NEW DATA IN PRADER-WILLI SYNDROME AND PERSPECTIVES

Maithé Tauber
Reference centre for Prader-Wili syndrome and other rare causes of obesity
Children Hospital, Toulouse
France
Disclosure:

Scientific board of Merck Serono, Novo-Nordisk, OT4B

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Consultant for Pfizer, Millendo, Merck

3 patents for Oxytocin related products in Prader-Willi Syndrome
- OVERVIEW OF PWS

- MENTAL HEALTH:
  - PWS as a model of addiction disorders
  - Epigenetics marks

- ENDOCRINE AND METABOLIC TROUBLES
  - Increased IGFBP-7 a new marker of PWS?
  - Diabetes in the transition period

- SCOLIOSIS
  - Is ghrelin a marker of the occurrence and severity of scoliosis?

- COVID-19
  - People with PWS are not at high risk for severe COVID-19 as a group

- THERAPEUTIC PERSPECTIVES
  - Many drugs in development
**Definition**

PWS is a neurodevelopmental genetic disorder due to loss of expression of paternal inherited maternal imprinted alleles in the chromosome 15q11-q13.

- **50%** paternal deletion (FISH +)
- **45%** maternal disomy
- **< 2%** imprinting déficit
- **1-3%** translocation
The hypothetical minimal paternal deletion region associated with PWS phenotype deduced from clinical cases with chromosomal translocations removes SNORD109A, the SNORD116 cluster (30 snoRNAs copies) and IPW.
Bieth , Eddiry et al
Europ J Human Genet
2014
A NEURODEVELOPMENTAL TRAJECTORY WITH 3 DIMENSIONS NUTRITIONAL, ENDOCRINE AND METABOLISM AND BEHAVIOUR

Figure 1: Natural history of Prader-Willi syndrome
Written informed consent was obtained from all patients or their guardians.

Tauber et al Lancet 2021
Impaired development and function of the hypothalamus explains most of the typical features of Prader-Willi syndrome.
Hypothalamic neuropeptides and neurocircuirties in Prader Willi syndrome

Felipe Correa-da-Silva¹,²,³ | Eric Fliers¹ | Dick F. Swaab³ | Chun-Xia Yi¹,²,³

Contrôls PSK1 ↓ MSH, insulin, oxytocin, GHRH, IGFBP-7

Hyperphagia
Hypothalamic neuropeptides and neurocircuits in Prader Willi syndrome

Damping of orexigenic (NPY) and anorexigenic (oxytocin and probably POMC) neurons with hyperactivation of circuits involved in food intake and motivation
# HYPOTHALAMIC NEUROPEPTIDES

<table>
<thead>
<tr>
<th>Neuropeptide</th>
<th>CNS</th>
<th>Hypoactivity/Hyperactivity</th>
<th>Plasma concentrations</th>
<th>Reference (##)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPY</td>
<td>Decreased expression and cell count</td>
<td>Hypoactivity</td>
<td></td>
<td>103</td>
</tr>
<tr>
<td>AgRP</td>
<td>Decreased expression and unchanged cell count</td>
<td>Hypoactivity</td>
<td></td>
<td>103,121</td>
</tr>
<tr>
<td>Hypocretin</td>
<td>Unchanged cell count</td>
<td>Unaltered/ Hyperactivity (?)</td>
<td>Increased</td>
<td>130,131</td>
</tr>
<tr>
<td>POMC</td>
<td>Decreased expression</td>
<td>Hypoactivity</td>
<td></td>
<td>121</td>
</tr>
<tr>
<td>OXT</td>
<td>Decreased expression and cell count</td>
<td>Hypoactivity</td>
<td>Increased</td>
<td>102,142</td>
</tr>
<tr>
<td>BDNF</td>
<td>Decreased expression</td>
<td>Hypoactivity</td>
<td>Decreased</td>
<td>121,146</td>
</tr>
</tbody>
</table>

Abbreviations: AgRP, agouti related protein; BDNF, brain derived neurotrophic factor; NPY, Neuropeptide Y; OXT, oxytocin; POMC, proopiomelanocortin.
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THERAPEUTIC PERSPECTIVES
- Many drugs in development
-obsession with food and food-related items

-foraging and storing, stealing food, craving for food

-food impulsivity

-before and during meals:
  -agitation and abnormal behaviours (excessive cleaning of the dishes, crumbs, over preoccupation with others), rituals
  -either excessively slow or rapid eating with high risk of choking and aspiration

-excessive quantities of food/drinking intake

Hyperphagia in Prader-Willi syndrome might be linked with addiction for food.
NON FOOD RELATED BEHAVIOURS

- other addictions: smoking +++alcohol rarely
- objects collections,
- global impulsivity
- thinking rigidity: difficulty to change mind
- disruptive behaviour
- perseverations, repetitions, rituals
- difficulty to evaluate quantities
What can we learn from PWS and SNORD116 genes about the pathophysiology of addictive disorders?

