

Report from the Scientific Meeting of the IPWSO 7<sup>th</sup> World Conference – held in Taipei city, Taiwan, Thursday and Friday, May 20-21, 2010.

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PWS, a multifaceted disorder, involving all the major body systems, has become a rich source of research into all the varied aspects of human development and behaviour. These were all covered well in the excellent scientific sessions, but due to space constraints, I can only present some of the more compelling/new data here.

### **Genetics**

Driscoll (USA - invited speaker) presented details on the basic genetics and the 3 ways PWS may arise – deletion of the PWS critical region (PWSCR), UPDmat or an imprinting defect. Among the deletions, he considers the differentiation between type I and type II important for phenotype, based on a gene dosage effect, as the 4 genes in the region between the type I and type II breakpoints are not imprinted.

Foncuberta (Argentina) presented data complementary to Driscoll in their population of PWS with 38 del type I and 44 del type II. They found no differences for hypopigmentation, sleep disturbance or epilepsy, but obesity was more common in girls  $\geq 3$  years, puberty more common  $\geq 8$  years in girls with del type II, and deletion type I had a smaller head circumference.

Sinnema (Netherlands), in a study of 102 adults with PWS, found 54% with deletion and 43% UPD. This distribution of less deletion than expected (statistically significant) suggested a shorter life span for PWSdel. Much discussion followed, as an Australian study considered death to be earlier in UPD and the Italian group found that death was not related to genetic subtype (presented at IPWSO Romania, 2007).

Chun-Hui Tsai (USA) presented findings of chromosomal abnormalities in PWS, in addition to either 15qdeletion or UPD. On a literature review, 9 were found to have a sex chromosome abnormality in addition to PWS. On an institutional database search for PWS co-existent with other chromosome abnormalities, she found 3/65 patients affected (4.6%) – quite a high figure! One of her patients had UPDmat PWS with XXY; the other two had delpatPWS together with another microdeletion (22q and 8p23). These results are intriguing – they show that some individuals may have instability of regions of low copy repeat (LCR) sequences, which we know flank the breakpoints of most common deletion syndromes. They also suggest that some individuals may have instability of chromosome segregation at cell division as UPD had occurred twice in one case. The data also provides one more explanation of why there is clinical or phenotypic heterogeneity in PWS.

Matsubara (Japan) presented data showing the maternal age effects of the genetic types of PWS, which is changing in Japan. The change seems to have occurred around 2003. Prior to that time, deletions comprised 82.3% of PWS, now deletions are 60.3%. UPD is now 34%. Their figures are based on comparison of data from 103 patients born at or before 2002 and 50 patients born 2003-2009. They classified the type of UPD into a type I rescue (being a meiosis I error and age dependent) and type 2 rescue (M2 - non age dependent) - of 26 cases, 23 were trisomy rescue with 17 in

MI and 6 in MII. This data complements and extends similar UK findings of increased UPD with age, presented at IPWSO, Romania 2007.

### **Neurology**

Swaab (Netherlands – invited speaker) presented fascinating data on his post mortem studies of 16 brains, collected over the last 25 years from two points of view – gene expression and premature aging in PWS. Of the 5 paternally essential genes in the PWS critical region – ZNF127,NECDIN (NDN), MAGEL2, C15orf2, and SNURF/SNRPN) – there was expression of NDN and C15orf2 in the hypothalamus, both at the mRNA and the protein level. The expression was throughout the paraventricular nucleus (PVN), mamillary body nucleus and supraoptic nucleus (SON) for both UPDPWS and del PWS. Expression of NDN and C15orf2 occurred in the cortex as well (youngest was a 6 month old infant) and expression was present in mouse and human controls. These unexpected findings seem to exclude these genes as major candidates for the symptoms of PWS – one theory suggested to explain the findings was that the effect is mainly during foetal life. However, snoRNA HBII-85 was not expressed in any of the hypothalamic nuclei after 6 months of age.

Re – Alzheimer disease, the characteristic plaques were present early in PWS – in the PVN and SON, areas not affected early by plaques in straight Alzheimer disease.

Nakada (Japan – invited speaker) gave a fascinating talk on the changes in brain cells which occur at birth, a rather understudied aspect of development in the past. Foetal to adult changes occur in the cytosol, to meet the greatly increased energy requirements post nately. Sophisticated electromagnetic spectroscopy techniques showed that taurine, the free amino acid in foetal brain cells is rapidly switched to another amino acid (N-acetyl-aspartate) to aid high energy phosphate transport, the mediator of energy in active cells.

Yamada (Japan) added further to the foetal-adult brain shift, showing (by advanced diffusion tensor imaging techniques) that the neuronal membrane increases its electrical activity after birth.

