The Etiology and Clinical Features of Non-CAH Gonadotropin-Independent Precocious Puberty: A Multicenter Study

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Aim: The causes of gonadotropin-independent precocious puberty are diverse, and often have overlapping clinical and biochemical features. With the exception of congenital adrenal hyperplasia (CAH), disorders that cause gonadotropin-independent precocious puberty (GIPP) are uncommon. The literature is devoid of any large-scale studies on the etiologic distribution of GIPP. The aim of this study was to determine the frequency of each etiology in a cohort of patients with GIPP (excluding those with CAH), and to evaluate the clinical and laboratory features of these patients.

Materials and Methods: This multicenter, nationwide web-based study collected data on patients who presented with non-CAH GIPP in Turkey.

Results: Data were collected for 129 patients (102 girls and 27 boys) from 29 centers. Based on the data collected, the estimated prevalence of non-CAH GIPP in the studied population was 14 in 1 000 000 children. Functional ovarian cyst was the most common etiology, accounting for 37% of all cases, followed by McCune-Albright syndrome (MAS) (26%). Among the patients with MAS, 11.7% had fibrous dysplasia, 32.3% had café-au-lait spots, and 52.9% had both. Human chorionic gonadotrophin-secreting tumors included choriocarcinoma of the liver, hepatoblastoma, and germ cell tumors of the sellar-suprasellar region and mediastinum. Patients with adrenocortical tumors presented at an earlier age than those with other etiologies. Ovarian tumors included mature cystic teratoma, dysgerminoma, juvenile granulosa tumor, and steroid cell tumor. Despite overlapping features, it was possible to identify some unique clinical and laboratory features associated with each etiology.

Conclusion: This largest cohort of patients with non-CAH GIPP to date yielded an estimation of the frequency of non-CAH GIPP in the general pediatric population and showed that girls were affected at a rate 4-fold greater than that of boys owing to functional ovarian cysts and MAS, which were the two most common etiologies. The data collected also provided some unique characteristics associated with each etiology. **(*J Clin Endocrinol Metab* 101: 1980–1988, 2016)**

Precocious puberty (PP) is classified as central PP (CPP) or gonadotropin-dependent PP, and peripheral PP or gonadotropin-independent PP (GIPP). CPP is caused by early activation of the hypothalamic-pituitary-gonadal axis, whereas GIPP arises as a result of exposure to exogenous or endogenous sex steroids, independent of hypothalamic-pituitary-gonadal axis activation. The etiologic spectrum of GIPP is broad and includes congenital adrenal hyperplasia (CAH), McCune-Albright syndrome (MAS), familial testotoxicosis PP (FMPP), functional ovarian cysts

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Abbreviations: ACT, adrenocortical tumor; AFP, α-fetoprotein; ΔBA-CA, Δbone age-chronologic age; CAH, congenital adrenal hyperplasia; CPP, central precocious puberty; CRF, case recording form; CT, computed tomography; DHEAS, dehydroepiandrosterone; FMPP, familial testotoxicosis precocious puberty; FOC, functional ovarian cyst; GIPP, gonadotropin-independent precocious puberty; hCG, human chorionic gonadotrophin; LCA, Leydig cell adenoma; MAS, McCune-Albright syndrome; MRI, magnetic resonance imaging; PP, precocious puberty; SDS, standard deviation score.

(FOC), human chorionic gonadotrophin (hCG)-secreting tumors, sex steroid-producing tumors of the ovaries, testes, and adrenal glands, aromatase excess syndrome, and hypothyroidism (Van Wyk-Grumbach syndrome). With the exception of CAH, each etiology is rare and there are few studies on their frequencies, or the clinical and laboratory features of each etiology. The present nationwide study aimed to determine the etiologic spectrum, the frequency of each etiology, and the clinical and laboratory features of non-CAH GIPP in Turkey.

Materials and Methods

This retrospective, multicenter, nationwide web-based study used a common case recording form (CRF) that was designed by two physicians (Z.A., A.B.) who are experienced with GIPP and electronic CRF preparation. The CRF was used to collect the demographic data and clinical and laboratory findings of the patients with GIPP. The CRF was uploaded to the FAVOR Web Registry System website (www.favorsci.org). Data were entered into the system and checked for consistency by a research assistant (E.Y.). All pediatric endocrinology centers (n = 42) in Turkey were asked to enter data of their patients with non-CAH GIPP using the online FAVOR Registry System. We asked the participating centers to include patients who, after clinical and laboratory examinations and follow-up, were diagnosed as having of GIPP from one of the following diseases MAS, FMPP, FOC, hCG-secreting tumors, sex steroid-producing tumors, aromatase excess syndrome, and GIPP from exogenous exposure to sex steroids. Data were registered during a 12-month period (January 5, 2014–January 5, 2015), after which time the collected data were entered into a Microsoft Excel database. Twenty-nine of 42 centers entered a total of 146 patients into the database. The participation ratio was 69%. Based on the latest population statistics in Turkey (1), an estimated coverage of the total population (relevant to the study criteria) was 70%.

