



MULTIFORM HYPOGONADISM IN MALE PATIENTS WITH PRADER-WILLI SYNDROME

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INTRODUCTION: Hypogonadism leading to hypogonitalism and early pubertal arrest is a main feature of PWS and is generally attributed to hypothalamic dysfunction, but data are not univocal. The aim of this study is to investigate the cause of the hypothalamic-pituitary-gonadal axis dysfunction in male subjects with PWS.

METHODS: We studied 36 patients with genetically confirmed diagnosis age from 1.2-42.7 yrs (median: 16.6 yrs). All subjects had history of cryptorchidism and have spontaneously started their pubertal development, but they had an arrest of gonadal development at a maximum pubertal stage of G3. Basal gonadotropin (FSH, LH), testosterone (T) and Inhibin B (InhB) levels were measured. 150 normal subjects, divided in pre-pubertal (50 pts, age: 0.8-10.5 yrs, pubertal stage: G1) and pubertal (100 pts, age: 9.7-17.8 yrs, pubertal stage: G2-G5) were used as a control group.

RESULTS: The 4 different patterns of gonadotropins levels by pubertal stage are shown in the table:

| | G1 (n=13) Age 1.2-32.3 | G2 (n=14) Age 9.6-42.7 | G3 (n=9) Age 15.3-33.3 |
|----------------------|---------------------------|---------------------------|---------------------------|
| normal FSH and LH | 23 % (n=3) | 7 % (n=1) | 22 % (n=2) |
| high FSH - normal LH | 46 % (n=6) | 72 % (n=10) | 56 % (n=5) |
| low FSH and LH | 23 % (n=3) | 7 % (n=1) | 11 % (n=1) |
| normal FSH - low LH | 8 % (n=1) | 14 % (n=2) | 11 % (n=1) |

T levels (range: 0.13-6.9 ng/ml) were below the normal range for age and pubertal stage in 27/36 (75%) patients and normal in 9/36 (25%). Serum InhB was undetectable in 14/36 (39%) patients. In pre-pubertal group (G1) InhB was undetectable in 4/13 patients (31%), low in 9/13 (69%, range 18.5-56.4 pg/ml) compared to pre-pubertal control group (InhB levels: 56.5-145.8 pg/mL). In pubertal group (G2-G3) (23 pts, age: 9.6-42.7) InhB was undetectable in 10/23 patients (43%), low in 12/23 (53%, range 5.2-64.3 pg/ml) and normal in 1/23 patients (4%, 104 pg/ml) compared to pubertal control group (InhB levels: 68.6-322.7 pg/mL). In the subgroup of patients with high FSH (n=21), the linear correlation analysis showed an inverse relation between InhB and both FSH ($r = -0.4652$, $r^2 = 0.22$, $p = 0.0388$) and age ($r = -0.5503$, $r^2 = 0.3029$, $p = 0.0119$), while FSH correlated positively with age ($r = 0.6431$, $r^2 = 0.4136$, $p = 0.0022$) independently to pubertal stage.



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DISCUSSION: Low InhB with high FSH levels suggest a damage of Sertoli cells displaying a hypergonadotropic hypogonadism that seems to be already present in early childhood (46% of pts with high FSH in G1 were aged 1.2-9.4 yrs) and that become more evident in older age. On the other hand we noticed that 18/27 (66%) pts with normal LH levels had low T levels. This suggests both a hypothalamic and Leydig cells damage displaying a combined hypogonadism pattern. In conclusion, our results confirm that PWS male patients have a multiform hypogonadism that could be of central, peripheral or combined origin detectable already in early age.