% Reduction  ≥ 50% Reduction

7.8%  21.1%  41.4%  64.8%
### Study population demographics

<table>
<thead>
<tr>
<th>Gender</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>199</td>
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<tr>
<td>Female</td>
<td>146</td>
</tr>
<tr>
<td>Total</td>
<td>345</td>
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<table>
<thead>
<tr>
<th>Age at implantation</th>
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<tbody>
<tr>
<td>Median</td>
<td>10.7 y</td>
</tr>
<tr>
<td>≤ 6 y</td>
<td>47</td>
</tr>
<tr>
<td>6 – 10</td>
<td>91</td>
</tr>
<tr>
<td>10-12</td>
<td>57</td>
</tr>
<tr>
<td>12-18</td>
<td>152</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age at epilepsy onset</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>1.5 y</td>
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</table>
Seizure frequency reduction

ITT population

<table>
<thead>
<tr>
<th></th>
<th>6 M</th>
<th>1 Y</th>
<th>2 Y</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>294</td>
<td>347</td>
<td>207</td>
</tr>
<tr>
<td>Seizure free</td>
<td>6,1</td>
<td>6,1</td>
<td>6,3</td>
</tr>
<tr>
<td>Seizure increase</td>
<td>5,8</td>
<td>5,5</td>
<td>8,2</td>
</tr>
<tr>
<td>&lt;25% decrease</td>
<td>15,6</td>
<td>17,3</td>
<td>13</td>
</tr>
<tr>
<td>25-50% decrease</td>
<td>33</td>
<td>37</td>
<td></td>
</tr>
<tr>
<td>50-100% decrease</td>
<td>45</td>
<td>44</td>
<td></td>
</tr>
</tbody>
</table>
Seizure severity

Ictal severity

1 Year
- Decreased: 32.2%
- Unchanged: 44.4%
- Increased: 4.7%
- Unknown: 18.7%

2 Years
- Decreased: 39.1%
- Unchanged: 44.6%
- Increased: 4.3%
- Unknown: 12%
**TABLE 2: Seizure outcomes reported by Engel class**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>I, 100%</th>
<th>II, &gt;90%</th>
<th>III, 50%–90%</th>
<th>IV, &lt;50%</th>
<th>Total*</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of patients (%)</td>
<td>121 (4.6)</td>
<td>200 (7.6)</td>
<td>1012 (38.4)</td>
<td>1301 (49.4)</td>
<td>2634</td>
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</table>
VNS: seizure-free rates

Refractory patients

<table>
<thead>
<tr>
<th>% seizure-free patients</th>
<th>% patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>20%</td>
</tr>
<tr>
<td></td>
<td>15%</td>
</tr>
<tr>
<td></td>
<td>12%</td>
</tr>
<tr>
<td></td>
<td>10%</td>
</tr>
<tr>
<td></td>
<td>8%</td>
</tr>
<tr>
<td></td>
<td>6%</td>
</tr>
<tr>
<td></td>
<td>5%</td>
</tr>
<tr>
<td></td>
<td>4%</td>
</tr>
<tr>
<td></td>
<td>2%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group</th>
<th>All</th>
<th>Renfroe 2002 (EAR; 3 m)</th>
<th>Helmers 2003 (12 m)</th>
<th>De Herdt 2007 (≥12 m)</th>
<th>Amar 2004 (Non-CS; 24 m)</th>
<th>Labar 2002 (Group 1; 12 m)</th>
<th>Labar 2004 (12 m)</th>
<th>Amar 2004 (CS; 24 m)</th>
<th>Labar 2002 (Group 2; 12 m)</th>
<th>Harms 2003 (Late; 12 m)</th>
<th>Renfroe 2002 (Control; 3 m)</th>
<th>Amar 1999 (15 m)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6%</td>
<td>15%</td>
<td>12%</td>
<td>9%</td>
<td>8%</td>
<td>7%</td>
<td>6%</td>
<td>5%</td>
<td>5%</td>
<td>5%</td>
<td>4%</td>
<td>2%</td>
</tr>
</tbody>
</table>

Quality of Life

Responder: much better or better than before VNS
Quality-of-life improvements over time are independent of seizure control

- <7% of patients reported worse or much worse outcome by any single measure

Effects on interictal discharges

- 15 children
- 24h ambulatory EEG at 3 and 9 months
- Analysis of no. of IEDs and interspike intervals (ISIs) – wake and sleep state
- 9 months – total IEDs reduced (p=0.04)
  - seizure numbers reduced (p=0.05)
- No direct correlation between reduction in IEDs and seizure reduction

Hallbook et al, Seizure 2005, 14, 727-33
Impact on cognition, behaviour, mood, quality of life

- Same 15 children
- Assessed with Bayleys, WPPSI-R or WISC-III
- QOL questionnaire
- Seizure severity scale (NHS3)
- Child behaviour checklist

Results
- 6/15 - >50% Sz reduction (1 Sz free)
- No improvement in cognition
- 12/15 – improvement in QOL
- 13/15 – improvement in NHS3
Effects on sleep

- Same 15 children!
- Ambulatory polysomnography – pre, 3 months and 9 months post VNS
- At 9 months
  - Increased slow sleep
  - Decreased sleep latency
  - Decreased Stage I sleep
  - Decreased movement times
- Sleep improvements (10 patients) associated with improvements in QOL (8) and behaviour (8)

Hallbook et al, Seizure 2005, 9, 399-407
Sheffield VNS experience

- M:F ~ 2:1
- Age at implantation-3y8m-20y2m (median 11.3)
- Onset of epilepsy 1d - 8y (median 21m)
- Previous AEDs 5 - 15 (median 9)
- Major seizures 8 - 352/month
- Severe learning difficulties in 85%