GIPP was defined as Tanner stage of at least 2 breast and/or pubic hair development before age 8 years and/or menarche before age 10 years in girls, and stage 2 genitalia and/or testicular volume of at least 4 ml before age 9 years in boys in whom the findings are progressive, associated with advanced somatic and skeletal growth, elevated adrenal/gonadal sex steroids, but absent hypothalamopituitary activation as assessed using the LH-releasing hormone test. Breast enlargement was evaluated by palpation and testicular volume was measured using an orchidometer. Ovaries were ultrasonographically evaluated in all girls. Patients with incomplete (partial/nonprogressive) forms of precocious puberty were excluded. Patients with CAH were excluded because CAH is a very common cause of GIPP, especially in regions with a high rate of consanguineous marriage such as Turkey.

Patients with PP who had larger than 1 cm ultrasonographically detected single ovarian cysts with elevated estradiol in the face of basal LH below the detection limit (<0.1 mIU/ml) and/or GNRH-stimulated peak LH lower than 5.0 mIU/ml and no skin or bone findings were classified as having GIPP resulting from FOC.

MAS was diagnosed in patients with GIPP who had café-au-lait spots, fibrous dysplasia, and/or an additional endocrine hyperfunction. Patients with PP who had adrenocortical tumor (ACT) demonstrated on computed tomography (CT)/magnetic resonance imaging (MRI) and proven histopathologically were included in the ACT group. All patients with Leydig cell tumors, Sertoli cell tumors, and ovarian tumors were also histopathologically proven. Patients with PP resulting from hCG-secreting tumors were diagnosed through elevated hCG levels (normal, 0–5 mIU/mL), CT/MRI, and also histopathologic analysis. Patients who had GIPP resulting from hypothyroidism had low free T4, high TSH, and all the other causes of GIPP were excluded through necessary evaluation. FMPP was diagnosed in patients who had bilateral testicular enlargement, elevated testosterone, family history of GIPP, CPP excluded with an LH-releasing hormone test, normal hCG levels (0–5 mIU/mL), and/or molecular genetic analysis of LH receptor. Patients with clinical and laboratory evidence of GIPP but a specific etiology that did not fit into previously mentioned diagnostic categories were classified as having GIPP of undetermined etiology. All centers were using semiautomated chemiluminescence methods for hormonal measurements; the commercial system and kits that were used differed among the centers. E2/T values above the reference range for the age and sex of the child in the assay used were considered elevated.

In addition to the relevant data, the CRF forms included the final diagnosis; however, the adequacy of the diagnoses was reviewed by two of the authors (Z.A., A.B.) for consistency and accuracy. In total, 129/146 patients formed the material of this study after excluding 17 patients because of incomplete data or nonconclusive diagnosis of GIPP after our reevaluation.

Statistical analysis was performed using SPSS v.16.0 for Windows and data are shown as mean (range). Nonparametric *t* test was used for comparison of two groups and one-way ANOVA test was performed for comparison of multiple subgroups for variance of difference. Written informed consent was obtained from the patients' parents and the study protocol was approved by the Marmara University Ethics Committee.

Results

Demographic and anthropometric features

The study included 129 patients (102 girls, 27 boys) with a mean age of 5.3 years at the time of final diag-

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nosis (range, 0.3–11.3 years; girls, 5.4; boys, 5.6 years). Patients with ACT presented at an earlier age (mean, 3.4 years; $P = .07$) than those with other etiologies for both girls and boys. However, subgroup analyses by sex showed a statistical significance only in the girls. The mean duration of symptoms before diagnosis was 6.7 months (range, 0–68 months; girls, 6.6; boys, 7.6 months). Duration of symptoms before diagnosis was significantly shorter in patients with FOC (mean: 1.8 ± 3.7 months; $P = .005$). The mean height standard deviation score (SDS) of the cohort at presentation was 0.75 ± 1.73 (girls, 0.57 ± 1.68; boys, 1.39 ± 1.78). The height SDS at presentation was lower in patients with GIPP because of hypothyroidism (girls, −0.85; boys, −0.56). ΔBone age-chronologic age (ΔBA-CA) of the total cohort was 1.3 ± 2.05 years (girls: 1.0; boys: 2.1 year). Bone age was retarded in patients with GIPP from hypothyroidism (ΔBA-CA, –1.7 years; girls, –1.3; boys, –2.7). Bone age advancement was less noticeable in patients with FOC, but was readily apparent in those with Leydig cell tumors and testotoxicosis. (Table 1) (Table 2).

In all, 9/102 girls (8.8%) and 4/27 boys (14.8%) had heterosexual PP. The etiology in the girls with heterosexual PP was adrenocortical tumors (n = 7) and ovarian tumors (n = 2) vs Sertoli cell tumors (n = 3) and adrenocortical tumor (n = 1) in the boys.