### **Psychiatry**

Einfeld (Australia – invited speaker) highlighted that behaviours in PWS span a number of different domains, and while some are well known (eg impulsiveness, aggression, perseveration), depression is less appreciated but also common. Thorough psychiatric understanding of PWS would enable an evaluation of the impact of therapies (eg oxytocin) on behavioural disturbances. The relationship between behaviours and executive function, which he said was not affected, drew many questions [One answer defined executive function as a higher level of functioning allowing one to control lower levels of functioning].

Woodcock and Bull (UK) presenting jointly, used fMRI imaging (8 PWS and 8 controls), to evaluate temper outbursts and rage. Those with PWS showed dysfunction in prefrontal, anterior cingulate and parietal regions, associated with poor attention switching. They then looked at strategies to circumvent these outbursts by making the environment more predictable but not allowing routines to become too established.

Benarroch (Israel) gave a fascinating insight into the ability of individuals with PWS to fast. Their religious holiday (Yom Kippur), requires fasting for 25 hours. The fast was explained to PWS individuals, there was no reward offered at the end of the fast –

just a regular meal. 30 individuals with PWS took part in the fast, and 22 completed it. It seemed that motivation to accomplish a task they had set out to do, was the main factor determining success.

### **Endocrinology**

Tauber (France – invited speaker) covered many areas. One was grehlin, a satiety hormone, found to be elevated in PWS throughout their life. Initially thought to be a cause of insatiable appetite and obesity, grehlin is in fact elevated before the hyperphagia begins. Adequate suppression of grehlin did not lead to decreased hyperphagia and obesity in their cohort, rather, from modern imaging techniques, grehlin is associated with thoughts about food in PWS, even though they are not really hungry. Another topic was impaired glucose tolerance (IGT) and diabetes in PWS – more patients have IGT than diabetes and the metabolic syndrome is less in PWS than in other obese individuals. This may be related to fat distribution in PWS, which is more peripheral, rather than the visceral distribution seen in the obese of the general population. Another topic was growth hormone (GH): her group found that patients with UPDmat have a higher prevalence of GH deficiency than other genetic subtypes. The benefits of GH in PWS are indisputable, particularly the increase in muscle mass and power. One doesn't need to use too much GH to get a good effect. Of < 300 children with PWS in France on GH, 5 developed type 2 diabetes, so we can be confident that GH does not lead to diabetes in PWS. There was also no difference in the death rate in PWS in France between those on GH and those not on GH. Another important area discussed was the level of cortisol in people with PWS – in her group, 60% had an insufficient ACTH response and she considers hydrocortisone treatment in times of stress, including mild URTI.

Farholt (Sweden) – gave the results of her study addressing the hydrocortisone issue. Over a 12 month period, a cohort of 57, aged 0-45 years, attending the PWS clinic, were tested by a standard high dose synacthen test. The results did not support an increased risk of central adrenal insufficiency (CAI) in PWS.

Grugni (Italy) gave their results re CAI in PWS, using the metapyrone test on his cohort of 38 patients (23 males, 15 females, aged 1- 16 years. Two subjects had evidence of CAI. He considered that this low level may have been related to the stimulation test adopted. There was a call from the audience for endocrinologists to standardise their testing, as CAI is potentially life threatening.

Viardot (Australia) presented a study using exenatide (Byetta) on 8 subjects with PWS and 8 obese controls matched for age, sex and body fatness. Byetta was well tolerated with no side effects in the PWS subjects (in contrast to the controls), and significantly increased fullness, lowered glucose and insulin levels but did not suppress appetite.

Kido (Japan) showed data on the use of testosterone in 18 males with PWS, age range 16-54 years, with a mean duration of therapy 4.6 years. The BMI did not change significantly, all developed increased pigmentation and beard growth, bone mineral density and muscle volume increased, self confidence clearly increased in 36% and significantly none showed worse behaviour.

### **Databases of PWS**

This was a very interesting and important session; while the concept of a database seems fundamentally attractive and useful for a rare disorder, it is not necessarily straightforward to implement. Many factors affect implementation, including requirements of ethical approval, which varies between countries. Several researchers spoke to this issue. Heinemann (USA) described the results of a survey of PWS in 2004, aiming to characterise the long term medical outcome and natural course of PWS in the USA (with 1787 respondents, from infancy to 67 years). This was followed by a recent 2<sup>nd</sup> survey of 520 individuals – the results clearly showed the value of such collected information. Diene (France) discussed their PWS database, set up in 2004 and well supported by various French bodies, including government. Scheermeyer (Australia) described the process for setting up a national data base in conjunction with the Australian Paediatric Endocrine Group, which has the basic aim to monitor GH efficacy. Holland (UK) presented the logistics and issues for the European PWS Database. As highlighted by Holland, the really important questions were 1. the aim of the database 2. who owns the data 3. who has access to the data 4. how is patient confidentiality ensured 5. who administers the database 6. how is it funded, at set up and in continuation.

In conclusion, participants at the Scientific Conference were brought up to date with the latest state-of-the-art PWS research, invaluable for the best evidence based care of patients. We look forward to the next Conference in 2013 in Cambridge, UK.