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17β-Hydroxysteroid dehydrogenase-3 deficiency: From pregnancy to adolescence

S. Bertelloni[1], A. Balsamo[2], L. Giordani[3], R. Fischetto[4], G. Russo[5], M. Delvecchio[3], M. Gennari[2], A. Nicoletti[2], M.C. Maggio[6], D. Concolino[7], L. Cavallo[3], A. Cicognani[2], G. Chiumello[5], O. Hiort[8], G.I. Baroncelli[1], and M.F. Faienza[3]

[1]Adolescent Medicine, Department of Reproductive Medicine and Paediatrics, Santa Chiara University Hospital, Pisa; [2]Department of Gynecologic, Obstetric and Pediatric Sciences, University of Bologna, Bologna; [3]Department of Biomedicine of the Developmental Age, University of Bari, Bari; [4]Perdiatric Endocrinology, Pediatric Hospital "Giovanni XXIII", Bari; [5]Department of Paediatrics and Adolescent Medicine, University "Vita e Salute", San Raffaele Hospital, Milan; [6]Maternal and child Health Department, University of Palermo, Palermo; [7]Department of Pediatrics, University of Magna Grecia, Catanzaro, Italy; [8]Division of Pediatric Endocrinology and Diabetes, Department of Pediatrics and Adolescent Medicine, University of Lubeck, Lubeck, Germany

ABSTRACT. ***Objective:*** **Aim of this study is to report on basal clinical phenotype and follow up after diagnosis, of patients with 17β-hydroxysteroid-dehydrogenase type 3 (17β-HSD3) deficiency in Italy.** ***Setting:*** **Pediatric Endocrine Departments, University Hospitals.** ***Patients:*** **The cases of 5 Italian subjects affected by 17β-HSD3 deficiency are presented in this study.** ***Interventions:*** **Laboratory and genetic assessment. Gonadectomy and female sex assignment (4 patients) or GnRH analog therapy to regress puberty and gender identity disorder (1 patient).** ***Results:*** **Presentation lasted from pregnancy (pre-natal diagnosis of a 46,XY fetus with female external genitalia) to infancy (inguinal hernia containing testes/clitoromegaly) and adolescence (virilisation). All subjects but one (subject 1, Central-Northern Italy) were from small areas of Southern Italy. Endocrine data (baseline and/or stimulated testosterone/Δ4-androstenedione ratio) were informative. Two girls were homozygous for 17β-HSD3 gene mutations (G289S/G289S; R80W/R80W), while the others were compound heterozygous (IVS325+4 A>T/A203V; L212Q/M235V; R80W/A235E). Four patients were confirmed as females and were well-adjusted with assigned sex; gender identity disorder improved during treatment with GnRH analog in the last subject.** ***Conclusions:*** **17βHSD3 deficiency may present from pregnancy to puberty for different clinical issues. Albeit testosterone/Δ4-androstenedione ratio represents the most accurate endocrine marker to diagnose the disorder, hCG-stimulation is mandatory in pre-puberty. Molecular analysis of 17β-HSD3 gene should be performed to confirm the diagnosis. Temporary GnRH analog treatment may regress gender identity disorder and provide time to confirm or change the birth sex assignment. Female individuals seems to be compliant with their sex, providing that virilisation does not occur. In Italy, the disorder seems to be more prevalent in the Southern regions and shows genetic heterogeneity.**
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INTRODUCTION