Functional ovarian cysts and MAS

FOC was the most common etiology, constituting 37% of all cases (46% of all cases among the girls) (Figure 1). In total, 11/47 patients with FOC presented with vaginal bleeding in addition to breast enlargement vs 36 with breast enlargement alone. All 47 patients with FOC had single, unilateral cysts, and 55% were located in the right ovary. The mean cyst size was 37.0 ± 13.7 mm (range, 10.0–88.0 mm). There was no correlation between cyst size and estradiol levels (r = –0.013, $P = .94$). Twenty-one

Table 1. Clinical and Laboratory Features in Girls With GIPP

Diagnosis	Ovarian Cyst	MAS	Hypothyroidism	Adrenocortical Tumor	Ovarian Tumor	Unknown	*P* Value
Number	47	34	5	7	5	4	
%	46	33.3	4.9	6.9	4.9	3.9	
Age[a]	5.4	5.2	6.4	3.4	7.3	4.3	.037
Min-max	0.4–10.1	0.8–9.6	2.8–9.6	0.8–6.1	4–11.3	3.3–6.5	
95% CI	4.7–5.9	4.4–6.0	4.8–8.4	1.6–5.2	3.7–11.0	2.8–5.8	
Duration of symptoms (months)	1.8	12.4	2.8	7.4	15.8	4.6	.005
	0–18	0–68	0.2–5	1–28	0.2–60	0.2–8	
	0.7–2.9	6.3–18.7	0.5–5.1	−1.6 to 16.5	−31.1 to 62.7	−0.6 to 9.7	
Height SDS	0.55	0.76	−0.85	0.90	−0.11	1.18	.34
	−1.72 to 3.11	−4.01 to 5.97	−4.47 to 2.88	−1.54 to 3.30	−0.66 to 1.02	0.50–1.73	
	0.19–0.91	0.05–1.48	−4.67 to 2.98	−0.81 to 2.60	−1.05 to 0.81	0.37–1.99	
BA-CA (y)	0.6	1.6	−1.3	1.9	1.6	3	.0004
	−2.0 to 4.9	−2.8 to 4.5	−2.9 to 1.4	−0.5 to 5.6	0–5.7	0.5–4.5	
	0.1–1.0	1.0–2.2	−3.4 to 0.8	−0.1 to 3.8	−1.4 to 4.5	0.06–5.88	
Basal FSH (mIU/ml)	0.56	0.68	4.99	0.39	1.50	0.19	<.0001
	0.01–3.60	0.01–3.10	1.60–11.70	0.17–0.70	0.10–4.76	0.01–0.68	
	0.31–0.81	0.36–1.01	−0.1 to 10.08	0.17–0.61	−0.96 to 3.97	−0.32 to 0.71	
Basal LH (mIU/ml)	0.11	0.11	0.09	0.15	0.97	0.06	.0015
	0.01–0.72	0.01–0.65	0.01–0.23	0.10–0.58	0.10–4.38	0.01–0.15	
	0.08–0.14	0.07–0.15	0.01–0.16	−0.07 to 0.37	−1.38 to 3.33	−0.04 to 0.16	
E2 (pg/ml)	211	193.5	80.5	15.6	28.4	74.6	.65
	6.2–879	5–2792	40.7–164	10–25	20–48	30–170.4	
	138.2–283.7	20–367	20.1–140.8	9.8–26.3	13.1–43.7	−28.2 to 177.5	
Peak LH (mIU/ml)	0.58	0.90					.34
	0.07–4.90	0.01–4.90					
	0.14–1.02	0.35–1.45					
Peak FSH (mIU/ml)	2.07	3.84					.13
	0.20–8.07	0.11–16.62					
	1.0–3.15	1.54–6.16					
T (ng/ml)				4.8	1.7		.06
				1.1–8.7	0.1–4.4		
				2.3–7.2	−1.4 to 4.7		
DHEAS (μg/dl)				823.9			
				30–1543			
				370.5–1277			
Free T4 (ng/dl)			0.4				
			0.3–0.8				
			0.2–0.7				
TSH (μIU/ml)			172.2				
			36–500				
			−61.1 to 405.5				

Abbreviations: CI, confidence interval; E2, Estradiol; min-max, minimum-maximum.

[a] For each parameter, the first, second, and third rows represent mean, minimum and maximum values, and 95% CI limits, respectively.

