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Title : Brainstem serotonin transporter availability in maternal uniparental disomy and deletion Prader-Willi syndrome.

Short title: Prader-Willi syndrome and serotonin transporter.

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Abstract

Prader-Willi syndrome (PWS) is a rare condition due to deletion (del PWS) of paternal chromosomal material, or a maternal uniparental disomy (mUPD PWS), at 15q11-13. Affective psychosis is more prevalent in mUPD PWS. We investigate the relationship between the two PWS genetic variants and brainstem serotonin (5-HTT) transporter availability in adult humans. Mean brainstem 5-HTT availability determined by [¹²³I]-beta-CIT SPECT was lower in 8 adults with mUPD PWS compared to 9 adults with del PWS (mean difference = -0.93; t=-2.85; p=0.014). Our findings confirm an association between PWS genotype and brainstem 5-HTT availability, implicating a maternally expressed/paternally imprinted gene, that is likely to account for the difference in psychiatric phenotypes between the PWS variants.

Prader-Willi syndrome (PWS) is a rare genetic disorder, with a UK population prevalence of ~1 in 52,000(1). PWS is caused by lack of paternal contribution to the critical chromosome region at 15q11-13, due to deletion on the paternally inherited chromosome (del PWS - 70%) or maternal uniparental disomy (mUPD PWS - 25%). Imprinted genes are monoallelically expressed in a parent-of-origin dependent manner. PWS is associated with a distinct physical phenotype including short stature, small hands and feet, hypogonadism and a characteristic facial appearance; and a behavioural phenotype characterised by increased appetite, mood swings, stubbornness, temper tantrums, aggression, repetitive speech(2). PWS is also associated with high rates of psychopathology, including affective disorders. Those with mUPD are considered at greater risk of developing an 'affective psychosis' compared to del PWS. The neurological pathophysiology underlying this phenomenon is far from clear(3, 4).

The serotonergic system is a prime candidate for explaining the high rates of affective disorders, and particularly affective psychosis in mUPD PWS. It is well established that serotonin plays a crucial role in brain development, and emotional regulation, and has been implicated in the development of affective disorders like major depression (MDD)(5). Through examining the role of imprinted genes in brain serotonin neurochemistry, it may be possible to shed light on the neurobiological basis of higher rates of affective psychosis in those with mUPD PWS. Previous research has shown greater serotonergic turnover, including increased monoamine oxidase activity in platelets and increased 5HIAA (breakdown product of serotonin) in the CSF of patients with PWS(6, 7). The aim of this project was to explore if serotonin transporter (5-HTT) availability differed significantly between the PWS variants. In keeping with the extant literature on serotonin turnover in PWS and 5-

HTT availability in MDD, we hypothesized that mUPD PWS will have greater depressive symptoms and lower 5-HTT availability compared to del PWS(8) .

Methods

This was a UK-wide, cross-sectional study, comparing 5-HTT availability in 8 adults with mUPD PWS and 10 with del PWS, approved by the West of Scotland Research ethics committee and the Administration of Radioactive Substances Advisory Committee. None of the participants were being prescribed medications that interact with 5-HTT uptake. Depressive symptomatology was assessed using the Glasgow depression scale(9). Past psychotic episodes were recorded. All participants underwent [¹²³I]-beta-CIT SPECT imaging using a previously validated protocol(10). Brain SPECT imaging was performed with a dedicated, 12 headed Neurofocus 900 scanner (spatial resolution 7mm full width at half maximum; Neurophysics, Massachusetts), which acquires sequential single transaxial brain sections. Subjects pretreated with 120mg of potassium iodide were scanned 3 – 4 hours after intravenous administration of [¹²³I]-beta-CIT in order to establish uptake in 5-HTT rich areas(11). Region of interest (ROI) analysis was carried out by an investigator (AN) blinded to the subject's clinical and demographic history(10). The ROI template consisted of manually drawn regions representing the brain stem (specific binding), and a reference ROI consisting of the occipital lobe (non-specific/non-displaceable binding) bilaterally. The 5-HTT BP_{ND} (ratio at equilibrium of specifically bound radioligand to that of non-displaceable radioligand in tissue) was compared between the two groups using a general linear model, with brainstem ROI [¹²³I]-beta-CIT uptake as dependent variable, and group (mUPD PWS vs. del PWS) as the categorical predictor variable, and occipital [¹²³I]-beta-CIT uptake, age and sex as covariates.

