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Adrenal function and mortality in children and adolescents with Prader-Willi syndrome attending a single centre from 1991-2009

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Dear Sir

We read with great interest the paper by de Lind van Wijngaarden *et al.*[1] in the *Journal for Clinical Endocrinology and Metabolism* regarding the high prevalence of central adrenal insufficiency (CAI) in patients with Prader-Willi syndrome (PWS), defined as an ACTH level of <33 pmol/l (<8.3 mU/l) at 7.30 a.m. following the single-dose administration of metyrapone 30mg/kg at 11.30 p.m. the previous evening. The rationale of the metyrapone stimulation test is that the acute inhibition of cortisol synthesis via inhibition of 11β-hydroxlyase mimics the stress situation and causes a sudden increased demand for ACTH production. The authors reported that the ACTH response was insufficient in 15 of 25 (60%) randomly selected PWS outpatients (median age 9.7 years) with values of 14-26 vs 49-76 pmol/l in the subnormal and normal groups, respectively. They concluded that the high percentage of CAI might explain the high rate of sudden death in these patients, particularly during infection-related stress, and advised consideration of treatment with hydrocortisone during acute illness in PWS patients unless CAI has recently been ruled out with a metyrapone test. The same group suggested in a subsequent paper that the children diagnosed with CAI on the above criteria had a higher central apnoea index and lower average overnight $Sa0_2$ before metyrapone (20 children/13 with CAI) and a greater increase in obstructive apnoea index than non-CAI children after metyrapone (10 children/6 with CAI).[2] However, the greater increase in central apnoea index in children with CAI after metyrapone did not reach signifcance due to the low number of patients. These findings have important implications for PWS management; instituting emergency steroid cover has major logistical consequences, while steroid treatment could exacerbate the existing tendency towards obesity in PWS.

Since 1991 we have held a dedicated PWS clinic at the Royal Hospital for Sick Children in Glasgow. In the light of the paper by de Lind van Wijngaarden *et al.*[1] we decided to examine retrospectively pituitary-adrenal axis function in subjects attending our clinic. We therefore

conducted a case-note review of all patients in whom pituitary testing was carried out and cortisol responses to hypoglycaemia, via the insulin tolerance test (ITT) or synthetic ACTH (1-24ACTH), were noted. The maximum stimulated cortisol level at any time after insulin or 1-24ACTH was recorded, and values of <500 nmol/l were considered suggestive of adrenal insufficiency according to current evidence.[3,4] We also collected details concerning patient mortality.

Of the 70 patients who have attended the Glasgow clinic since its inception in 1991 until 2009, 25 (19M:6F) have undergone anterior pituitary stimulation testing, median (range) age 7.16 (0.43-16.27) years. Fifteen patients received insulin (0.15 u/kg) as part of an ITT while 10 received 1-24ACTH, six standard dose (250 μg) and four low-dose (1μg), and their data are shown in the Figure. Median (range) basal and peak cortisol results were 328 (105-851) nmol/l and 915 (479-1481) nmol/l, respectively. There was no statistical difference between hypoglycaemia-induced or 1-24ACTH-induced basal (p=0.64) or peak values of cortisol (p=0.72). Only one patient of 25 (4%) showed a peak cortisol <500 nmol/l in response to hypoglycaemia, with a value of 479 nmol/l.