Table 2. Clinical and Laboratory Features in Boys With GIPP

Diagnosis	Testotoxicosis	Hypothyroidism[a]	Adrenocortical Tumor	HCG Secreting Tumor	Leydig Cell Tumor	Sertoli Cell Tumor[a]	*P* Value
Number (n = 27)	5	2	5	7	5	3	
%	18.5	7.4	18.5	25.9	18.5	11.1	
Age[b]	4.1	7.6	3.4	7	6.1	6.1	
Min-max	1.4–8.3	7.4–7.6	1.2–7.7	0.3–10.6	4.6–8.8	4.6–7.2	.24
95% CI	0.0/8.2		0.2–6.7	3.5–10.6	4.2–8.1		
Duration of symptoms (months)	8.6	18	9.2	6.5	3.6	5.3	
	1–12	18–18	1–27	1–24	1–6	1–12	.27
	2.9–14.3		−3.4 to 21.9	−2.7 to 15.7	0.7–6.5		
Height SDS	3.06	−0.56	0.92	1.11	1.69	0.90	
	0.90–6.26	− 1.03 to − 0.1	−0.65 to 3.66	−0.18 to 4.68	−0.41 to 3.96	0.03–1.40	.16
	0.3–5.77		−1.10 to 2.96	−0.43 to 2.65	−0.30 to 3.68		
BA-CA (y)	3.1	−2.7	1.3	2.2	4.1	0.7	
	1.8–4.6	− 3.4 to − 1.9	0.3–2.4	0.2–5.4	0.1–9.2	−0.2 to 1.5	.02
	1.4–4.6		0.2–2.4	0.3–4.1	−0.7 to 8.8		
Basal FSH (mIU/ml)	0.38	1.60	0.20	0.20	0.46	0.12	
	0.05–1.03	0.30–2.90	0.09–0.31	0.05–0.56	0.10–0.75	0.1–0.15	.02
	−0.10 to 0.87		0.02–0.38	0.04–0.35	0.12–0.81		
Basal LH (mIU/ml)	0.11	0.16	0.10	0.11	0.15	0.08	
	0.07–0.2	0.10–0.23	0.05–0.20	0.01–0.22	0.10–0.21	0.05–0.1	.50
	0.04–0.17		0.03–0.17	0.04–0.17	0.08–0.21		
E2 (pg/ml)			42.5			29	
			11–73.9			9–48	.65
Peak LH (mIU/ml)	1.83						
	0.44–2.70						
	0.79–2.87						
Peak FSH (mIU/ml)	4.39						
	1–6.69						
	1.52–7.26						
T (ng/ml)	15.6	0.52	3.7	10.9	4.7	0.1	
	2.7–32.0	0.2–0.84	1.6–5.1	0.1–23.9	0.9–16	0.03–0.2	.05
	−1.4 to 32.6		1.7–5.7	3.6–18.1	−3.2 to 12.6		
DHEAS (μg/dl)			94.2				
			206–1500				
			364.4–1518				
fT4 (ng/dl)		0.22					
		0.14–0.30					
TSH (μIU/ml)		417.5					
		75–760					
HCG (mIU/ml)				149			
				27–604			
				−87 to 385			

Abbreviations: CI, confidence interval; E2, Estradiol; min-max, minimum-maximum.

[a] Because of the small number of patients, only mean, minimum, and maximum of values are given.

[b] For each parameter, the first, second, and third rows represent mean, minimum and maximum values, and 95% CI limits, respectively.

In the ACT group, two patients had estradiol levels.

of 47 patients with FOC who had recurrent cysts were evaluated using bone scintigraphy, all of which were normal. MAS was the second most common etiology, accounting for 26% of the cohort, all of which were in girls. Some 52.9% (18/34) of the patients with MAS had the classic triad with both café-au-lait spots and fibrous dysplasia, 32.3% (11/34) and 11.7% (4/34) had café-au-lait and fibrous dysplasia alone, respectively. Among the 34 patients with MAS, 10 presented with vaginal bleeding (2 with no breast enlargement). Overall, 59% (20/34) of the patients with MAS had vaginal bleeding. Hyperthyroidism was the sole additional endocrine hyperfunction observed in 20.5% (7/34) of the patients with MAS.

Estradiol levels did not differ between patients with FOC and MAS ($P = .83$). Pelvic ultrasonography showed asymmetric ovarian enlargement in 19 of the 34 patients with MAS, of which 12 had a single ovarian cyst (6 in the right ovary and 6 in the left ovary). The mean single cyst size in the patients with MAS was 27.9 ± 9.07 mm (range, 16.0–43.0 mm), which was significantly smaller than those in patients with functional ovarian cysts (mean, 37.0 ± 13.7 mm; range, 10.0–88.0 mm) ($P = .018$). In the remaining 15 patients with MAS, there was no significant difference in right and left ovary size; 5 of these 15 patients had bilateral slightly enlarged ovaries. The mean uterine volume (7.3 ± 6.0 ml) and mean uterine length (42.6 ± 11.3 mm) in patients with FOC did not differ from those of patients with MAS (6.1 ± 4.6 ml and 40.4 ± 11.5 mm, respectively).

Tumoral causes

In all, seven patients had hCG-secreting tumors, including choriocarcinoma of the liver, hepatoblastoma, and germ cell tumors of the sellar-suprasellar region and mediastinum.