Juliette Salles\textsuperscript{1,2,3,4} · Emmanuelle Lacassagne\textsuperscript{3} · Sanaa Eddiry\textsuperscript{3} · Nicolas Franchitto\textsuperscript{1,5} · Jean-Pierre Salles\textsuperscript{3} · Maithé Tauber\textsuperscript{1,3,4,6}
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RESULTS: 29,234 differentially methylated cytosines, corresponding to 5,308 differentially methylated regions (DMRs), which matched with 2,280 genes. The DMRs in patients with PWS were associated with neurodevelopmental pathways, endocrine dysfunction, and social and addictive processes consistent with the key features of the PWS phenotype.

CONCLUSION: The PWS is associated with epigenetic modifications with differences in SNORD116 and MAGEL2 mutations, which seem to be relevant to the different associated phenotypes.
Results of hierarchical clustering; dendrogram including: PWS1: male infant patient with deletion type1, PWS2: male child patient with deletion type1, PWS3: female adult patient with deletion type2, PWS4: male adult patient with deletion type2, PWS5: male infant patient with uniparental disomy (UPD), PWS6 (SNORD116 MD): female adult patient with SNORD116 deletion, PWS7 (MAGEL2): male adult patient with MAGEL2 mutation, CTRL1: male infant control, CTRL2: female infant control.
The separate analysis for the *SNORD116* and *MAGEL2* deletions revealed that the DMRs associated with the *SNORD116* microdeletion were found in genes implicated in metabolic pathways and nervous system development, whereas *MAGEL2* mutations mostly concerned genes involved in macromolecule biosynthesis.
METHYLATION MARKS IN PWS

Salles J et al. Clinical epigenetics 2021
Representation of the methylation level of the genes of interest. The darkness of the color indicates the level of methylation (pale colors indicate low level of methylation, while dark colors indicate high level of methylation).
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AIM: To clarify the role of SNORD116 in cellular and animal models with regard to growth hormone therapy (GHT).

METHODS: We collected serums and induced pluripotent stem cells (iPSCs) from GH-treated PWS patients to differentiate into dopaminergic neurons, and in parallel used a Snord116 knockout mouse model. We analyzed the expression of factors potentially linked to GH responsiveness.

RESULTS: We found elevated levels of circulating IGFBP7 in naive PWS patients, with IGFBP7 levels normalizing under GHT.

CONCLUSION: SNORD116 deletion affects IGFBP7 levels, while IGFBP7 decreases under GHT in PWS patients. Modulation of the IGFBP7 level, which interacts with IGF1, has implications in the pathophysiology and management of PWS under GHT.
We found elevated IGFBP7 levels in the brains of Snord116 knockout mice and in iPSC-derived neurons from a SNORD116-deleted PWS patient. ↑IGFBP7 in PWS patients may result from both ↑IGFBP7 expression and ↓IGFBP7 cleavage, by downregulation of the proconvertase PC1.
Loss of SNORD116 results in an increase in IGFBP7 mRNA expression and a decrease in potential IGFBP7 cleavage by PC1, with high levels of secreted IGFBP7 in naive PWS patients.

GHT stimulates IGF1 production, which downregulates IGFBP7 mRNA expression and lowers its circulating level.
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AIM: was to describe the natural history of T2DM in patients with PWS before the age of 25 years and to develop screening and preventive strategies.

POPULATION: Thirty-nine patients followed in the French PWS Reference Center were included (25.6 years [23.7; 31.7]). Twenty-one had been treated with growth hormone (GH), fifteen had not, and three had an unknown status.