46,XY disorders of sex development (DSD) are a heterogeneous group of clinical conditions characterized by 46,XY karyotype, either normal or dysgenetic testes and female or ambiguous phenotype of external (and possibly internal) genitalia (1). Among them, 17β-hydroxysteroid dehydrogenase type 3 (17β-HSD3) deficiency (OMIM #264300), also described as 17-ketosteroid reductase deficiency, is a very rare autosomal recessive DSD in Western countries, whereas it is relatively frequent in the Arab population of the Gaza strip (2, 3).
17β-HSD3 deficiency is due to an impaired testosterone (T) biosynthesis for the lack of conversion of Δ4-androstenedione (Δ4-A) to T as a consequence of mutations in 17β-HSD type 3 gene (2-7). 17β-HSD3 enzyme is a member of the short-chain dehydrogenase/reductase protein superfamily ant its gene, on chromosome 9q22, consists of 11 exons, ranging in size from more than 264 bp to as little as 35 bp (3, 4). The gene encodes a microsomal enzyme of 310 aminoacids (molecular mass 35 kDa), that has been localized in the fetal and adult testes; it preferentially favors, in the presence of NADPH as cofactor, the reductive conversion of the weak C_{19}-steroid Δ4-A to the biologically active androgen T (2-7).
In this paper, we report on the clinical, endocrine, gonadal histology, genetic findings, and decision on the sex assignment of subjects affected by 17β-HSD3 deficiency, in whom diagnosis lasted from early infancy to adolescence. The genetics of 17β-HSD3 deficiency in this Italian series in comparison with other reports are reviewed, too.

PATIENTS AND METHODS

Data of children, in whom a diagnosis of 17β-HSD3 deficiency was established from 2000 to 2007 in the centers participating to the Study Group on Physiopathology of Puberty of the Italian Society of Pediatric Endocrinology and Diabetes, were collected by a dedicated survey. Main clinical data, sex of rearing and presumptive diagnosis before our examination are summarized in Table 1. Karyotype was 46,XY in all the subjects.

Key-words: 17β-hydroxysteroid dehydrogenase type 3 deficiency, 17β-hydroxysteroid dehydrogenase type 3 gene, disorders of sex development, male/female sex reversal, testotesterone/Δ4-androstenedione ratio.

Correspondence: S. Bertelloni, MD, Adolescent Medicine, Department of Reproductive Medicine and Paediatrics, Santa Chiara University Hospital, Via Roma, 67, 56126 - Pisa, Italy.

E-mail: s.bertelloni@med.unipi.it

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Table 1 - *Clinical findings in the 5 subjects with 17β-hydroxysteroid dehydrogenase type 3 deficiency at the first examination.*

no.	Age at		Length/Height			Clinical	Clitoris		Vagina	Testes[c]	Internal genitalia		Presumptive
	1st identification[a]	1st examination[b]	cm	F-SDS	M-SDS	phenotype(8)	mm	SDS	length cm	Right/Left	male	female	diagnosis[a]
1	pregnancy[d]	1 m	56.0	1.5	1.0	4b	19	12.1	1.5	I/A	Yes	No	Not done
2	1.0 yr[e]	2.3 yr	88.5	–0.21	–0.56	4b	23	15.3	4.7	I/I	Yes	No	AIS
3	1 m[f]	2.6 yr	94.0	0.65	0.20	4b	32	23.3	3.5	I/I	Yes	No	AIS
4	11.4 yr[g]	12.0 yr	158.2	0.88	1.04	3	45	6.8	2.5	I/I	Yes	No	Not done
5	12.0 yr[g]	12.6 yr	156.0	0.92	0.81	3	31	2.9	8	A/A	Yes	No	5α-D

[a]by referring centres; [b]by the centres involved in the present study; [c]by clinical evaluation and/or sonography; F: female; M: males; I: inguinal; A: abdominal; AIS: androgen insensitivity syndrome; 5α-D: 5α-reductase deficiency; SDS: SD score. [d]discordance between 46,XY karyotype and female external genitalia plus penis-like clitoris at prenatal sonography; [e]bilateral inguinal hernia containing testes at surgery; [f]bilateral inguinal hernia containing testes at sonography; [g]clitoris enlargement and virilization after the onset of puberty.

Methods

Phenotype was staged according to Sinnecker et al. (8). Height was expressed as raw measured values and as SD scores (SDS) according to Italian reference values for both males and females (9); clitoral size was also expressed as real measured values and SDS according to published reference values (1). As there were no significant changes in clitoral size before puberty (10), values in term neonates were used to calculate SDS in pre-pubertal subjects, while adult values were used for subjects 4 and 5 (1).