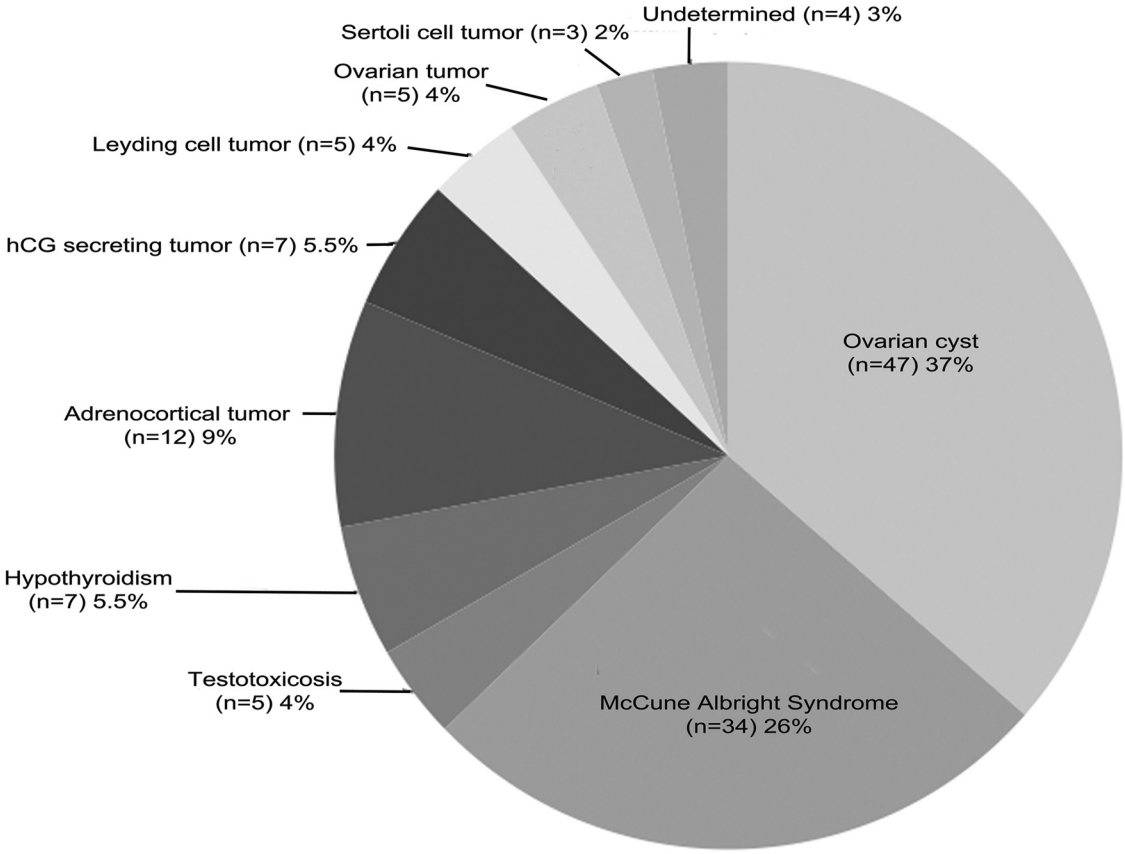

Figure 1. Etiologic spectrum of patients with GIPP.

Patients with ACT presented with a significantly elevated dehydroepiandrosterone (DHEAS) (median DHEAS: 998 μg/dl; range, 30–1543 μg/dl), with the exception of one patient who had a DHEAS level of 30 μg/dl. Testosterone and Δ4-A levels were high in all patients with ACT. 17-OH progesterone was also elevated in 9 of 12 patients with ACT (mean, 9.6 ng/mL; range, 0.5–40.4 ng/mL). Among the 12 patients with ACT, 10 had carcinomas and both adrenals were affected equally. The ACTs were large (mean, 57.6 ± 30.7 mm). Ovarian tumors included mature cystic teratomas, dysgerminomas, juvenile granulosa cell tumors, and steroid cell tumors.

Testicular size and T levels

Testicular enlargement was bilateral in patients with Grumbach syndrome, testotoxicosis, and hCG-secreting tumors, and in one of the patients with a Sertoli cell tumor vs unilateral in patients with Leydig cell adenomas and in two patients with Sertoli cell tumors. Mean testicular volume did not differ significantly between the patients with testotoxicosis (4.0 ± 1.6 ml) and hCG-secreting tumors (5.9 ± 2.1 ml), (P = .113). The mean volume of unilaterally enlarged testes was 8.8 ± 6.8 ml in patents with Leydig cell tumors. There was no significant difference in the mean T levels between patients with testotoxicosis (15.6 ± 13.7 ng/ml) and hCG-secreting tumors (10.9 ± 7.8 ng/ml).

Discussion

With the exception of CAH, disorders that cause GIPP are uncommon and the literature is devoid of any studies on the frequency or etiologic distribution of GIPP in a large cohort. We included a national cohort of 129 children with non-CAH GIPP from among a population of nearly 16 million (covering 70% of the country's children). Based on these data, the prevalence of this condition was estimated to be 14 in 1 000 000 in the general pediatric population studied. Because no other researchers have reported the frequency of GIPP, a comparison with the present findings was not possible. To the best of our knowledge, the present study is the first to investigate all etiologies of GIPP in detail and includes the largest cohort of any study on GIPP.

