# Etiological spectrum and clinical characteristics of 129 children with gonadotropin independent precocious puberty: A nationwide cohort study

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**Background:** Gonadotropin independent precocious puberty (GIPP) is caused by a heterogenous group of disorders. With the exception of congenital adrenal hyperplasia (CAH), disorders causing GIPP are uncommon, and there are no studies evaluating the etiologic distribution of GIPP in a large cohort.

**Objective and hypotheses:** To find out the relative frequencies of each etiological group in patients with non-CAH GIPP and also to evaluate the clinical and laboratory features of these patients.

**Method:** In this multicenter, nationwide, web-based study; data regarding the patients presenting with GIPP (excluding those with CAH) were gathered.

**Results:** We were able to enroll a national cohort of 129 children ( 103 female/26 male ) with non-CAH GIPP covering a population of nearly 16 million living children which enabled us to estimate the prevalance of this condition as 5 in 1.000.000. Mean age at diagnosis was 5.3 years (range:0.3-11.3). Mean duration of complaints before diagnosis was 6.7 months (range:0-68). Mean height SDS at presentation was 0.75±1.73 SDS. ΔBone age-Chronological age (ΔBA-CA) was 1.3±2.05 years. 9/103 (8.7%) female and 4/26 (18.2 %) male patients had heterosexual PP. Functional ovarian cysts (FOC) were the most common etiological diagnosis constituting 37% of all cases. The average cyst size was 37±13.7 mm (range: 10-88mm). MAS was the second most common etiology comprising 26% of the cohort. Cafe au lait spots and fibrous dysplasia were seen in 32% (11/34) and 44% (15/34) respectively in MAS patients, 18% (6/34) had both. Hyperthyroidism was the sole additional endocrine hyperfunction seen in 20.5% (7/34) of these cases.

| Diagnosis | Ovarian cyst | MAS | Testo-toxicosis | Hypo-thyroidism | ACT | HCG secreting tumor | Leydig cell tumor | Ovarian tumor | Sertoli cell tumor | Unknown |
|---|---|---|---|---|---|---|---|---|---|---|
| Number (%) | 47 (37%) | 34 (26%) | 5 (4%) | 7 (5.5%) | 12 (9%) | 7 (5.5%) | 5 (4%) | 5 (4%) | 3 (2%) | 4 (3%) |
| Sex F/M | 47/0 | 34/0 | 0/5 | 5/2 | 7/5 | 0/5 | 0/5 | 5/0 | 0/3 | 4/0 |
| Age (Min-Max) | 5.4 (0.4-10.1) | 5.2 (0.8-9.6) | 4.1 (1.4-8.3) | 6.8 (2.8-9.6) | 3.4 (0.8-7.7) | 7 (0.3-10.6) | 6.1 (4.6-8.8) | 7.3 (4-11.3) | 6.1 (4.6-7.2) | 4.3 (3.3-6.5) |
| Height SDS | 0.55 (-1.72/3.11) | 0.76 (-4.01/5.97) | 3.06 (0.9/6.26) | -0.76 (-4.47/2.88) | 0.91 (-1.54/3.66) | 1.1 (-0.18/4.68) | 1.69 (-0.41/3.96) | -0.11 (-0.66/1.02) | 0.9 (0.03/1.4) | 1.18 (0.5/1.73) |
| BA-CA (year) | 0.6 | 1.6 | 3.1 | -1.7 | 2 | 2.2 | 4.1 | 1.6 | 0.3 | 3 |
| Basal FSH (mIU/ml) | 0.6 (0.01-3.6) | 0.7 (0.01-3.1) | 0.4 (0.05-1.03) | 4 (0.3-11.7) | 0.3 (0.09-0.7) | 0.2 (0.05-0.6) | 0.5 (0.1-0.8) | 1.5 (0.1-4.8) | 0.12 (0.1-0.2) | 0.2 (0-0.7) |
| Basal LH (mIU/ml) | 0.1 (0-0.7) | 0.1 (0-0.65) | 0.1 (0.07-0.2) | 0.1 (0-0.23) | 0.1 (0-0.6) | 0.1 (0.01-0.2) | 0.2 (0.1-0.2) | 1 (0.1-4.8) | 0.08 (0.05-0.1) | 0.06 (0.01-0.2) |
| E2 (pg/ml) | 211 (6.2-879) | 193.5 (5-2792) | | 80.5 (40.7-164) | 25 (10-73.9) | | | 20 (28-48) | 29 (9-48) | 74.6 (30-170.4) |
| Peak LH (mIU/ml) | 0.6 (0.07-4.9) | 0.9 (0-5.1) | 1.83 (0.4-2.7) | | | | | | | |
| Peak FSH (mIU/ml) | 2.1 (0.2-8.7) | 3.8 (0.1-16.6) | 4.4 (1-6.7) | | | | | | | |
| Testosterone (ng/ml) | | | 15.6 (2.6-32) | | 4.3 (1.08-8.79) | 10.9 (0.1-23.9) | 4.7 (0.9-1.6) | 2.2 (0.6-4.4) | 0.1 (0.03-0.2) | |
| DHEAS (µg/dl) | | | | | 827 (30-1543) | | | | | |
| fT4 (ng/dl) | | | | 0.4 (0.14-0.8) | | | | | | |
| HCG (mIU/ml) | | | | | | 149.2 (27-604) | | | | |
| TSH (µIU/ml) | | | | 242 (36-760) | | | | | | |

