

Testicular Adrenal Rest Tumors Develop Independently of Long-Term Disease Control: A Longitudinal Analysis of 50 Adult Men With Congenital Adrenal Hyperplasia due to Classic 21-Hydroxylase Deficiency

Nicole Reisch, Marietta Rottenkolber, Anais Greifenstein, Nils Krone, Heinrich Schmidt, Martin Reincke, Hans-Peter Schwarz, and Felix Beuschlein

Department of Endocrinology (N.R., A.G., M.R., F.B.), Medizinische Klinik und Poliklinik IV, University Hospital Munich, D-80336 Munich, Germany; Institute of Medical Information Sciences, Biometry, and Epidemiology (M.R.), Ludwig-Maximilians-Universität, 82152 Munich, Germany; Centre for Endocrinology, Diabetes, and Metabolism (N.K.), School of Clinical and Experimental Medicine, University of Birmingham, Birmingham B15 2TT, United Kingdom; and Department of Endocrinology (H.S., H.-P.S.), von Haunersches Kinderspital, University Hospital Munich, D-80336 Munich, Germany

Context: Testicular adrenal rest tumors (TARTs) and hypogonadotropic hypogonadism are the two most common causes for male infertility in classic 21-hydroxylase deficiency. Current hypotheses suggest the quality of disease control to be one of the main pathogenic factors for TART development.

Objective: The aim was to study long-term predictors for TART development in a retrospective longitudinal study.

Design: Fifty men with classic 21-hydroxylase deficiency (31 salt wasting, 19 simple virilizing) were investigated. Testicular ultrasound at a median age at investigation of 27 years detected TARTs in 28 of 50 subjects (19 salt wasting, 9 simple virilizing). TART presence was correlated with long-term parameters of disease control during childhood and adolescence obtained from patients' charts: 24-hour urine pregnanetriol, serum 17-hydroxyprogesterone, onset and stage of pubic hair development, testicular growth, and bone age in relation to chronological age.

Results: There was no difference in pregnanetriol excretion over lifetime between patients with and without TARTs. Similarly, neither development of pubic hair and testicular volume (Tanner) nor bone age in relation to chronological age differed between the two groups. Furthermore, the two groups had the same body mass index and the same impairment of final height in relation to midparental target height.

Conclusion: Our longitudinal analysis demonstrates no association between TART presence and parameters of disease control. These data, therefore, argue for other mechanisms more relevant for TART induction including those occurring during fetal development. (*J Clin Endocrinol Metab* 98: E1820–E1826, 2013)

Congenital adrenal hyperplasia (CAH) ranks among the most common inherited metabolic disorders, with the classic form affecting about 1 in 10 000 to 20 000

newborns. Steroid 21-hydroxylase deficiency (21-OHD) accounts for more than 95% of CAH cases (1). A major complication in males with 21-OHD is the development of

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Abbreviations: ATII, angiotensin II; AUC, area under the curve; BMI, body mass index; CAH, congenital adrenal hyperplasia; GEE, generalized estimating equation; 21-OHD, 21-hydroxylase deficiency; 17-OHP, 17-hydroxyprogesterone; SDS, SD score; SV, simple virilizing; SW, salt wasting; TART, testicular adrenal rest tumor.

testicular adrenal rest tumors (TARTs) (2). TARTs are benign tumors occurring in up to 94% of adult male patients with classic 21-OHD (3, 4). The adrenal cortex and the testes share a common developmental origin. The adrenal-like features of TARTs are a major argument for the hypothesis that TARTs originate from aberrant adrenal cells within the gonads. TARTs together with hypogonadotropic hypogonadisms are the main causes for male infertility in classic 21-OHD. Poor quality of disease control has been advocated to be one of the main predictive factors for TART development.

