P1-P024

GONADOTROPIN-DEPENDENT PUBERTAL DISORDERS ARE COMMON IN PATIENTS WITH VIRILIZING ADRENOCORTICAL TUMORS IN CHILDHOOD

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INTRODUCTION

- Androgen-secreting adrenocortical tumors (ACTs) usually cause peripheral precocious puberty, linear growth acceleration and bone age advancement.
- The late effects of early exposure to androgen excess on gonadotropin-dependent pubertal development (GDPD) and on final height (FH) have been scarcely reported in ACT.

OBJECTIVE

- To investigate the impact of early exposure to androgen excess on GDPD and on FH of patients with virilizing ACTs in childhood.

METHODS

- This was a retrospective cohort study of 63 patients with virilizing ACT in childhood, followed at the University Hospital of Ribeirão Preto Medical School, University of São Paulo, Brazil, from 1975 until 2017.
- Data from patients with normal puberty (n = 26) and pubertal disorders – central precocious puberty (CPP, n = 7) and early fast puberty (EFP, n = 3) – were compared.

RESULTS

General features

Table 1. General features of the 63 patients with virilizing ACT < 18 years.

Features	Total (%) (n = 63)
At diagnosis of ACT	
Sex: Female / Male	44 (69.8) / 19 (30.2)
Age (months)	25.8 (2.1 – 192.2)
Duration of ACT signs (months)	6 (0 – 60)
Family history of ACT	8 (12.7)
Family history of other types of cancer	21 (33.3)
Stature SDS	0.5 (-3.5 – 3.9)
BMI SDS	1.4 (-1.9 – 6.3)
DHEA-S* (µg/dL)	748 (32 – 4950)
Testosterone (ng/dL)**	242.5 (33.6 – 1800)
Δ bone age (months)***	14.7 (-27.9 – 85.4)
Tumor type: Virilizing ACT / Mixed ACT	8 (12.7) / 55 (87.3)
Tumor stage (IPACTR): I / II / III / IV	38 (60.3) / 8 (12.7) / 11 (17.5) / 6 (9.5)
P53 p.R337H mutation	
Present / Absent	48 (76.2) / 4 (6.3)
Data not available	11 (17.5)
During follow-up	
Chemotherapy	17 (27)
Recurrence or metastasis after surgery	16 (25.4)
Death	14 (22.2)
Loss of follow-up / Discharge after 10 years	16 (25.4) / 5 (7.9)
Duration of follow-up (months)	73.7 (0.2 – 295.4)

*n=55; **n=54; ***n=52

Pubertal outcomes

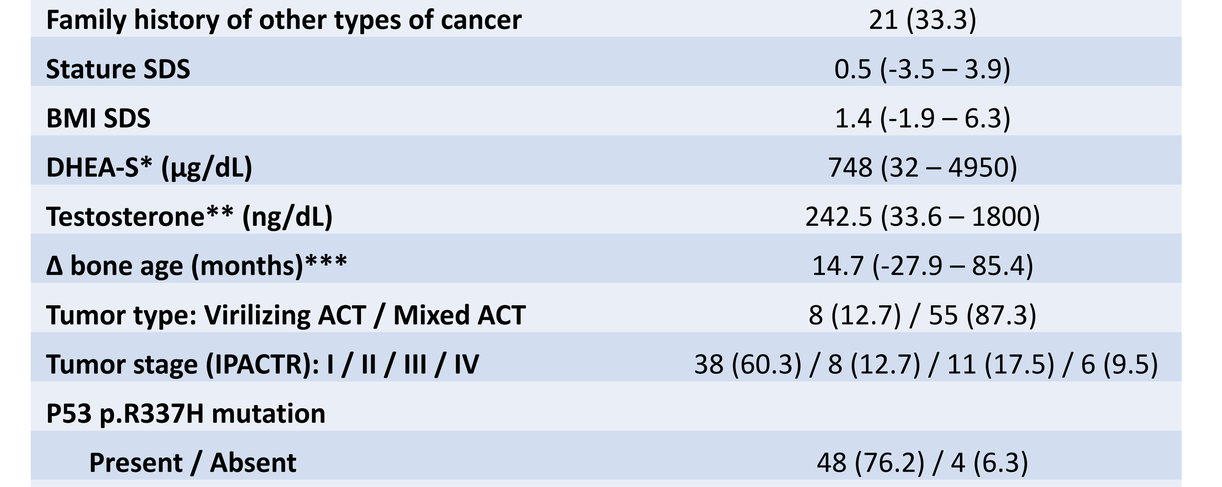

Figure 1. Pubertal outcomes in 63 patients with ACT in childhood.