RESULTS: The median age at T2DM diagnosis was 16.8 years (11–24) and the median BMI was 39 kg/m² [34.6; 45], with 34/35 patients living with obesity. The patients displayed frequent psychiatric (48.3% hospitalization,) and metabolic (56.4% hypertriglyceridemia,) comorbidities and a parental history of T2DM (35.7%) or overweight (53.6%) compared to the PWS general population. There was no difference in BMI and metabolic complications between the GH-treated and non-GH-treated groups at T2DM diagnosis.

CONCLUSIONS Patients with PWS who develop early T2DM have severe obesity, a high frequency of psychiatric and metabolic disorders, and a family history of T2DM and overweight. These results underline the need for early identification of patients at risk, prevention of obesity, and repeated blood glucose monitoring during the transition period.
CHANGE IN BMI AS A FUNCTION OF AGE IN THE WHOLE POPULATION.

TRANSITION PERIOD : A STRONG NEED TO CONTROL BMI
Glycemic control is more difficult to achieve in patients with PWS and diabetes than in patients with diabetes but no PWS. Metformin treatment, which was prescribed for 94.7% of patients, was often insufficient as a monotherapy. Insulin was or had been used in 70.3% of the cases and the patients had a median of three anti-diabetic treatments [2; 3]. SGLT-2 inhibitors show promising results as they allow for significant weight loss along with improved blood sugar control. Three cases of an SGLT-2 inhibitor prescribed in combination with a GLP-1 agonist have been described in PWS, with marked improvement in HbA1c and significant weight loss following initiation of treatment.
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BACKGROUND: To explore (1) whether ghrelin levels differ between children with PWS with and without EOS and correlate with scoliosis severity, and (2) whether ghrelin levels in the first year of life are associated with the later development of EOS.

METHODS: We used a case control study design for the first question and a longitudinal design for the second. Thirty children<10 years old with EOS and 30 age- and BMI-matched controls without EOS from our database were included. The Cobb angle at diagnosis was recorded. In addition, 37 infants with a ghrelin measurement in the first year of life were followed until 4 years of age and assessed for EOS.

RESULTS: EOS children had an AG/UAG ratio statistically significantly lower than controls. The Cobb angle was positively correlated with Total Ghrelin and UAG. TG and AG in the first year of life were higher in infants who later develop EOS without reaching a statistically significant difference.

CONCLUSIONS: Our results suggest that ghrelin may play a role in the pathophysiology of EOS in PWS. Higher ghrelinemia in the first year of life required careful follow-up for EOS.
### Table 1  Clinical characteristics and TG, AG, UAG and AG/UAG of PWS children with and without EOS

<table>
<thead>
<tr>
<th></th>
<th>PWS children with EOS (cases) n = 30</th>
<th>PWS children without EOS (controls) n = 30</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex—girls, n (%)</td>
<td>20 (66.7)</td>
<td>16 (53.3)</td>
<td>0.285</td>
</tr>
<tr>
<td>Age—years, median (IQR)</td>
<td>3.7 (2.0–5.2)</td>
<td>3.9 (2.3–5.0)</td>
<td>–</td>
</tr>
<tr>
<td>BMI—WHO z-score, median (IQR)</td>
<td>0.0 (−0.8–1.4)</td>
<td>0.1 (−0.9–1.4)</td>
<td>–</td>
</tr>
<tr>
<td>Genetic subtype—deletion, n (%)</td>
<td>12 (40.0)</td>
<td>19 (63.3)</td>
<td>0.090</td>
</tr>
<tr>
<td>Age at start GH—months, median (IQR)</td>
<td>12 (9–13)</td>
<td>13 (10–16)</td>
<td>0.043</td>
</tr>
<tr>
<td>GH dose—mg/kg/d, median (IQR)</td>
<td>0.0263 (0.0215–0.0334)</td>
<td>0.0277 (0.0184–0.0321)</td>
<td>0.614</td>
</tr>
<tr>
<td>IGF-1—z-score, median (IQR)</td>
<td>1.4 (0.3–2.5)</td>
<td>0.7 (−0.2–1.7)</td>
<td>0.065</td>
</tr>
<tr>
<td>HbA1c—%, median (IQR)</td>
<td>5.4 (5.2–5.6)</td>
<td>5.4 (5.2–5.8)</td>
<td>0.364</td>
</tr>
<tr>
<td>Insulin—μUI/ml, median (IQR)</td>
<td>5.2 (2.5–8.2)</td>
<td>4.9 (3.0–7.2)</td>
<td>0.084</td>
</tr>
<tr>
<td>TG—pg/ml, median (IQR)</td>
<td>314.0 (207.2–481.0)</td>
<td>317.1 (231.7–618.4)</td>
<td>0.797</td>
</tr>
<tr>
<td>AG—pg/ml, median (IQR)</td>
<td>161.3 (89.6–210.6)</td>
<td>194.6 (154.2–256.8)</td>
<td>0.079</td>
</tr>
<tr>
<td>UAG—pg/ml, median (IQR)</td>
<td>152.3 (81.7–263.5)</td>
<td>120.1 (71.2–219.2)</td>
<td>0.382</td>
</tr>
<tr>
<td>AG/UAG, median (IQR)</td>
<td>0.783 (0.559–1.993)</td>
<td>1.589 (1.166–2.433)</td>
<td>0.005</td>
</tr>
<tr>
<td>Age at EOS diagnosis—years, median (IQR)</td>
<td>3.4 (1.8–5.2)</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Cobb angle at diagnosis—degrees, median (IQR)</td>
<td>20 (12–27)</td>
<td>–</td>
<td></td>
</tr>
</tbody>
</table>
Fig. 2 Correlation between TG (A) and UAG (B) with Cobb angle (n = 27)
Fig. 3 Comparison of TG, AG, UAG and AG/UAG among infants with PWS at the first year of life according to their EOS status at the age of 4 years.
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THERAPEUTIC PERSPECTIVES
- Many drugs in development
**BACKGROUND**: To assess prevalence and medical course of SARS-CoV-2 infection in children and adults with PWS. From November 2020 to January 2021, we performed a detailed medical survey on 342 adults and 305 children with PWS followed in the French reference center.