This view is supported by the fact that TARTs are ACTH-responsive (5) and express adrenal-specific steroidogenic enzymes, as well as the ACTH and angiotensin II (ATII) receptors (6–9). ACTH-suppressive glucocorticoid treatment with dexamethasone efficiently reverses TART growth and restores sperm count and fertility (10, 11). However, in cross-sectional studies there was no correlation between parameters of endocrine control and either the presence of TARTs or TART size. In fact, TARTs even occurred in overtreated patients with suppressed ACTH and 17-hydroxyprogesterone (17-OHP) concentrations (3, 4, 12). Similarly, neither the incidence nor the morphology of TARTs correlates with parameters of disease control (13). Based on these findings, it has recently been suggested that TART development might be primed during fetal life (14) in response to high ACTH concentrations during this critical period.

To gather further evidence on the natural course and influence between long-term parameters of disease control and the development of TARTs in 21-OHD patients, we performed a cross-sectional study with detailed retrospective longitudinal analysis in a cohort of 50 male patients with classic 21-OHD. Herein, we analyzed the presence of TARTs in relation to several parameters of biochemical and clinical endocrine control over a lifetime.

Subjects and Methods

Patient population

The subjects included in this study were adult male patients with confirmed classical 21-OHD with regular hormonal follow-up from infancy until adulthood at the Endocrine Outpatient Clinic of the University Hospital Munich, Germany (University Children’s Hospital during childhood and adolescence, and Endocrine Clinic of the University Hospital Munich as adults). The parameters on biochemical, hormonal, and clinical endocrine control were extracted from the patients’ health records. The patients were classified as salt wasting (SW; n = 31) or simple virilizing (SV; n = 19) based on biochemical criteria (electrolytes, renin concentration). At the time of data acquisition, the median age of participants in the study was 27 years (range, 18–49 y), their median height was 169 cm (range, 142–181 cm; SD score [SDS], –1.3; Q1/Q3, –2.1/–0.7), and median body mass index (BMI) was 25.2 kg/m² (range, 19.3–32.9 kg/m²; SDS, 1.1). The median age at diagnosis of 21-OHD for all patients was 0.19 years (or 2.3 mo) (range, 0.0–16.0 y); for patients with the SW form, 0.06 years (22 d) (range, 0.0–4.9 y); and for patients with the SV form, 6.1 years (range, 2.0–16.0 y). Patients’ characteristics are summarized in Table 1. The treatment strategy and aims of disease control in our patient cohort were according to pediatric and adult guidelines in patients with CAH (15, 16). Exclusion criteria were: other diseases with impairment of gonadal capacity, severe general diseases (transaminases >3 times elevated levels, creatinine >1.8 mg/dL [159 μmol/L]), psychiatric disorders, or alcohol abuse. The study was approved by the local ethics committee, and written informed consent was obtained.

Testicular ultrasound

Testicular ultrasound of all patients was performed in the Department of Endocrinology in the University Hospital Munich and/or in the Department of Radiology at the University Children’s Hospital Munich (Siemens Sonoline Elegra). Testicular ultrasound was performed documenting testicular masses. Greyscale and color Doppler ultrasonography were obtained in the longitudinal and transverse planes.