Blood samples were drawn in the morning (08:00-09:00 h) and serum was stored at –20 C until analysis. Serum levels of LH, FSH, Δ4-A, T, cortisol, and ACTH were measured by commercially available immunoradiometric assay (IRMA) or radioimmunoassay (RIA) kits. The cut-off values chosen to define an abnormal T/Δ4-A ratio were 0.84 and 0.94 before and after hCG stimulation, respectively (11).

Serum inhibin B was measured in duplicate by an enzyme-linked immunoabsorbent assay (Serotec, Kidlington, UK) using two different antibodies directed against distinct epitopes on the α- and β-subunits. For all measurements, the coefficients of variation were <9% and <6% for intra-assay and inter-assay, respectively.

A hCG-stimulation test was performed by administering 1500 IU/dose for 3 days and measuring Δ4-A and T at the days 0, +3, and +5. GnRH test (100 mg/m^2 iv) was performed at 08:00 h after an overnight fast.

Genomic DNA was extracted from peripheral leukocytes using standard methods Genetic analysis of subjects 1 and 5 was performed in Bologna (methods and primers sequences available on request: annalisa.nicoletti@unibo.it). Molecular genetic analysis of the individuals 2 and 3 was performed in Lübeck according to procedures previously described (12) (methods and primers sequences available on request: hiort@paedia.ukl.muluebeck.de). Genetic analysis of the subject 4 was performed in Bari (methods and primers sequences available on request: mf.faienza@endobiomol.uniba.it).

Informed consent by both parents was obtained before the endocrine and genetic assessment.

RESULTS

Presentation and clinical findings

Five subjects with proven diagnosis of 17β-HSD3 deficiency were identified (Table 1); they were classified as female at birth, although mild signs of androgenization was present at least in the 3 girls from birth (Table 1).

The patients were from various Italian regions mainly located in the Southern area (Emilia-Romagna, no.=1; Sicily, no.=1; Calabria, no.=1; Puglia, no.=2) and were born from unrelated parents; no evidence of familial relationship was present between the two adolescents from Puglia. Medical history was negative for DSD in all the subjects. Misdiagnosis [androgen insensitivity syndrome (AIS), no.=2; 5α-recuctase deficiency, no.=1] was present in 60% before our assessment.

Endocrine and genetic data are shown in Table 2. Evaluation of androgen secretion (baseline and/or after hCG test) demonstrated increased Δ4-A values and impaired T levels; the T/Δ4-A ratio was in keeping with 17β-HSD3 deficiency at baseline (subjects 1, 4, 5) or after hCG stimulation (subjects 2, 3) (Table 2). LH, FSH, and inhibin B serum values were within the age related reference range for males, in all but the pubertal subjects (patient 4 and 5), who showed increased LH levels (Table 2).

Molecular analysis demonstrated different mutations of the 17β-HSD3 gene in each subject; compound heterozygous state was found in 3 subjects (patients 1, 2, 5) and homozygous in the other 2 (patients 3 and 4) (Table 2). Indeed, the mutation G289S (patient 3) has been reported as possible polymorphism (14).

Management

Before diagnosis, sex of rearing was female (Table 1) and it was confirmed in 4 subjects (patients 1-4).

For subjects 1-3, the choice was taken after meetings among parents, pediatric endocrinologists and psychologists. It was principally based on the phenotypic appearance/structure of the genitals (Table 1) and the wishes of the parents. Gonadectomy was performed when the patients were 2.5, 3.0, and 3.3 yr old, respectively.

Bilateral gonadectomy and surgical correction of the external genitalia in female direction were performed after diagnosis in the patient 4; the decision was based on the opinion of the girl and her parents together with psychological evaluation confirming her female gender behavior and identity.

At now (follow-up period 2.5, 8.0, 4.5, and 2.5 yr for subjects 1, 2, 3, and 4, respectively), all the patients appeared to have age-appropriate psychological development and age-typical behavior for sex of rearing and did not show signs of cross-gender playing or role; only patient 2 was involved in a male sport (football).