The frequency of GIPP among all PPs varies according to genetic and ethnic characteristics of the studied population. As with CPP, more girls than boys have GIPP (2). In the present study, girls constituted 79.8% of the patients with GIPP, which was most likely due to the exclu-

sion of patients with CAH. Whereas ovarian disorders are the most common etiology of GIPP in girls, adrenal problems, specifically CAH, are the predominant etiology in boys with GIPP (2).

Age at the time of diagnosis in patients with GIPP differed according to etiology in our subjects. Lee et al. (3) reported that girls with GIPP presented at a mean age of 3.9 ± 2.3 years, whereas this was 5.3 ± 2.4 years in the present study, which is still significantly younger than the mean age of idiopathic CPP (7.5 years) (4). Our patients with ACT and FMPP presented earlier (mean age, 3.4 and 4.1 years, respectively), than those with other etiologies. This is consistent with previous reports, which documented 3.3 years for ACT (5) and younger than 4 years for FMPP (6).

The etiologic spectrum of GIPP is highly heterogeneous. A Taiwanese study reported that only 7% of patients with PP had GIPP and FOC was the most common etiology (34%) of the girls (3). A Chinese study reported that FOC was the most common etiology (26.3%), followed by CAH (22%) (2). In the present study, FOC was the most common etiologic diagnosis, accounting for 37% of all patients with GIPP. Although ovarian cysts are common in prepubertal girls, occurring in 2–5% of this population, hormonally active cysts comprise only 5% of those with ovarian cysts (7). Cysts associated with GIPP are generally large. A recent literature review of FOC reported that the median cyst size in 26 patients was 41.5 mm (8). The mean cyst size in our patients was 37.0 mm (median, 44.3 mm). Estradiol levels were markedly elevated in almost all of our patients and were not correlated with cyst size. Despite the observed high E2, bone-age advancement was not remarkable, which suggested a short duration of exposure to elevated E2 (1.8 months).

The second most common etiology of GIPP in our cohort was MAS (n = 34). In addition to its classic form, characterized by the triad of café-au-lait spots, GIPP, and fibrous dysplasia of bone, atypical/incomplete forms that manifest with one or two of the classic symptoms also occur. The classic triad was reported in 50% (n = 16/32) of patients with MAS (9). In the present study, the classic triad was present in 52.9% of the patients, café-au-lait spots + GIPP was observed in 32.3%, and fibrous dysplasia + GIPP was present in 11.7%. In total, 85.2% of our patients with MAS had café-au-lait spots and 64.6% had fibrous dysplasia. In a National Institutes of Health cohort of fibrous dysplasia/MAS; café-au-lait spots, GIPP, and thyroid abnormalities were reported in 66%, 50%, and 66% of patients, respectively (10). Hyperthyroidism with multinodular goiter was the only associated finding in one of our patients with MAS, which highlighted the need to carefully screen patients with GIPP for incomplete forms of MAS. In fact, GIPP can be the only manifestation in a girl who is mosaic for the activating mutation of Gs-alpha, which is noted in blood samples in 25–33% of patients with isolated GIPP or exaggerated thelarche (11, 12).

Some patients with MAS may have a large solitary ovarian cyst, as did 12 of our patients. Although the mean cyst size was smaller in patients with MAS who had solitary cysts than those with FOC (27.9 vs 37.0 mm, respectively, $P = .014$), there was some overlap between these two etiologies in this regard. Furthermore, uterine volume and length were also similar in both conditions; therefore, patients with a presumptive diagnosis of FOC should be thoroughly screened for features of MAS (Figure 2). The clinical signs of PP in patients with MAS can occur as early as the first year of life (9). In the present study, the youngest patient presented at 0.8 years. Breast enlargement is not always readily apparent and vaginal bleeding can occur in the absence of breast tissue, as occurred in two patients in the present study.

First described in 1960 by Van Wyk and Grumbach (13), severe primary hypothyroidism is also a rare cause of GIPP. Although the mechanism of such is not clearly understood, an FSH-mediated process seems plausible. Markedly elevated TSH might exert FSH-like action on gonadal FSH receptors, causing testicular enlargement with selective tubular hyperplasia in the presence of relatively low T and little virilization in boys, and premature thelarche and/or vaginal bleeding with multicystic large ovaries in girls (14). As a second mechanism, an increase in prolactin levels that reduces GnRH pulsatility, which in turn increases FSH expression and suppresses LH expression has been proposed (14). In such patients, as seen in the present study, FSH levels are normal to high compared with patients with other forms of GIPP who have suppressed FSH/LH. Prolactin was high in three of seven of our patients with Van Wyk-Grumbach syndrome; as the prolactin level increased, so did the FSH (in one patient, prolactin was 109 ng/mL and FSH was 11.9 mIU/mL), which supports the second pathophysiology mechanism. On the other hand, four of seven of our patients had normoprolactinemia, which suggests that the former mechanism or perhaps yet unidentified mechanisms may be operational in such cases. In general, as the severity of hypothyroidism increases the probability of developing PP increases. Cabrera et al (15) studied 33 children with Hashimoto thyroiditis with initial TSH greater than 100 mIU/mL, and reported that 24% (n = 8) had evidence of PP; however, three of our seven patients with hypothyroidism had TSH lower than 100 mIU/mL, of which 1 had TSH of 36 mIU/mL, which indicates that mild hypothyroidism could also cause GIPP and such patients should be evaluated carefully with regard to PP. As expected, our