Table 1. Clinical Characteristics of the Patient Cohort

No. of Patients	Phenotype	TART Presence	Age at Cross-sectional Investigation, y	Age at Diagnosis, y	Final Height, cm	Final Height Minus Target Height, cm (n = 47)	BMI, kg/m ²
19	SV		28.4 (22.2/32.2)	6.1 (4.4/9.1)	170 (162/171)	–7.5 (–15.2/–3.8)	25.0 (23.3/29.2)
					SDS – 1.2 (–2.3/–0.9)	SDS – 1.1 (–2.2/–0.5)	SDS 1.0 (0.5/2.0)
9		+	29.4 (27.9/30.8)	7.1 (4.3/13.2)	168 (157/171)	–13.3 (–15.5/–3)	25.0 (23.1/29.0)
					SDS – 1.5 (–3.0/–1.2)	SDS – 1.9 (–2.2/–0.5)	SDS 1.0 (0.4/2.0)
10		–	27.8 (21.9/32.2)	5.7 (4.4/8.6)	170 (163/172)	–5.8 (–8.4/–4.9)	25.5 (24.4/29.6)
					SDS – 1.2 (–2.2/–0.9)	SDS – 0.9 (–1.2/–0.7)	SDS 1.2 (0.9/2.1)
31	SW		23.7 (19.8/30.5)	0.06 (0.04/0.11)	169 (164/178)	–7.5 (–11.2/–1)	25.4 (23.2/28.4)
					SDS – 1.3 (–2.0/–0.2)	SDS – 1.1 (–1.6/–0.2)	SDS 1.1 (0.4/1.9)
19		+	26.2 (20.0/33.1)	0.06 (0.03/0.12)	167 (163/174)	–7.9 (–12.1/–1.25)	26.3 (23.2/28.5)
					SDS – 1.6 (–2.2/–0.6)	SDS – 1.2 (–1.9/–0.2)	SDS 1.4 (0.4/1.9)
12		–	21.1 (18.8/26.9)	0.06 (0.03/0.12)	172 (165/178)	–6.9 (–7.8/0.7)	24.5 (23.4/28.3)
					SDS – 1.0 (–1.8/–0.1)	SDS – 1.1 (–1.2/0.2)	SDS 0.9 (0.5/1.8)
50	All		27.3 (20.5/30.8)	0.19 (0.04/5.17)	169 (164/173)	–7.5 (–12.9/–2.55)	25.2 (23.3/28.7)
					SDS – 1.3 (–2.1/–0.7)	SDS – 1.1 (–1.9/–0.4)	SDS 1.1 (0.5/1.9)

Data are given as median (Q1 [25th]/Q3 [75th] percentile).

Hormonal evaluation

In each patient, disease control was assessed by documented measurements of pregnanetriol in 24-hour urine samples and serum 17-OHP over a lifetime at least in yearly intervals. Blood drawing for serum 17-OHP concentration was performed in the morning 2 hours after the intake of the morning medication.

Pregnanetriol in 24-hour urine samples was determined by a semiautomatic capillary gas-liquid chromatographic method (17). 17-OHP in serum was measured by a commercially available assay (IBL International GmbH Elisa).

Clinical evaluation

The size and consistency of the testes were evaluated by an experienced endocrinologist using an orchidometer as part of each clinical evaluation from the initial diagnosis of the disease until the end of data collection (H.-P.S. during childhood, and N.R. during adulthood). In patients with a testis volume exceeding 25 mL, an additional magnetic resonance tomography was performed, calculating the exact testis volume in these cases. During childhood and adolescence, the onset of pubic hair development and Tanner stages were assessed by a single experienced pediatric endocrinologist (H.-P.S.). Bone age was assessed by x-rays of the left hand according to Greulich and Pyle (31) by an experienced pediatric endocrinologist (H.-P.S.) and independently reported by a radiologist. The bone age in relationship to the chronological age was evaluated in yearly intervals during development. Clinical data during childhood and adolescence were retrospectively collected from the patients' charts. Final height of the patients was measured, and target height was calculated from the height of both parents according to the following formula: (paternal height + maternal height in cm)/2 + 6.5. Final height SDS corrected for target height and BMI (SDS) were calculated (18). BMI-SDS values have been calculated according to Cole et al (19). Glucocorticoid equivalent doses have been calculated with factor 5 for prednisolone and factor 40 for dexamethasone.

Statistical analysis

For group comparisons, statistical analyses were performed with the nonparametric Mann-Whitney *U* test. Two-sided *P* values are reported, and *P* values <.05 were regarded as significant. A smooth curve fitted on each scatterplot revealed the relation between age and the single variable pregnanetriol, 17-OHP, bone age, pubic hair status, and testis volume. The bivariate smoother "lowess" (ie, locally weighted scatter plot smoothing) was used for plotting the curves because the calculation is based on the algorithm of Cleveland (20). Lowess is a nonparametric and very flexible regression technique. It is a simple method without the necessity of assumptions about the relationship between the variables. The method produces a line, which shows the trend of the relationship between two variables. The smooth span, which specifies the proportion of points that influence the smooth at each point, was set to 2/3; the number of iterations was 3. Each scatterplot presents a separate "lowess" curve for patients with TARTs and patients without TARTs. Only patients with regular follow-up until at least the age of 18 years and documented parameters of disease control, with intervals of less than 1 year from the time of diagnosis, were included in the analysis of the parameters of disease control. There were 36 patients in our cohort with regular follow-up until at least the age of 18 and documented parameters of disease control with inter-