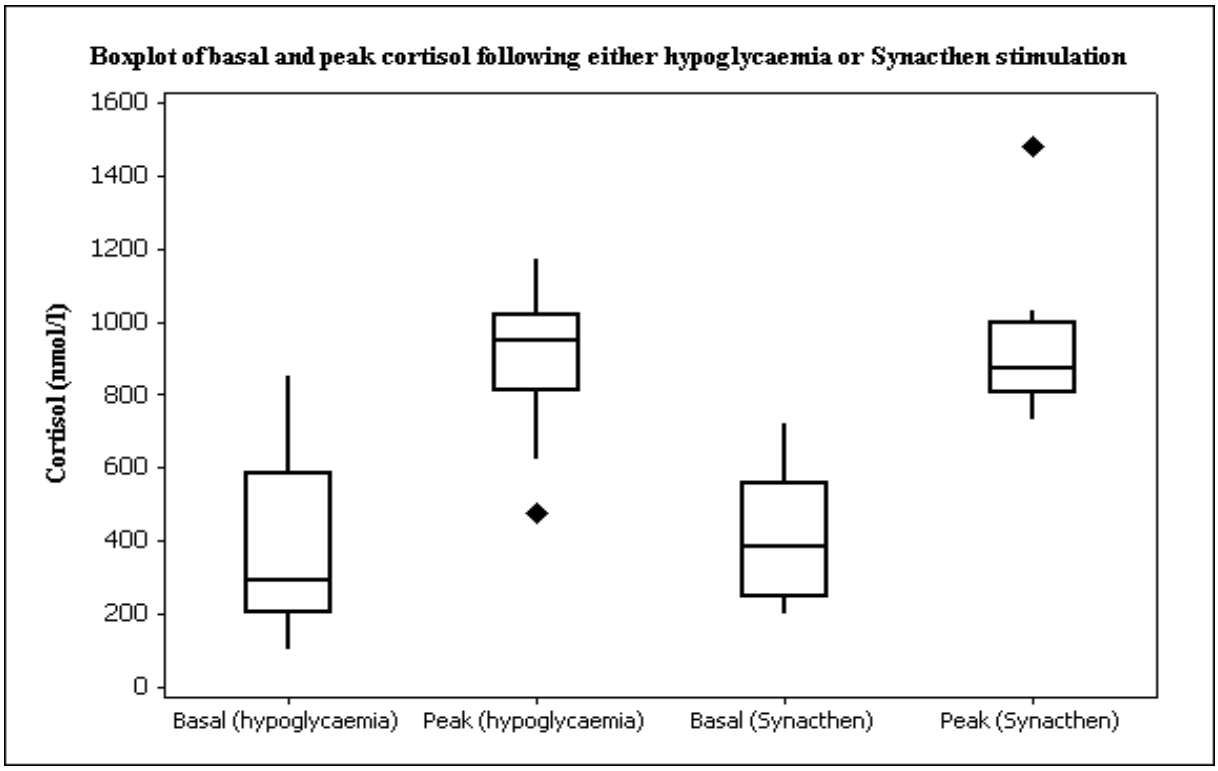

Figure. Boxplot of basal and peak cortisol values following either hypoglycaemia or Synacthen stimulation. 15 patients ITT; 10 patients ACTH. Median basal cortisol 328 (105 - 851) nmol/l. Median peak cortisol 915 (479 – 1481) nmol/l. Outliers: inadequate peak cortisol 479 (basal 205) nmol/l (one patient); cortisol 1481 (basal 260) nmol/l (one patient).

Details of the seven patient deaths in our clinic at the median (range) age of 25.3 (14.8–40.8) years are shown in the Table. Two of the seven deaths occurred in tested patients and the remaining five occurred in untested patients. Four patients had type 2 diabetes. One patient, a boy aged 14 years, died from complications of portal hypertension unrelated to PWS. The other six deaths were all in subjects within the adult age range and all but one of these patients were severely obese with BMI >40 kg/m^2. The only unexpected death was in a 40-year-old woman with type 2 diabetes who was not severely obese but who had been on oxygen therapy for central hypoventilation syndrome and who died while being treated at home for pneumonia.

Of the tested patients one death occurred in the patient with the borderline low peak cortisol of 479nmol/l, this patient being severely obese and suffering from skin sores (see Table). The other tested patient had demonstrated an adequate peak cortisol of 973 nmol/l.

Patient	Age of Death	Gender	Cause of Death	Latest BMI (age)	Peak Cortisol nmol/L (age)
1	23.1	Male	?Cause; severe infected eczema, sleep apnoea, CCF	44 (19.6)	-
2	29.3	Male	?Sepsis from skin ulcer	55.40 (29.1)	-
3*	14.8	Male	Renal failure; portal hypertension, DM	38.84 (12.4)	-
4*	26.7	Male	?Sepsis from skin lesion	48.78 (26.7)	479 (15.8)
5*	17.8	Male	Sepsis from skin lesion	49.98 (17.6)	-
6*	40.8	Female	Pneumonia	33.92 (39.9)	-
7	25.3	Female	Died in sleep; sleep apnoea, cellulitic legs	51.58 (25.0)	973 (14.0)

Table. Data showing age of death, gender, cause of death, BMI and peak cortisol values in seven patients with PWS attending the dedicated clinic in Glasgow. *The four patients with type 2 diabetes.

Our data, using the peak cortisol response to either insulin-induced hypoglycaemia or 1-24ACTH stimulation, do not support a high prevalence of CAI in our PWS clinic. The optimal index of CAI is debatable. For example, Berneis *et al* state that most definitions of normal

ACTH response to metyrapone give presumed safety values rather than true normal values.[5] De Lind van Wijngaarden *et al.* consider the overnight single-dose metyrapone test as the best dynamic test, using a cut-off value of <33 pmol/l to indicate an insufficient ACTH response, as proposed by Steiner and colleagues.[6] This figure is based on control data from twenty healthy adults, mean (range) age 48 (20 – 82) years, who demonstrated ACTH responses between 33 and 193 pmol/l to 30 mg/kg metyrapone. Interestingly, Steiner *et al* also describe a 'dose-response' relationship between plasma ACTH and cortisol and suggest that plasma ACTH levels in the region of 13 pmol/l will usually be sufficient to raise plasma cortisol physiologically into the 'normal' range. Further, a recent report using the ITT as the gold standard dynamic test suggests that the metyrapone test with an ACTH cut-off of 33 pmol/l yields a high false positive rate.[3] In comparison, a cut-off of 18 pmol/l ACTH improves specificity (from 47.1% to 100%) and reduces false positive results without significantly reducing sensitivity (78.6% to 71.4%). This result is in keeping with physiological studies demonstrating that endogenous ACTH concentrations of 15 to18 pmol/l induce near maximal adrenal response in normal subjects. Low dose 1-24ACTH (1 μg) with a cortisol cut-off value of 480 nmol/l and high dose ACTH (250 μg) with a cortisol cut-off value of 580 nmol/l in patients with known hypothalamic-pituitary dysfunction is thought to be similar to the metyrapone test in terms of accuracy.[3]

Obesity is the major contributor to morbidity and mortality in PWS, the deaths in our patients being strongly but not exclusively linked to this complication. Although well-titrated glucocorticoid cover for intercurrent illness should not in theory exacerbate the obesity of PWS patients, there is in our view insufficient evidence at present to indicate that CAI is a significant problem in this disorder. In particular, we are cautious about making the diagnosis of CAI on the basis of fixed cut-off levels for stimulated cortisol and ACTH, it being recognized in endocrine practice that peak cortisol values after 1-24ACTH not infrequently fall within the 'gray' zone of 400-550 nmol/l.

We believe that all PWS patients should undergo pituitary function testing before starting growth hormone therapy, preferably with the ITT to best assess the adrenal axis (although this is not recommended in children <5 years). Unless there is compelling evidence for CAI in individual patients we would counsel against *ad hoc* steroid cover during intercurrent illness in PWS.

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