Patient 5 developed gender identity disorder after the onset of puberty and virilisation, but without the preva-

Table 2 - *Endocrine and genetics findings in the 5 subjects with 17β-hydroxysteroid dehydrogenase type 3 deficiency.*

no.	Δ4-A ng/ml		T ng/ml		T/Δ4 ratio		Inhibin B ng/l	LH, IU/l		FSH, IU/l		Cortisol ng/ml	ACTH ng/ml	Exon	Mutation
	b	p	b	p	b	p		b	p	b	p				
1(a)	1.44[a]	n.d.	0.8	n.d.	0.55	n.a.	n.d.	<0.1	—	<0.3	—	142	65	3/9	IVS325+4 a>t/A203V
(b)	0.37[b]	1.05	0.2	0.5	0.54	0.48	n.d.	2.6	—	0.6	—	206	114		
2	0.10	1.10	<0.25	0.60	n.a.	0.54	178.0[c]	0.3	1.2	2.2	4.3	175	43	9/10	L212G/M235V
3	0.45	3.05	<0.25	0.41	n.a.	0.13	490.0[c]	<0.1	1.5	2.4	3.6	210	31	11	G289S/G289S
4	19	n.d.	3.3	4.0	0.17	n.a.	47[d]	13.1	46.4	6.1	9.3	840	26	3	R80W/R80W
5	4.9	6.7	1.8	2.4	0.36	0.36	–	21.0	n.d.	7.0	n.d.	245	37	3/9	R80W/A203E

[a]at birth; [b]at age 1 month; n.d.: not done; n.a.: not applicable; b: basal; p: peak; [c]normal values (n.v.) 42-268 ng/l; [d]n.v. 74-470 ng/l [n.v. from Crofton et al. (13)]. Δ4-A conversion factor to SI units: 0.3492; T conversion factor to SI units: 0.3467; Cortisol conversion factor to SI units: 0.2799.

lence of one sex. After extensive psychological evaluation, according to the parents, a treatment with the GnRH analog triptorelin depot (3.75 mg/28 days) was started to regress androgen secretion; full gonadal suppression was reached (T values <0.3 ng/ml). The patient reversed male sexual findings during treatment (1 yr) and she resulted better female sex-oriented, but at present a definite decision on the sex assignment has not been reached.

Gonadal histology

The data of histologic examination (patients 1-4) are summarized in Table 3. They demonstrated gonads of adequate volume for age and pubertal stage as well as the presence of normal epididymi in all the subjects. In patient 1, a pre-pubertal gonadal tissue was found with mainly Sertoli cells in the tubules. In patients 2 and 3, pre-pubertal testicular tissue was found with seminiferous tubules containing Sertoli cells and spermatogonia. In patient 4, seminiferous tubules with Sertoli cells and sparse spermatogonia, normal interstitial stroma, and hyperplastic Leydig cells were found. No signs of germ cell degeneration was found, but testicular microcalcifications were found in the tubules of patient 2.

DISCUSSION

Albeit 17β-HSD3 deficiency is considered the commonest form of T biosynthetic defects, it is very rare at least in the Western countries (2, 3, 11). A nation-wide survey in the Netherlands (11) showed a minimal incidence of 17β-HSD3 deficiency of about 1:147.000 newborns (11). In a recent USA series of 250 children with DSD, cases of 17β-HSD3 deficiency were not present (17) and in the UK DSD database, patients with 17β-HSD3 represent about the 4% of the total 46,XY DSD subjects (13/322) (18). However, increased frequency has been described in populations with a high intermarriage rate as the Arab population of the Gaza strip (1:300-1:150 males) (19).