vals of less than 1 year from the time of diagnosis. These patients were included for subanalysis of pregnanetriol and 17-OHP concentrations, as well as pubic hair status and testis volume. To address the longitudinal structure of the data and to compare the patients with TARTs and patients without TARTs, the area under the curve ($AUC = \int_a^b F(X) dX$) of pregnanetriol concentrations in 24-hour urine collection, 17-OHP, glucocorticoid equivalent dose, Δ bone age, pubic hair stage, and testicular volume (both sides) was calculated separately for both groups. A generalized estimating equations model (GEE multivariate) was used to account for the longitudinal structure of the data (21). Time-dependent models were calculated, including pregnanetriol or 17-OHP as the dependent variable; TART (yes/no), phenotype (SV/SW), and age as independent variables; and an "exchangeable" covariance structure. A normal distribution with a log link function was chosen to model these data. The proc genmod procedure in SAS 9.2 was used for the calculation. Statistical analysis was performed using R 2.14.1 (31) and SAS 9.2 (SAS Institute Inc).

Results

Quality of disease control

The AUC of pregnanetriol concentrations in 24-hour urine collections from the age of 5 years onward was 127 141 $\mu\text{g}/24 \text{ h} \cdot \text{y}$ (median; quartile 1 [Q1 = 25th percentile] to quartile 3 [Q3 = 75th percentile], 80 975–215 312) in all patients; 163 318 (median; Q1–Q3, 58 974–405 497) in patients with TARTs; and 111 363 (median; Q1–Q3, 84 283–140 477) in patients without TARTs (Figure 1A). There was no difference in the AUC of pregnanetriol concentrations over lifetime in patients with and without TARTs ($P = .35$). Pregnanetriol was measured in $\mu\text{g}/24 \text{ h}$ (conversion factor, 2.97 to nmol/L). The AUC of 17-OHP was 774 ng/mL $\cdot \text{y}$ (median; Q1–Q3, 466–1569) in all patients, 855 in patients with TARTs (median; Q1–Q3, 448–2540), and 719 (median; Q1–Q3, 546–1156) in patients without TARTs (Figure 1B). Again, no difference in the AUC of 17-OHP concentrations over lifetime in patients with and without TARTs ($P = .35$) was evident. Serum 17-OHP concentrations were measured in ng/mL (conversion factor, 3.026 to nmol/L). The GEE model adjusted for age and phenotype yielded the same results as the AUC analysis. The presence of a TART (pregnanetriol, regression coefficient 0.0387, $P = .1488$; 17-OHP, regression coefficient 0.0668, $P = .6092$) has no significant influence on pregnanetriol and 17-OHP, respectively (Table 2).

Glucocorticoid substitution therapy in patients with and without TARTs

Patients with TARTs had a mean glucocorticoid dose equivalent of $16.5 \pm 5.8 \text{ mg}/\text{m}^2$, and patients without TARTs had a mean glucocorticoid dose equivalent of $15.6 \pm 7.0 \text{ mg}/\text{m}^2$ ($P = .56$). Because this reflects only