Courtesy: Dr Rittey
Long term follow-up (Sheffield)

- 31 patients followed for 5-11 years (complete data available for 30/31)
- All had detailed assessment 10-12 weeks prior to implantation
  - Response rate based on 3 month average seizure frequency prior to implantation
- Follow-up at 1, 3, 5, 8 and 11 years post-implantation
Lennox Gastaut, 5
Multifocal epilepsy, 3
Dravet, 2
Symptomatic focal, 3
West syndrome, 1
Cryptogenic generalised, 2

HIE 2
Neonatal stroke 1
PVL 1
Hypothalamic Hamartoma 1
Focal cortical Dysplasia 3
Polymicrogyria 3
Hippocampal sclerosis 4
Multifocal epilepsy, 3
Symptomatic focal, 3
West syndrome, 1
Cryptogenic generalised, 2
Lennox Gastaut, 5
## Reduction in seizure frequency

<table>
<thead>
<tr>
<th>% seizure reduction</th>
<th>0 -10</th>
<th>10-50</th>
<th>50 -90</th>
<th>90 -100</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 months</td>
<td>13 (43%)</td>
<td>11 (37%)</td>
<td>3 (10%)</td>
<td>3 (10%)</td>
<td>30</td>
</tr>
<tr>
<td>1 year</td>
<td>9 (30%)</td>
<td>11 (37%)</td>
<td>7 (23%)</td>
<td>3 (10%)</td>
<td>30</td>
</tr>
<tr>
<td>3 years</td>
<td>10 (36%)</td>
<td>6 (21%)</td>
<td>10 (36%)</td>
<td>2 (7%)</td>
<td>28</td>
</tr>
<tr>
<td>5 years</td>
<td>9 (33%)</td>
<td>6 (22%)</td>
<td>10 (37%)</td>
<td>2 (7%)</td>
<td>27</td>
</tr>
<tr>
<td>8 years</td>
<td>3 (17%)</td>
<td>6 (33%)</td>
<td>7 (39%)</td>
<td>2 (11%)</td>
<td>18</td>
</tr>
<tr>
<td>11 years</td>
<td>1 (17%)</td>
<td>2 (33%)</td>
<td>3 (50%)</td>
<td>0 (0%)</td>
<td>6</td>
</tr>
</tbody>
</table>
Efficacy:

- Long latency period for effect
- Maintained positive effects

Meta-analysis: Englot et al J Neurosurg 2011
- 74 clinical studies, 3321 patients, (incl 3 blinded RCT, 2 non blinded RCT, 10 prospective studies)
- > 1 year after implant 51% sz reduction, at last follow up seizure reduction of at least 50% in 50%

VNS vs Callosotomy
Drop attacks: responder rates 64% with callosotomy vs 70% with VNS
Special populations:

1. Hypothalamic hamartoma
   - 34% responders (6 patients), 4/6-improved autistic behaviour

2. Ring chromosome 20

3. TSC:
   - 90% responders (10 patients) - 22 mo F U
   - 50% responders (16 patients) - 48 mo F U
   - 72% responders (11 patients) - 32 mo F U
   - 82% 67% sz decrease (11 patients) - 4-9 year F U

4. LGS: 4-46 patients, responder rates 25-80%
   (10 studies, 1997-2009)
VNS – relevance in TS?
Parain et al 2001

10 patients with medically refractory epilepsy and TS age

Age: 7 – 20 years (matched with 10 non-TSC patients)

seizure onset at age < 1 year (9)

seizure type focal 8, GTCS 7, myoclonic 1

daily sz frequency 5 – 19 (7)

All with LD

duration of trial: 6 – 36 months (22 months)
VNS – relevance in TS?

**outcome:**

- no change: 1/10
- >50% sz reduction: 9/10
- >90% sz reduction: 5/10
- 3/10 more alert
- 1/10 reduced self injurious behaviours
- 1/10 transient increase in ‘psychotic behaviour’ immediately post insertion (90% seizure reduction)

**control:**

- 7/10
- 2/10
- 1/10
- 1/10
VNS – complications

- Infection
- Vocal cord dysfunction - usually mild and temporary
- Horner’s syndrome – usually related to damage to sympathetic plexus in carotid sheath
- Rarely – temporary lower facial weakness probably related to high surgical incision involving lower branches of facial nerve
- Bradycardia and asystole - reported during lead testing in theatre to check integrity of system – incidence < 0.1% - responds to atropine
VNS – adverse effects during treatment

Mechanical

- Lead breakage – rare
- Battery failure - inevitable and related to settings required

Scarring

Stimulus related

- Coughing, hoarseness, throat discomfort, dyspnoea
- Voice alteration, swallowing difficulties
VNS Therapy is a proven treatment with a unique safety profile

- More than 60,000 patients worldwide
- No known interactions with medications
- No reported systemic neurotoxic effects, rash, renal impairment, or bone marrow suppression
- No increase in sudden, unexpected death in epilepsy (SUDEP)
- Gestational outcomes
  - Animal study has shown no evidence of impaired fertility or harm to the fetus due to VNS Therapy
  - Pregnancies have gone to term with VNS

VNS – summary

Efficacy appears to be established but no different to new AEDs

Seizure frequency and severity may be reduced but rarely seizure free

Response is not predictable and it often takes at least six months for response to be seen
Thank you!

Acknowledgements:
Dr Chris Rittey, Sheffield Children’s Hospital

Cyberonics