The incidence of the disorder in Italy is unknown, but, to our knowledge, only one other report from Balducci et al. (20) described 3 affected girls from a single family in 1985 before the present series. Thus, in our country the frequency of 17β-HSD3 deficiency seems to be extremely rare or misdiagnosis may lead to underreport (11). In fact, the majority of the Italian subjects had a misdiagnosis of AIS or 5α-reductase deficiency before adequate assessment [subjects 2, 3, 5, and those reported by Balducci et al. (20)]; these two latter DSD represent the principal differential diagnoses in infancy and adolescence, respectively (3, 7, 20). The clinical phenotype of Leydig cell hypoplasia (21) may also resemble that of 17β-HSD3 deficiency before puberty, but the absence of all testicular androgens (baseline and after hCG stimulation) and the lack of pubertal development or isosexual pubertal arrest should allow to differentiate between them (3).

Today, some cases of 46,XY DSD come to medical attention during pregnancy, because of a mismatch between genetic sex at amniocentesis and phenotypic sex at birth or even at fetal sonography, as in subject 1. While pre-natal diagnosis of AIS has been previously reported (22), the present girl is likely the first case of 17β-HSD3 deficiency prenatally identified. Indeed, for a definitive diagnosis, perinatal hormonal assessment is mandatory taking into account the physiological increase of androgens in this period of life (3).

The endocrine hallmark of 17β-HSD3 deficiency is an abnormal T/Δ4-A ratio due to increased concentrations of Δ4-A and impaired synthesis of T (2-7, 11, 12, 19). As underlined by this report, an abnormal baseline T/Δ4-A ra-

Table 3 - *Gonadal findings in the 4 subjects with 17β-hydroxysteroid dehydrogenase type 3 deficiency and gonads removed.*

no.	Epididimus	Testes ml[a]	Testes SDS	Spematogonia cells	Sertoli cells	Leydig	Microcalcificantions
1	Yes	1.4	–1.0	Scarce	Normal	Normal	No
2	Yes	1.0	–0.5	Present (sub-normal)	Normal	Normal	Yes
3	Yes	2.0	2.0	Present	Normal	Normal	No
4	Yes	9.0	1.3	Absent/very scarce	Normal	Hypertrophic	No

[a]mean of the two gonads; SDS: SD score. Normal values from Cassorla et al. (14) for patients 1-3 and from Taranger et al. (15) for patient 4.

tio is informative after the onset of puberty (patients 4 and 5), likely avoiding for a hCG stimulation (3); in fact, in patient 5 similar T/Δ4-A ratio has been found in baseline and stimulated status. Our data also suggest that baseline T/Δ4-A ratio evaluation may be able to screen for 17β-HSD3 deficiency in perinatal period, when androgens show a physiological surge, even if a stimulatory test may be required in older infants (3, 12). A hCG stimulation is mandatory to endocrinologically screen prepubertal children (2, 3, 11, 12).

The mechanism overcoming the impaired T synthesis in adolescence and adulthood is likely related to extra-testicular conversion of Δ4-A by one or more unaffected 17β-HSD isoenzymes (2, 3, 6, 7). Alternatively, in the patients, in whom 17β-HSD3 gene mutation causes the formation of an enzyme with some residual activity, as for the mutation R80Q in Arabs (16), an increased secretion of T directly from the testes, induced by the higher pubertal LH values, may account for the virilization (19). Recently, Lee et al. (7) speculated that some subjects may manifest uncommonly robust extra-testicular Δ4-A to T metabolism, possibly mediated by genetic and/or environmental induction of enzyme activities of the aldoketoreductase family 1C (AKR1C), such as 17βHSD type 5 (3). This hypothesis is consistent with the low basal T: Δ4-A ratio, which rises after several days of hCG administration, during which time testicular Δ4-A may be converted to testosterone in peripheral tissues (7).

While male adults with 17βHSD deficiency are invariable infertile (3, 19), we found normal values of inhibin B, a reliable marker of seminiferous tubular function (23), in 2 pre-pubertal girls with evidence of germ cells at gonadal histology, suggesting that in some patients spermatogenesis may be unimpaired in the first years of life. This finding is in keeping with the other recent reports showing the presence of germ cells in testes of infants and young children with 17βHSD deficiency (7, 24). Thus, germinal damage may develop, at least in part, as the consequence of undescended testes. In our patients, gonadal histology demonstrated a complex picture, but was in line with a progressive deterioration of germ cell lineage from infancy to adolescence (3, 7, 11). Regarding cancer risk, we did not found histological signs of germ cell neoplasia in keeping with the data of Lee et al. (7), but testicular microcalcifications was in one child. Since this finding may represent a pre-malignat lesion mainly in patients with other risk factors for testicular cancer (25) and tumor risk remains unknown in 17β-HSD3 deficiency (3, 23), additional studies are required on this issue.