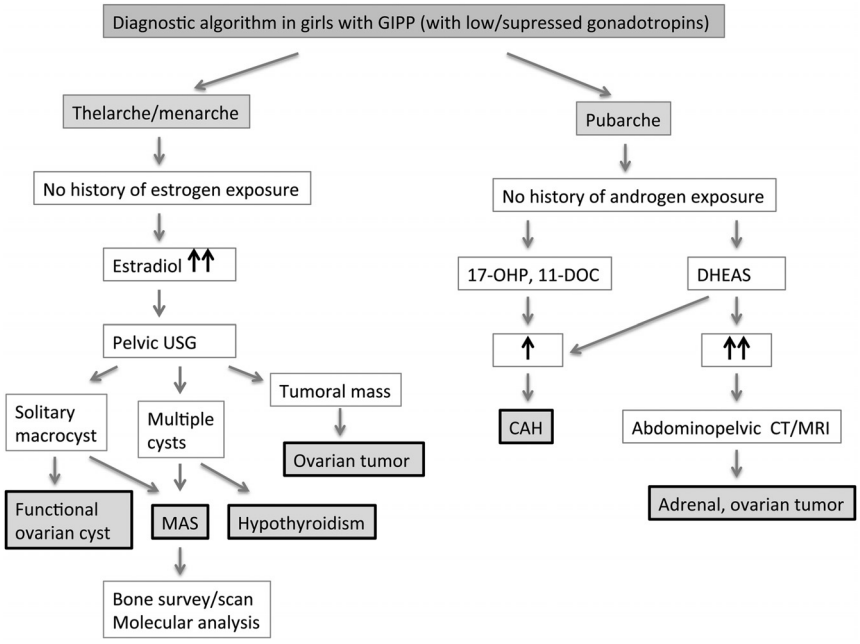

Figure 2. Diagnostic algorithm in girls with GIPP. 11-DOC, 11-deoxycortisol; 17OHP, 17-hydroxyprogesterone.

patients who had GIPP resulting from hypothyroidism had significantly lower height-SDS and retarded bone age, as compared with patients with GIPP from other etiologies, which provides a clinical clue for diagnosis.

In the present study, patients who had GIPP resulting from ACT presented at the youngest age. Adrenocortical tumors are very rare in children, with a prevalence of just 0.3 cases/million/year (16). Consistent with the literature, the present study comprised girls predominantly. All of the girls in the present study had heterosexual PP, whereas all the boys, except one with gynecomastia, had isosexual PP. Adrenocortical carcinoma was more common in the present study than previously reported; Chen et al (5) reported that 56% of children with adrenocortical tumors had adenoma. A marked elevation in DHEAS could be a clinical clue for the diagnosis of ACT because 95% of DHEAS is secreted by the adrenals; however, normal DHEAS levels do not completely eliminate the diagnosis of ACT. In a cohort of 34 children with ACT, Chen et al (5) observed that 84.6% (11/13) of patients had elevated DHEAS. All of our patients had significantly elevated DHEAS levels (median DHEAS, 998 μg/dl), with the exception of one girl with Adrenocortical adenom who had normal DHEAS but elevated T, 4-A, and 17-OH progesterone. An increase in 17-OH progesterone also occurs in patients with ACT, as noted in nine of our patients, of which two had a level greater than 20 ng/mL, which resulted in an initial diagnosis of CAH. Subsequent adrenal imaging in those patients yielded the correct diagnosis of adrenocortical tumor; therefore, it is essential to perform adrenal CT/MRI in patients with elevated androgens, even if 17-OH progesterone is also elevated.

Testotoxicosis is caused by germline-activating mutations in the LH/hCG receptor of Leydig cells and usually presents before the age 4 years (6). However, two patients in our cohort presented at age 7 and 8 years. The patients with testotoxicosis had bilateral mild testicular enlargement (mean testicular volume, 4.0 ml), with a markedly high T level and had remarkably advanced bone age at presentation. Leydig cell adenoma (LCA) has also been reported to harbor activating mutations of the LH receptor. The difference is that the mutation in LCA is somatic. Age at presentation is higher in LCA (7 years) in the literature (17) and 6.1 years in the present study. Unilateral testicular enlargement in boys with isosexual GIPP supports the diagnosis of LCA (Figure 3).

