The psychological and psychiatric aspects of PWS:
Understanding and management

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Outline

• Introduction to PWS
  – Characteristics over the lifespan (phenotype)
  – Genetics (genotype)

• Eating behaviour and risk of obesity

• Mental ill-health and problem behaviours
  – Repetitive and ritualistic behaviours
  – Temper outbursts
  – Skin picking
  – Mental illness

• Implications for services and support
  – Importance of the environment

• Potential for new treatments
PWS over the lifespan

Intra-uterine (placental)
- Poor growth
- Limited foetal movement
- High rates atypical births

Gender specific genomic imprinting
C/D box snoRNA SNORD 116 (HBII-85)

Infancy
- Extreme hypotonia
- Failure to thrive

Childhood
- Developmental delay – intellectual disabilities
- Short statute – relative growth hormone deficiency
- Sexual immaturity – sex hormone deficiencies
- Over-eating - risk of severe obesity and its complications
- Scoliosis, respiratory disorders, maladaptive behaviours

Adulthood
- Increased risk of obesity (with greater independence)
- Age-related physical and psychiatric morbidity

Display of normal human chromosome complement
Pairs 1 to 23

Chr 15 pair

Y chromosome

X chromosome
Schematic of chromosome abnormalities resulting in PWS

Chromosome 15

- Deletion (70%)
- Maternal uniparental disomy (25%)
- Methylation defect (<5%)
Characteristics of probable hypothalamic origin: a) hyperphagia, b) growth and sex hormone deficiencies; c) poor regulation of temperature; d) high pain threshold
### Mental health & behaviour in PWS

Population-based study

#### Prevalence (%) of specific behaviours (n=65)

<table>
<thead>
<tr>
<th>Behaviour</th>
<th>Definite</th>
<th>Sometime</th>
<th>None</th>
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<tbody>
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<td>21</td>
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<tr>
<td>Obsessional</td>
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<tr>
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<td>67</td>
<td>27</td>
<td>6</td>
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<tr>
<td>Skin picking</td>
<td>59</td>
<td>22</td>
<td>19</td>
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<tr>
<td>Mood swings</td>
<td>38</td>
<td>19</td>
<td>43</td>
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Holland et al 2003, Psychological Medicine
Eating disorder in PWS

• Initial presentation
  – Failure to thrive
  – Development of over-eating

• Mechanisms
  – Abnormality of satiety
  – Increased reward value of food

• Implications
  – Childhood
  – Adult life
Intra-uterine and peri-natal problems

• Abnormal foetal growth (small for dates at gestation) (imprinted genes and placental function)
• Reduced foetal movement
• Increased rates of caesarean section
• Polyhydramnios (excess intra-uterine fluid)

Dudley et al 2007 Early Human Development 83: 471
Weight and height in infancy
Deletions only

<table>
<thead>
<tr>
<th>Age</th>
<th>N</th>
<th>Mean difference between wt &amp; ht centiles</th>
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<td>-3</td>
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<tr>
<td>3m</td>
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<td>-1</td>
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<tr>
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<td>24y</td>
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<td>20</td>
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<tr>
<td>25y</td>
<td>9</td>
<td>19</td>
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</tbody>
</table>

Mean  no centiles +- 2 SE

[Graph showing the mean difference between weight and height centiles by age, with deletions noted at specific ages.]
Weight chart of young adult with PWS

Figure 2 The weight chart of a person with Prader–Willi syndrome showing the large weight increase which occurred when access to food was unsupervised in a group home for people with learning disabilities.

Journal of Intellectual Disability Research 39, 3 3–3. i
The high calorie meal (in comparison to fasting) did not result in the same pattern of brain activation that was found following food intake in those without PWS. No activations survived the analysis once the correction for multiple comparisons was applied.

Fig. 2. The 'satiety cascade' consists of different processes, i.e. sensory, cognitive, postingestive and postabsorptive, which mediate the inhibition of eating. Aberrations or faults in these processes lead to disturbances in the expression of appetite.
Regulation of food intake is controlled by a combination of signals to and from the brain.

People with PWS have delayed and impaired satiety and may be lacking or insensitive to peripheral signals to the brain.