**RESULTS**: We obtained responses from 288 adults (84%) and 239 children (78%). Thirty height adults (13.2%) and 13 children (5.4%) with PWS had SARS-CoV-2 infection. Mean age of adults was 34.1±11.9 years and mean body mass index was 40.6±12.7 kg/m²; **82% had obesity and 37% had diabetes**. Only 3 children (23%) had obesity and none had diabetes. The most frequent symptoms of COVID-19 were asthenia, fever, cough, headache and shortness of breath. **All patients had a favorable outcome**.

**CONCLUSION**: PWS itself is **not a risk factor for severe COVID-19** in children and adults. On the contrary, evolution of SARS-CoV-2 infection in adults with PWS seems more favorable than expected, given their comorbidities.
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- THERAPEUTIC PERSPECTIVES
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Current and emerging therapies for managing hyperphagia and obesity in Prader-Willi syndrome: A narrative review

Qiming Tan | Camila E. Orsso | Edward C. Deehan | Lucia Triador
Catherine J. Field | Hein Min Tun | Joan C. Han | Timo D. Müller | Andrea M. Haqq

Combinatorial pharmacotherapies

Methionine aminopeptidase 2 inhibitor (Beloranib)

Cannabinoid receptor antagonists (DIS037, CB5 Oral Solution)

Melanocortin-4 receptor agonist (Setmelanotide)

GH treatment

Physical activity
- ↓ energy expenditure
- ↑ endocannabinoids signaling
- ↑ growth hormone
- ↓ expression of oxytocin receptors

Dietary management
- ↑ food-seeking behaviors
- ↓ signaling of the fed-state
- ↓ ghrelin to PYY ratio

Triple monoamine re-uptake inhibitor (Tresafpens/Metapalol)

GLP-1 receptor agonists (Liraglutide, Exenatide)

UAG analog (AZF-531); GOAT inhibitor (BM-ES3)

Hyperphagia & Obesity in PWS

↑ Burden

Children with
- ↑ Morbidity
- ↑ Mortality
- ↑ Dependence
Caregivers
- Strict control of access to food (e.g., locking food, constant supervision)

Pathophysiology
Non-Pharmacologic approaches
Pharmacologic approaches

Publication submitted

FDA required another study

FDA required more data
CONCLUSIONS AND PERSPECTIVES

- What can we learn from addictive disorders?

- How to use the new markers IGFBP-7 and ghrelin?

- A challenge for preventing and treating diabetes in the transition period

- How to explain the «good outcome» of Covid19?

- What drug and what target?
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