Results

We scanned 8 participants with mUPD and 10 participants with del PWS. The SPECT scan from one of the del PWS participants did not pass quality control and was discarded. Demographic and clinical details are shown in table 1. The mUPD group had greater GDS scores (non-significant) and had more past episodes of psychosis (non-significant) compared to the del group. On the general linear model, PWS variant was a significant predictor of $5HTBP_{ND}$ ($F(1,12)=8.15;p=0.014$). The mUPD PWS group had significantly lower $5HTBP_{ND}$ compared to the del PWS group (mean difference = -0.93; $t=-2.85$; $p=0.014$; $d= 2.35$; $95\%CI = 1.12 - 3.59$) (figure 1).

Discussion

This is the first study to explore brainstem 5-HTT availability in PWS (12). Our findings reveal an association between PWS genotype and brainstem 5-HTT availability. The mUPD group had lower brainstem 5-HTT availability compared to the del group. MDD has previously been associated with low 5-HTT availability due to the compensatory down-regulation of 5-HTT secondary to low synaptic serotonin concentrations(8). In keeping with this, we postulate that those with mUPD have a lower synaptic serotonin concentration compared to those with del PWS, and that this may indeed account for the greater prevalence of affective psychotic illness in this population(8). Greater serotonin turnover (greater plasma MAO-B and CSF HIAA) has been previously demonstrated in patients with PWS, compared to healthy controls(6, 7). In addition, treatment with SSRIs have been found to be effective in tackling affective and behavioural problems in individuals with PWS. Together with the above findings, our results, suggest that those with mUPD PWS have lower

synaptic serotonin concentrations compared to del PWS - a finding that has not been previously demonstrated. Although Akefeldt et al found evidence for lower synaptic serotonin in PWS as a group, compared to healthy controls, they did not test if this finding was driven primarily by the mUPD variants within the group. The lack of a control group in our study prevented us from exploring if 5HTT availability was indeed lower in the del PWS group compared to healthy controls. Future studies will be required to explore the relationship between serotonin availability and turnover in PWS variants in relation to healthy population.

Children with mUPD PWS have been found to have smaller cortical and subcortical grey matter volumes compared to neurotypical children(13, 14). In this context, lower 5HTT availability may also be due to smaller volume of serotonergic neurons in the brainstem. However, Honea et al found no difference in brainstem volumes between the two genotypes, suggesting that the lower 5TT availability is unlikely to be the result of smaller volume of brainstem serotonergic neurons(15). Nevertheless, serotonin influences neurogenesis, cell migration, synaptic plasticity, dendritic growth and normal spine formation and our findings could therefore be the result of a combination of the above(16).

Our study has strengths and limitations. It was a UK-wide study with the support from the UK PWS Association. Despite the small sample sizes, at the end of study recruitment, the pool of eligible adults with mUPD PWS who fulfilled the inclusion criteria was exhausted. The 12-detector dedicated head SPECT unit ensured high spatial resolution; and, although more selective ligands for 5-HTT are available, the uptake of [¹²³I]-beta-CIT in the brainstem at 4 hours is a validated measure of 5-HTT availability(11) . Lack of a neurotypical comparison group prevented us from comparing our findings to the healthy population. A cross sectional design and the

relatively small sample size precluded a mediation analysis to ascertain causal relationship between 5-HTT availability differences and affective psychosis.

In summary, we have shown that a group of adults with mUPD PWS have lower 5-HTT availability compared to the del PWS group. Our findings provide preliminary evidence for the pathophysiology underlying greater affective psychopathology associated with the mUPD group of patients, and the potential reasons why drugs like SSRIs are effective in treating this cohort of patients.

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Declaration of Interest

The authors have no conflict of interest to declare pertaining to this study and the manuscript.

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Table1. Demographic and clinical variables in the two patient groups.

	mUPD PWS (8)	Del PWS (9)	Statistic	p(two tailed)
Mean age in years (s.d.)	31.25 (9.09)	29.78 (7.13)	t=0.37	0.72
Sex (female-n)	6 (75%)	6 (66.7%)	$\chi^2=0.14$	0.71
Mean GDS score (s.d.)	6.75 (5.11)	4.55 (2.65)	t=1.09	0.3
Past history of psychosis (n)	5 (62.5%)	3 (33.5%)	$\chi^2=1.45$	0.23

GDS = Glasgow depression scale for people with a learning disability; mUPD = maternal uniparental disomy Prader-Willi syndrome; Del PWS = deletion Prader-Willi syndrome.