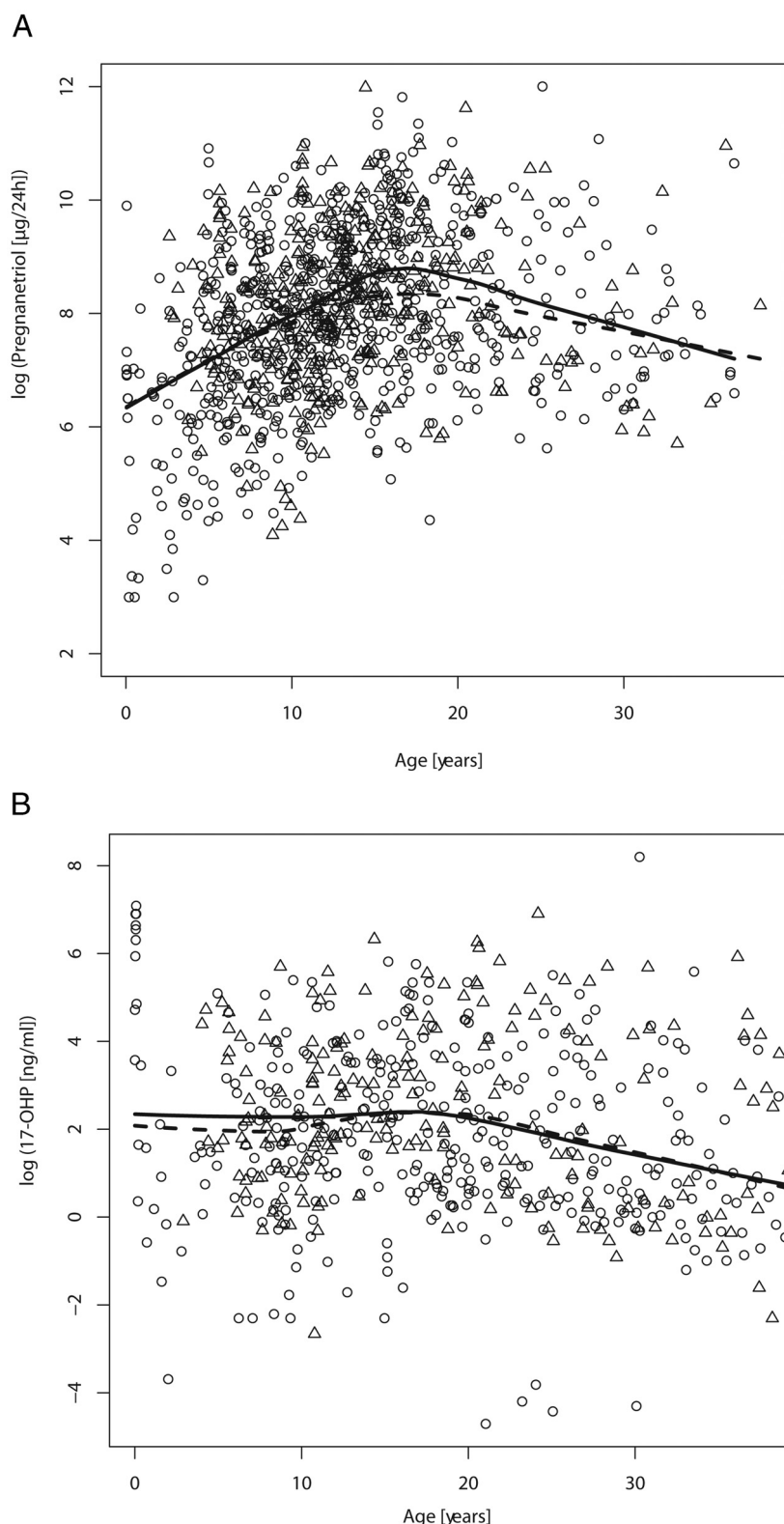


Figure 1. Pregnanetriol (A) and 17-OHP (B) in patients with and without TARTs. Course of median pregnanetriol and median 17-OHP concentrations over lifetime in patients with (continuous line) and without (dotted line) TARTs. Pregnanetriol concentrations at individual time points of measurements are shown by circles in patients with the SW phenotype and by triangles in patients with the SV phenotype.

treatment modalities at a given time point, we also analyzed glucocorticoid equivalent doses over a lifetime in both groups. There was no statistically significant difference comparing the AUC of glucocorticoid equivalent doses over a lifetime in patients with and without TARTs ($P = .66$). Patients with TART were on the following glucocorticoid regimen: hydrocortisone (16 of 28), predniso(lo)ne (7 of 28), and dexamethasone (1 of 28); four patients with the SV phenotype had stopped their glucocorticoid substitution. In the group of patients without TART, hydrocortisone was taken by 8 of 22 patients, predniso(lo)ne by 10 of 22, and dexamethasone by 1 of 22; three patients with the SV phenotype had stopped their medication.