Farooqi, Oxford Textbook of Medicine

Brain control of food intake

Signals from fat cells

Signals from the gut
Why the eating disorder?

• The Paradox of PWS: a genetic model of starvation

• Disruption of the hypothalamic feeding pathways or high threshold set for satiety (Barker hypothesis)
Eating disorder in PWS

• Feeding support after birth and in infancy

• At transition biological abnormality of satiety and/or reward mechanisms associated with food becomes apparent;

• No specific treatment as yet for the eating disorder;

• Supervised access to food prevents obesity (and associated morbidity) and may help wellbeing;

• Strategies to help manage the tension between choice and the need to control access to food
Repetitive and ritualistic behaviours and temper outbursts

- Characteristics
- Mechanisms
- Implications
Repetitive behaviour in PWS and autism

Childhood Routines Inventory

<table>
<thead>
<tr>
<th></th>
<th>PWS N=80;</th>
<th>Autism N=89</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total score</td>
<td>13.1 (5.1)</td>
<td>14.1 (4.2)</td>
</tr>
<tr>
<td>Just right factor score</td>
<td>3.4 (1.6)</td>
<td>3.8 (1.4)</td>
</tr>
<tr>
<td>Repetitive factor score</td>
<td>3.6 (1.6)</td>
<td>3.8 (1.2)</td>
</tr>
<tr>
<td>Total freq/intensity</td>
<td>52.6 (16.6)</td>
<td>54.3 (15.6)</td>
</tr>
<tr>
<td>Just right freq/intensity</td>
<td>13.1 (5.2)</td>
<td>14.3 (5.1)</td>
</tr>
<tr>
<td>Repetitive freq/intensity</td>
<td>14.6 (5.8)</td>
<td>15.5 (4.7)</td>
</tr>
</tbody>
</table>

Strongly significant negative association between DQ and frequency/intensity scores in PWS less so in autism

Greaves et al, 2006 JIDR, 50, 92-100
Deficit in attention switching

Brain functional abnormalities

Physiological arousal

Temper outbursts

Repetitive questions

"What are we going to do now? When? Are we going to do that in a minute?"

Courtesy of Woodcock, University of Birmingham, UK
Hypothesis: genes to behaviour in PWS
Woodcock et al 2009 JIDR, 53: 493-500

- Repetitive and ritualistic behaviours and temper outbursts cluster together;

- Children with PWS reported to show a preference for predictability with negative emotional behaviour and arousal following change (Woodcock et al, 2009);

- Repetitive questions focused on the future and occurred more frequently following change in routine;

- Change produces high demand on cognitive resources – in PWS specific deficit in task switching from one cognitive set to another (cognitive endophenotype) (Woodcock et al Cognitive neuropsychology)
Implications

• Biological determined deficit in set-switching predisposes to pattern of repetitive and ritualistic behaviours and temper outbursts

• Pattern of behaviour becomes established through reinforcement over time
  • Early intervention to minimise establishment of behaviours
  • Psychologically informed support strategies
  • Training to improve set-switching

• Poor emotional control – role of the autonomic nervous system (Polyvagal Theory put forward by Porges)
Skin picking in PWS

• Possibilities
  – Mood related
  – Part of ‘obsessive compulsive disorder’
  – Absence of negative feedback due to high pain threshold
  – Functional

Modulation of the glutaminergic pathway using N-Acetylcysteine in 35 children and adults with PWS. Assessed before and after 12 weeks of treatment on numbers and size of lesions. All improved 10 did not resolve completely.

Differentially high levels of skin picking were observed in the *alone* and *ignore* conditions for eight of the twelve participants (i.e., S1, S2, S3, S5, S6, S9, S10, and S11). **Fig. 1** shows the mean percentage of skin picking observed in each condition of the functional analysis for these eight participants.