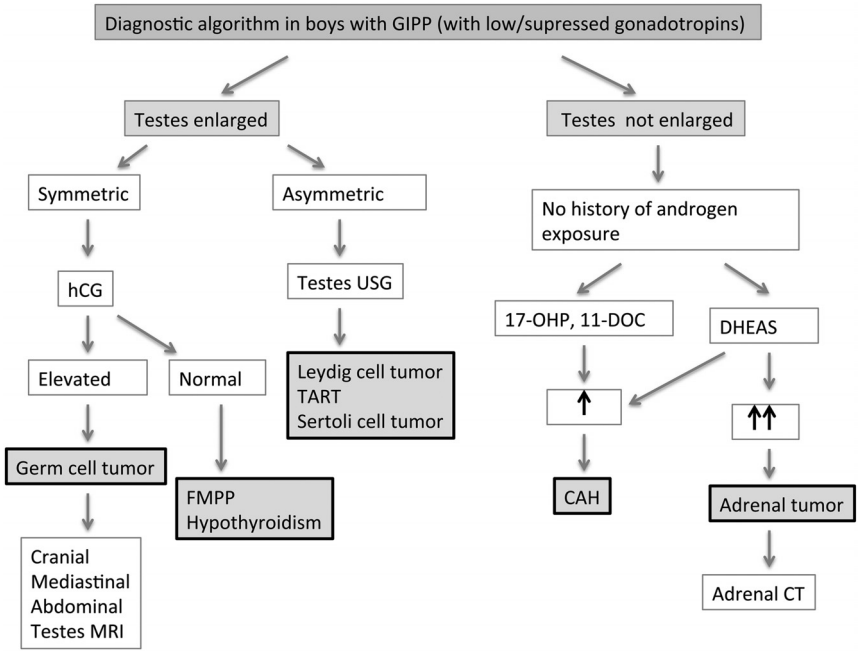

Figure 3. Diagnostic algorithm in boys with GIPP.TART, testicular adrenal rest tumor.

Neoplastic causes of GIPP other than ACT and Leydig cell tumors in-

clude hCG-secreting tumors, ovarian tumors, and Sertoli cell tumors of the testes. Wendt et al (18) reported that the most common tumors that cause GIPP are pineal germ cell tumors and hepatoblastomas, all of which secrete hCG. In the present study, locations of the hCG-secreting tumors were sellar-suprasellar (n = 4), hepatic (n = 2, one hepatoblastoma and one choriocarcinoma) and mediastinal (n = 1). The mean testicular volume in our patients with hCG-secreting tumors was 5.9 ml, which did not differ significantly from that in patients with testotoxicosis (4.0 ml). The mean testosterone level was very high in both groups (15.6 and 10.9 ng/ml, respectively), and did not differ significantly. Elevated hCG was the clue that led to the differential diagnosis between these two conditions (Figure 3). In addition to hCG, α-fetoprotein (AFP) was also elevated in two of the four patients with intracranial germ cell tumors, and in the patients with hepatoblastoma and choriocarcinoma. The highest AFP level was in the patient with hepatoblastoma, as expected, because the primary tumor marker of hepatoblastoma is AFP.

Ovarian tumors can manifest as iso- or heterosexual PP, depending on the type of hormone secreted. In the present study, three patients with ovarian tumors (mature cystic teratoma, n = 2; dysgerminoma, n = 1) had isosexual PP, whereas one patient (steroid cell tumor) presented as heterosexual PP. One patient with a juvenile granulosa cell tumor had breast and pubic hair development, a slightly elevated E2 level, and very high T level.

Sertoli cell tumors are rare, accounting for 0.4–1.5% of all testicular malignancies (19). Only 11–25% of reported cases had an elevated E2 level that resulted in gynecomastia. The present study included 3 boys with GIPP with Sertoli cell tumors, and all presented with testicular enlargement and gynecomastia. One of these patients had Peutz-Jeghers syndrome with bilateral testicular involvement (testicular volume, 6 ml); the other two had unilateral involvement of the left testis (testicular volume, 5 and 6 ml). The E2 level was elevated (30 and 48 pg/ml) in two patients with Sertoli cell tumors and was relatively lower (9 pg/ml) in the third. Based on these findings, we think that Sertoli cell tumors should be a consideration in all prepubertal boys with gynecomastia.

In conclusion, the present study included the largest cohort of patients with non-CAH GIPP, and is the first to estimate its frequency in a general pediatric population and to determine the distribution of GIPP etiologies. We found that non-CAH GIPP is more common in girls owing to FOC and MAS being the two most common etiologies, which can exhibit overlapping features. It is important to note that solitary ovarian cysts could be a component of MAS; therefore, evaluation of skin for café-au-lait spots, bone X-rays/scintigraphy, and hormonal profiles for endocrine hyperfunction are necessary before diagnosing functional ovarian cysts. Primary hypothyroidism should be considered in GIPP, with a low height SDS, retarded bone age, and nonsuppressed FSH. ACTs, specifically carcinomas, are the most common neoplastic causes and present at earlier ages. A very high DHEAS level is the rule, but there are exceptional cases with normal DHEAS levels. Gonadal tumors that present with GIPP have many histopathologic subtypes. hCG-secreting tumors produce an anthropometric and hormonal picture similar to that of testotoxicosis. Hepatoblastoma, as an extragonadal and extra-adrenal malignancy, deserves a specific mention. The clinical and laboratory findings reported herein for this large cohort will improve our understanding and management of children with GIPP.

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