Clinical characteristics during development in patients with and without TARTs

To gather evidence on differences in long-term disease in patients with or without TARTs, clinical parameters that are affected by glucocorticoids and sex steroids were evaluated. However, consistently the long-term markers of disease control (testicular volume, bone age, pubic hair stage) did not differ in patients with and without TARTs over time (Figure 2, A–C). The AUC of Δ bone age over chronological age in all patients was 13.3 y*y (median; Q1–Q3, 11.4–16.6); 13.3 in patients with TARTs (median; Q1–Q3, 8.0–16.5); and 11.9 in patients without TARTs (median; Q1–Q3, 7.0–13.4). There was no statistically significant difference in patients with and without TARTs ($P = .76$).

The median pubic hair stage AUC (Q1–Q3) was 77 years (53–123) in all patients, 85 (53–123) in patients with TARTs, and 65 (50–122) in patients without TARTs ($P = .73$, with TARTs vs without TARTs).

For testicular volume (both sides), the median AUC (Q1–Q3) was 430

Table 2. TART Presence and Pregnanetriol and 17-OHP Concentrations

	Coefficient	SE	Lower Limit 95% CI	Upper Limit 95% CI	Wald Statistics Z	P Value
Dependent variable pregnanetriol						
TART (reference no)	0.0387	0.0268	−0.0138	0.0912	1.44	.1488
Phenotype (reference SW)	0.0271	0.0289	−0.0295	0.0836	0.94	.3482
Age	0.0049	0.0018	0.0015	0.0084	2.80	.0051
Dependent variable 17-OHP						
TART (reference no)	0.0668	0.1307	−0.1893	0.3229	0.51	.6092
Phenotype (reference SW)	0.2764	0.1291	0.0233	0.5295	2.14	.0323
Age	−0.0112	0.0074	−0.0256	0.0032	−1.52	.1280

Abbreviation: CI, confidence interval. Analysis of the influence of TART on the pregnanetriol and 17-OHP concentrations by a GEE model (GEE multivariate) adjusted for age and phenotype.

mL*y (269–655) for all patients, 484 (424–657) in patients with TARTs, and 313 (269–524) in patients without TARTs (*P* = .28, TARTs vs without TARTs).

Similarly, there was no difference in BMI: SDS was 1.1 (median; Q1/Q3, 0.5/1.9) in all patients, 1.4 (median; Q1/Q3, 0.4/1.9) in the TART group, and 0.9 (median; Q1/Q3, 0.5/1.8) in the patients without TARTs. Final height SDS was −1.3 (median; Q1/Q3, −2.1/−0.7) in all patients, −1.6 (median; Q1/Q3, −2.2/−0.6) in the TART group, and −1.0 (median; Q1/Q3, −1.8/−0.1) in the group without TARTs. SDS of the final height compared to calculated target height was −1.1 (median; Q1/Q3, −1.9/−0.4) in all patients, −1.2 (median; Q1/Q3, −1.9/−0.2) in the TART group, and −1.1 (median; Q1/Q3, −1.2/0.2) in the patients without TARTs (Figure 2, A and B).

Discussion

In humans, gonads and the adrenal cortex derive from the same embryological structure, the adrenogonadal primordium (22). This common cellular origin is fundamental for our current understanding of the development of TARTs in patients with classic 21-OHD. It is thought that TARTs originate from adrenal cells nested within the male gonad that are subjected to a chronic ACTH drive in CAH (5). Thus, poor disease control in 21-OHD with a lack of negative feedback toward the pituitary and hypothalamus is thought to induce the growth of TARTs. High-dose glucocorticoid therapy can reverse TART growth. Although the latter is often observed in clinical practice (10, 11), a correlation of parameters of disease control and TART growth has not been found (3, 4, 12, 13). The association of TARTs and disease control so far has only been explored in cross-sectional studies. This approach, however, disregards the impact of long-term disease control and, thus, may not allow clear-cut conclusions on hormonal dependencies of TART induction and growth.