Mental illness

- Characteristics
- Prevalence
- Mechanisms
- Implications
Skin picking

• Uncertainty as to reasons for this behaviour – maybe several factors

• Records of skin picking behaviour to look for patterns – boredom, mood etc

• Activities incompatible with skin picking

• Environmental changes to reduce anxiety (structure, visual support etc)

• Treatment of mood disorder
Psychiatric illness in PWS

• Kollrack and Wolff 1966

• Since then, over 20 studies describing the association of PWS with psychiatric illness

• Most describe an affective psychosis with characteristic features

• However, some methodological problems:
  – Small sample size
  – Not genetically confirmed
### Population-based Study of PWS Psychotic Illness

**Number with psychotic illness 7/25 (28%)**

<table>
<thead>
<tr>
<th></th>
<th>Age 18-27</th>
<th>age 28+</th>
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<tbody>
<tr>
<td>Del (15q11-13)</td>
<td>0/4</td>
<td>1/9 (11%)</td>
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<tr>
<td>UPD</td>
<td>0/3</td>
<td>5/5 (100%)</td>
</tr>
<tr>
<td>Other</td>
<td>0/3</td>
<td>1/1*</td>
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<tr>
<td><strong>Total</strong></td>
<td><strong>0/10</strong></td>
<td><strong>7/15 (49%)</strong></td>
</tr>
</tbody>
</table>

*Imprinting centre mutation

Boer et al, Lancet, 2002
Method
Soni et al 2008

- 46 of 119 (38.7%) adults screened positive for psychopathology
  - 24 Deletion, 22 mUPD

- Further assessment included:
  - Psychiatric Assessment Schedule for Adults with Developmental Disability (PAS-ADD)
  - Operational criteria checklist for psychotic and affective illness (OPCRIT)
  - Family History Questionnaire
  - modified Life Events Questionnaire
  - Wechsler Adult Intelligence Scale (WAIS)
Prevalence of psychiatric illness

Psychotic illness more common in mUPD than deletion p<0.001, effect size 0.45

Soni et al 2008, Psychological Medicine, 38, 1505
Graph to show symptoms in participants with psychotic symptoms (n=31)

*Difference between genetic subtypes on scores of “agitation”: Fishers Exact test 2 sided; p<0.05
Frequency of psychotic symptoms

![Frequency of psychotic symptoms graph]

- **Auditory hallucinations**
- **Visual hallucinations**
- **Tactile hallucinations**
- **Olfactory hallucinations**
- **Thought disorder**
- **Any delusion**
- **Catatonic symptoms**
- **Insight present**

**Number of people**

- **Deletion (n=12)**
- **Disomy (n=19)**
Symptoms of hypomania in people with psychotic symptoms (n=31)

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Number of people</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expansive mood</td>
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<tr>
<td>Pressing, racing thoughts</td>
<td></td>
</tr>
<tr>
<td>Overtalkativeness</td>
<td></td>
</tr>
<tr>
<td>Distractibility</td>
<td></td>
</tr>
<tr>
<td>Overactivity</td>
<td></td>
</tr>
<tr>
<td>Exaggerated self esteem</td>
<td></td>
</tr>
</tbody>
</table>

![Bar Chart](image-url)

- **Expansive mood**: Deletion (n=12) vs. Disomy (n=19)
- **Pressing, racing thoughts**: Deletion (n=12) vs. Disomy (n=19)
- **Overtalkativeness**: Deletion (n=12) vs. Disomy (n=19)
- **Distractibility**: Deletion (n=12) vs. Disomy (n=19)
- **Overactivity**: Deletion (n=12) vs. Disomy (n=19)
- **Exaggerated self esteem**: Deletion (n=12) vs. Disomy (n=19)
Summary of phenomenology

- Evidence of mood related psychiatric illness;
- Hypomaniac symptoms and agitation more pronounced in those with mUPD;
- Delusions predominately persecutory in both deletion and mUPD;
- Auditory and visual hallucinations present in both groups.
Interventions for co-morbid psychiatric disorder

- Determined by the formulation
- If there is evidence of a co-morbid psychiatric disorder (e.g., psychotic illness)?
  - Immediate
  - Short term
  - Long term
- Pharmacological
- Psychological
- Social
Interventions for co-morbid psychiatric disorder

• Short term
  – Keep safe (admission)
  – Lower demand
  – Keep family/care workers informed
  – Use of medication to bring mental state and therefore behaviour under control

• Medium term
  – Establish formulation to inform treatment
  – Evaluate progress and treatment (risk)
  – Structure, predictability
  – Medication
Interventions for co-morbid psychiatric disorder