- GnRHa effectively treated 3 girls and 1 boy with CPP, and all 3 girls with EFP.
- Only 1 girl with CPP had precocious menarche, before GnRHa treatment, but had no recurrence after treatment initiation.

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RESULTS

Table 2. General features of the 36[#] patients that developed gonadotropin-dependent puberty.

Features	Pubertal disorders (n = 10)	Normal puberty (n = 26)
At diagnosis of ACT		
Sex: Female / Male	7 (70%) / 3 (30%)	15 (57.7%) / 11 (42.3%)
Age (months)	67.7 (5.3 – 95.5)	24.7 (4.7 – 192.2)
Duration of ACT signs (months)	6 (1 – 12)	6 (1.5 – 18)
Stature SDS	1.63 (-1.96 – 2.44)	1.29 (-3.55 – 3.29)
BMI SDS	1.07 (-0.31 – 5.22)	1.44 (-0.63 – 3.22)
DHEA-S (µg/dL)	735 (33 – 3968)	763 (32 – 4678)*
Testosterone (ng/dL)	381 (58 – 900)	235 (33.6 – 1728)*
Δ bone age (months)	37.7 (-1.5 – 79.7)**	19.7 (-5.6 – 49.1)***

[#] The patient with precocious thelarche was not included in the analysis. *n = 23; **n = 8; ***n = 22

Table 3. Relative risk for the development of CPP or EFP in pediatric patients with ACT.

FEATURES AT DIAGNOSIS OF ACT		CPP/EFP	NP	RR	CI 95%
N		10	26		
SEX	F	7	15	1.48	(0.46; 4.81)
	M	3	11		
AGE AT DIAGNOSIS	**≥ 48 months**	**6**	**6**	**3.00**	**(1.04; 8.65)**
	< 48 months	**4**	**20**		
DURATION OF ACT SIGNS	≥ 6 months	5	14	0.90	(0.31; 2.56)
	< 6 months	5	12		
TANNER STAGE – PUBIC HAIR	> PH2	6	15	1.07	(0.36; 3.15)
	≤ PH2	4	11		
STATURE SDS	> 2	4	4	2.33	(0.27; 6.29)
	≤ 2	6	22		
BONE AGE	Advanced	6	13	1.74	(0.42; 7.17)
	Not advanced	2	9		
DHEA-S (µg/dL)	≥ 300	8	17	1.28	(0.34; 4.84)
	< 300	2	6		
TESTOSTERONE (ng/dL)	≥ 300	6	8	2.03	(0.71; 5.88)
	< 300	4	15		
TUMOR TYPE	V-ACT	0	6	*	*
	M-ACT	10	20		
TUMOR STAGE	III / IV	4	4	2.33	(0.87; 6.29)
	I / II	6	22		
RECURRENCE / METASTASIS	**Present**	**5**	**4**	**3.00**	**(1.12; 8.02)**
	Absent	**5**	**22**		

- In addition, tall stature at diagnosis of ACT and recurrence or metastasis during follow-up were associated with the development of CPP alone [RR 4.17 (95%CI 1.17 – 14.80) and RR 4.17 (95%CI 1.17 – 14.80), respectively].

Final height

- 19 patients (8M: 11F) with FH.
  - 2 with short stature.
- Stature SDS:
  - At diagnosis of ACT: 1.42
  - At FH: -0.02

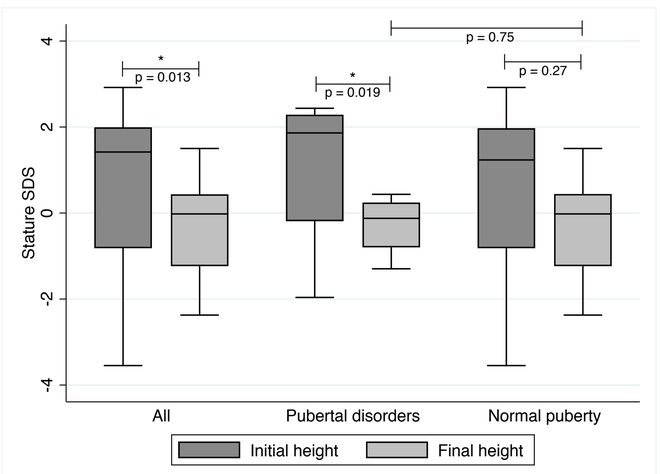

Figure 2. Initial and final height according to pubertal development.

CONCLUSION

- Gonadotropin-dependent pubertal disorders are more common than previously expected in patients with childhood virilizing ACTs.
- Final height is usually not impaired in these patients, reiterating the good prognosis for linear growth after successful ACT removal.
- This study reinforces the importance of close and prolonged follow-up after surgery, not only to detect ACT-related complications, but also to promptly identify and treat consequences of early exposure to androgen excess.