Therefore, we performed a longitudinal analysis of the quality of disease control based on clinical and biochem-

ical parameters in men with classic 21-OHD. Interestingly, none of our endpoints correlated with TART development. In fact, lifetime disease control parameters and clinical parameters were identical in patients with and without TARTs. We only noticed a trend toward poorer disease control in the group of 10- to 12-year-old boys with TARTs, which, however failed to reach statistical significance. This could also be due in part to a limited sample size. Although puberty could be regarded as a crucial time period influencing TART growth, our data support the hypothesis that TART development is mostly independent of postnatal disease control. This statement is also endorsed by our previous analysis in which there was no discernible correlation between disease control parameters and TART size in the subcohort comprised only of patients with TARTs (13). According to our analysis, disease control of the 21-OHD does not seem to be a major determinant in the initial pathogenesis of TARTs. Instead, our data are in accordance with three mechanisms of TART development: the misplacement of adrenal cells in the gonads as a precondition for TART development, the significant influence of prenatal exposure to unopposed high ACTH levels on TART development (23), and the presence of multipotent cells with the ability to differentiate into adrenocortical cells after ACTH stimulation. As previously suggested (13), men without ectopic adrenal cells may be resistant to TART development, even in the context of poor disease control. By contrast, patients with adrenal rest tissue in their testes might be prone to tumor development, even with only periodic exposure to higher ACTH or ATII stimulation. Based on our data, we hypothesize that the amount of ectopic adrenal cells in the gonads in combination with the prenatal ACTH dose sets the stage in utero for subsequent TART development. Conversely, it is possible that multipotent cells differentiate at a very early developmental stage in utero into adrenocortical-like cells in response to ACTH stimulation. The hypothesis of a significantly higher prenatal vs postnatal influence on the persistence of adrenal rest cells

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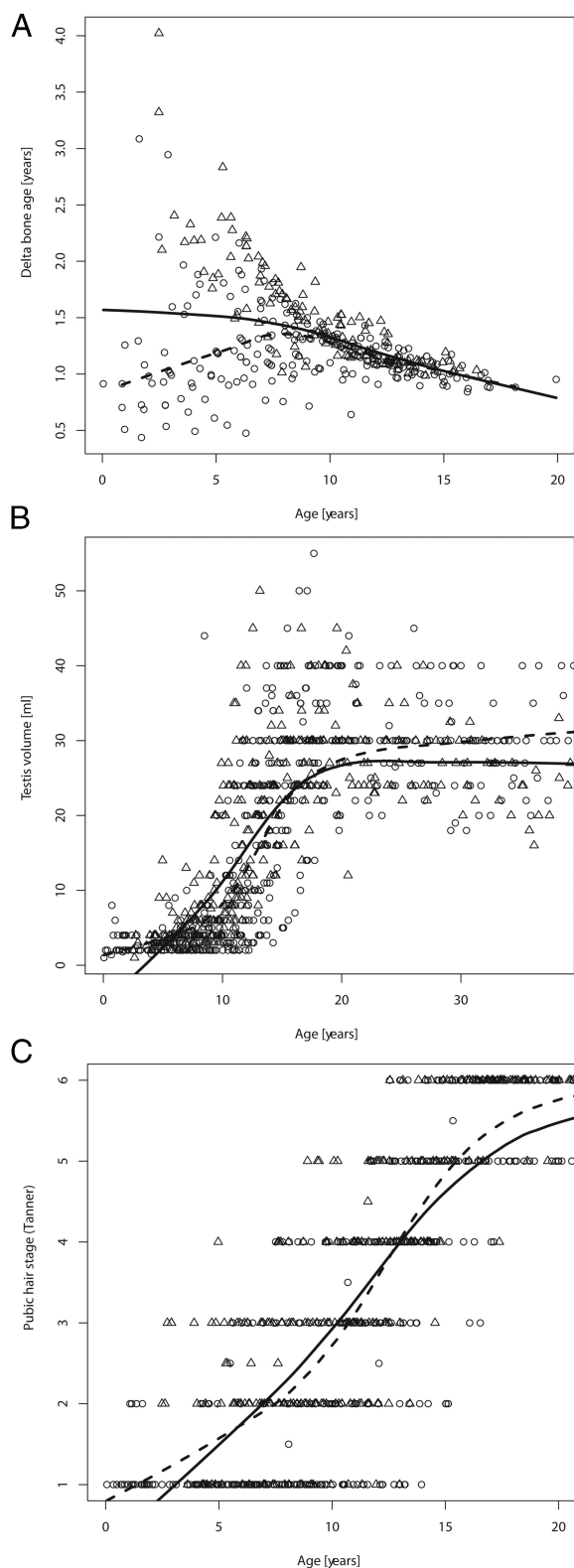