• Longer-term
  – Support (weight control, visual support etc)
  – Monitor
  – Activity (structure)
  – Medication
Psychiatric medications
some basic rules

• The prescribing of medication should be guided by a diagnosis and formulation;

• Medication should be prescribed for diagnosed conditions where there is evidence, at least in the general population, of benefit;

• In PWS if psychiatric medications are indicated start at lower and normal dose and increase with care;

• Before starting psychiatric medications collect baseline data (mental state/behaviour) so that benefit or not can be determined;

• Medication is but part of the intervention and should be prescribed in the context of an overall treatment plan that considers the short, medium and longer term.
Psychiatric medications for serious comorbid mental illness in PWS

Some uncertainties:

- Depression and associated anxiety: SSRI such as citalopram
- Psychosis: antipsychotics such as risperidone, aripiprazole – avoid olanzapine!
- Mood stabilisers: carbamazepine, sodium valproate, lithium, lamotrigine
Oxytocin in PWS

Human PWS hypothalamus
38% reduction in total PVN neurons
42% reduction in PVN oxytocin neurons
*Swaab et al. JCEM 80:573-579, 1995*


Tauber et al (2011) Oxytocin may be useful to increase trust in others and decrease disruptive behaviours in patients with PWS: a randomised placebo controlled trial in 24 patients Orphanet J Rare Dis, 6: 47-52.

Results
Weight and Body Composition

- Participant 1 gained weight - continued to increase when VNS off, no abnormality of BMR - VNS not physiologically responsible for increase.

- Participant 2 has shown very modest weight loss – c. 2.9% decrease in body weight.

- Participant 3 has shown relatively stable weight throughout – now showing weight loss two years 6 months later (4 kg since July 2013) – is this VNS?.
Results
Unexpected behavioural change

• Participants 2 & 3 described positive effects on temperament, behaviour and social functioning (behavioural data was not collected prior to this).

• Semi-structured interviews characterised these changes as involving increased emotional and cognitive flexibility, with reduced tendency for temper outbursts when routines or expectations are disrupted.

• Not due to alleviation of depressive symptoms.

• Participant 1 did not show the same extent of behavioural issues prior to VNS.

• Improvements have led Participants 2 & 3 to continue VNS beyond study
Two years on...

• K – VNS switched off. Moved to her own flat with support – severely obese – weight fluctuates

• S – VNS still activated – still described as ‘Mr Chill’ by his mother – no serious outbursts for two years - p/t job, living at home in food supervised environment – occasionally ‘steals’ food

• J – VNS still activated – lives with husband with daily support – some weight increase followed by 11 Kg loss on diet – no serious outbursts
Formulation

Reason for referral

FORMULATION

Accepted models of understanding

Evidence-base for different interventions

Intervention

Good Clinical Practice

History

Examination

Investigations

Observations
Matrix

- Biological
- Developmental
- Psychological
- Environmental

Onset and continuation of ‘behaviour’ and/or abnormal mental state

- Predispose
- Precipitate
- Maintain
Mechanisms

• Different mechanisms link the PWS genotype to different aspects of the PWS behavioural phenotype
  – Temper outbursts/repetitive behaviours – delayed development – impaired set shifting
  – Mood disorder – shift in ‘liability threshold’
  – Psychotic illness – additional genetic vulnerability particularly in mUPD

• Interventions will be different depending on underlying mechanisms
Cause for concern in people with PWS

• The onset of new maladaptive behaviours or significant change in mental state;

• An increase in the frequency and/or severity of existing maladaptive behaviours;

• Evidence of physical ill-health, complaining of pain, vomiting etc.
What is so difficult about the environment?

- The visibility and availability of food and money to buy food – having to resist in such circumstances very difficult
- Changing and unpredictable environment difficulty switching attention
- Difficulty with emotional regulation – low threshold for responding adversely to environmental demands
- Social impairments, other ‘autistic-like’ disabilities makes it very difficult to negotiate the demands of the adult world.
Final points

• Physical illness maybe difficult to detect in a person with PWS: remember obesity related problems (e.g. sleep apnoea);

• The importance of formulation to guide intervention – data collection allows the management of uncertainty;

• Combination of approaches from the pharmacological to the psychological and social;

• New problems may arise during the life course.