Table 1. Clinical and laboratory features of each diagnostic group.
(Values are given as mean(range), MAS: McCune Albright Syndrome, ACT: Adrenocortical tumor)

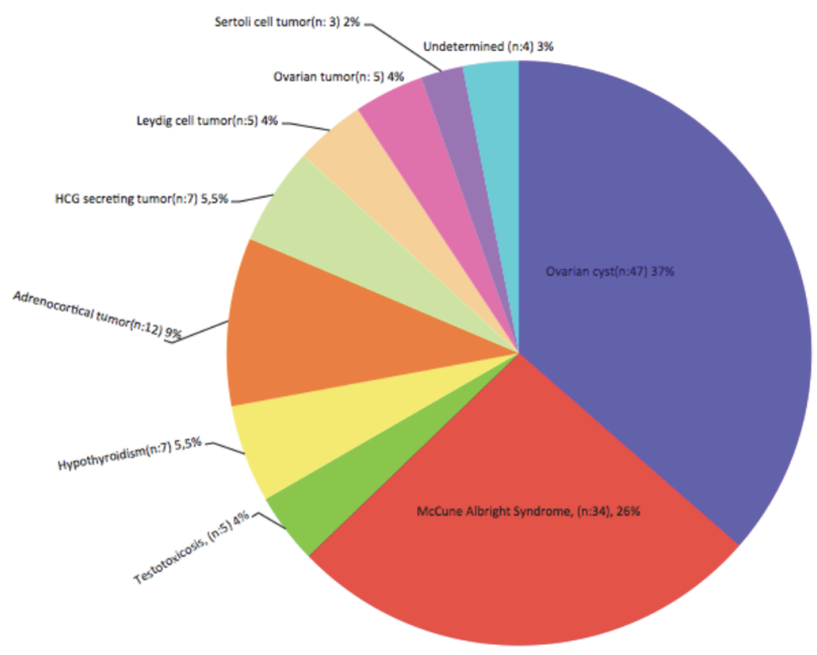


Figure 1. Etiological spectrum of patients with GIPP

HCG secreting tumors were choriocarcinoma in the liver, hepatoblastoma and germ cell tumors of sellar-suprasellar region. Adrenocortical tumors presented with significantly high DHEAS levels (median DHEAS: 998µg/dl). 9/12 patients also had elevated 17-OH progesterone levels (Mean: 9.6 ng/ml, range (0.5-40.4 ng/ml). Among adrenocortical tumors, 10/12 were carcinomas and both adrenals were affected equally. The size of adrenocortical tumors was large, averaging 57.6±30.7mm. Ovarian tumors were mature cystic teratoma, dysgerminoma, juvenile granulosa cell tumor and steroid cell tumor. Testicular involvement was bilateral in Grumbach syndrome, testotoxicosis, HCG secreting tumors and one of the patients with Sertoli cell tumor while it was unilateral in Leydig cell adenoma and the other two patients with Sertoli cell tumor.

**Conlusion:** This largest cohort of non-CAH GIPP patients provide an estimation of its frequency in the general pediatric population and the etiologic distribution of GIPP for the first time. Functional ovarian cysts and MAS comprise the most common etiological groups and may have overlapping features. Although relatively rare, primary hypothyroidism should also be considered in patients with GIPP especially in those with lower height SDS and retarded bone age and nonsupressed FSH. Neoplastic causes of GIPP are various. Adrenocortical tumors specifically carcinomas are the most common and present at earlier ages. Gonadal tumors presenting with GIPP, either germ cell or sex-cord stromal tumors have many histopathologic subtypes. Hepatoblastoma, as an extragonadal and extraadrenal malignancy deserves specific mentioning in the etiology of GIPP. At last, we believe that detailed evaluation of clinical and laboratory findings of this large cohort of GIPP provides information which may help in approach to children with GIPP.

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