Figure 2. Δ Bone age (bone age – chronological age) (A), testicular volume (B), and pubic hair stage (C) during development in patients with (continuous line) and without (dotted line) TARTs. The development of bone age was assessed according to Greulich and Pyle, pubic hair stage was assessed according to Tanner, and testicular volume was measured by palpation with an orchidometer (values are represented as median values, circles represent individual values in patients with the SW phenotype, and triangles represent individual values in patients with the SV phenotype).

within the gonad is supported by the fact that TARTs tend to be more frequent and bigger in size in SW patients in our cohort (4). Furthermore, a higher prevalence and increased volume of TARTs in SW CAH has been described (3, 4). This is of particular interest because all patients included in our study were diagnosed before the newborn screening era, which led to the diagnosis of 21-OHD in the SV form at a median age of 6 years. Therefore, the patients in our cohort with SV CAH were untreated for a median of 6 years, resulting in unopposed high ACTH drive. Despite this clear difference in treatment schedule, they still had neither higher TART prevalence nor increased TART size compared to the SW group with an early diagnosis and treatment in the first weeks of life.

So far, there are no animal data supporting our hypothesis of prenatal hormonal environment predisposing a male to develop TARTs. In wild-type mice, adrenal-like and ACTH-responsive cells in the testes have been described (24), suggesting that these are the mouse equivalent of the precursors of human TARTs. In 21-hydroxylase-deficient mice, however, this aspect has not yet been investigated (25–29). Interestingly, hydrocortisone was found to be more frequently used in patients with TARTs. The shorter half-life and the pharmacokinetics of hydrocortisone resulting in phases of over- and undertreatment throughout the day might predispose for TART development. However, the data are not entirely conclusive. To answer this question, a large prospective multicenter study is necessary.

Another limitation of our retrospective approach is that it remains unclear how long TARTs were present before initial detection. We also have no information about how rapid TART growth appeared or even disappeared again in some patients. In agreement with data from others, we found that most patients with bigger tumors showed hypo- and hyperechogenic appearance on ultrasound compared to the uniform hypoechogenic characteristics of the small tumors (30). This may imply different tumor stages with various degrees of fibrosis or dedifferentiation, with loss of response to ACTH or ATII stimulation hampering correlation analysis of tumor size and disease control. Another limitation of the retrospective analysis is that the individual parameters have not been evaluated to the same extent in each patient, eg, for some patients there are more data available in shorter time intervals than for others. Therefore, a prospectively designed study with a standardized study protocol would be necessary to clarify these remaining aspects.

In conclusion, our data provide indirect evidence that the presence or absence of TARTs is rather dependent on testicular misplacement of adrenal cells during development, with significant influence of the prenatal hormone milieu on TART growth in later life.

Acknowledgments

Address all correspondence and requests for reprints to: Nicole Reisch, MD, Klinikum der Universität München, Ziemssenstrasse 1, D-80336 München, Germany. E-mail: nicole.reisch@med.uni-muenchen.de.

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