The molecular basis of 17β-HSD3 deficiency relies on mutations in the 17β-HSD3 gene (2-5, 11, 18, 24, 27). Details in the present series and patients previously reported in literature sharing the same mutations are summarized in Table 4. Only 2 girls (patient 3 and 5) harbored an unreported mutation. Although we did not perform expression studies, each mutation in exon 9 located from residues 205 to 215 inactivates the enzyme almost completely (4, 5), suggesting that this region is critical for protein function. The G289S mutation (subject 3) was previously reported in heterozygous form in normal women and in women with polycystic ovary syndrome (14). *In vitro* studies, demonstrated that enzymes bearing either glycine or serine at this position have similar substrate specificities and kinetic constants (14). However, Margiotti et al. (28) found that G289S polymorphism confers a significant increase in prostate cancer risk, reported 2 men with prostate cancer homozygous for this mutation, and suggested that such a variant may be associated with increased androgenic activity. Thus, whilst clinical and biochemical data are strongly suggestive of 17β-HSD3 deficiency in child 3, the pathogenicity of this mutation remains to be proven, especially considering that parent's study were not possible. This mutation has been also detected in a compound heterozygous state with a proven pathogenetic mutation in a West Indian patient (11). The possibility of another mutation outside the coding region or large rearrangements or different behavior of the mutation *in vivo* and *in vitro* has been not explored in these two patients.

The fact that the girls reported in this series are genetically heterogeneous regarding 17β-HSD3 gene mutations suggests that a single common ancestor is not operative in Italy; the IVS325+4 A>T and R80W mutations may be imported during the Norman and Spanish domination of the Southern Italian regions, but a large sample should be collected before to reach conclusions on this matter.

Recent literature reviews showed that in 17β-HSD3 deficiency female to male gender role change occurs frequently (39-64%), but not invariably, usually in late adolescence or early adulthood (29, 30). In areas with high prevalence of the disorder (Gaza strip), a spontaneous

Table 4 - *17β-hydroxysteroid dehydrogenase type 3 gene mutation in the present Italian series and the other patients in literature sharing the same mutations.*

Mutation	Pt[a], no.	Previously reported from	*In vitro* studies
325 +4; A>T	1	The Netherland, Brazil, Germany, USA (4, 5, 11, 27)	The transcripts were out of frame and thus non-functional (5, 11).
A203V	1	Brazil (6)	Inactivated the enzyme (6).
L212Q	2	Unreported	Not done
M235V	2	USA (African-American) (4)	Completely inactivated the enzyme (4).
G289S	3	The Netherland (West Indian patient) (11), USA (normal women and women with polycystic ovary syndrome) (14); USA (men with prostate cancer) (28)	Unaffected enzyme activity (14).
R80W	4[a] 5[a]	Spain (Caucasian infant with various associated malformation) (24)	Not done. The R80Q mutation presents a residual enzyme activity of ~20% (19)
A203E	5	Unreported	Not done. The mutation A203V inactivated the enzyme (6).

[a]no associated malformation.

change in gender role has been reported in the great majority of these individuals (19), while this is not the rule in the other areas, where the female sex assigned at birth is usually confirmed after diagnosis and gonads removed (3), as in 4 of our individuals. It is not clear why changes in gender role occurs in some patients but not in others (6, 29, 30), but, to date, there is no clear relationship between the severity of enzymatic defect and the decision about adult social sex (6), suggesting that sociocultural issues, unidentified pre-natal and post-natal factors and a better knowledge of natural history of the disorder in some areas may play a role (3, 6, 19, 29). In the present series, the patients who underwent gonadectomy were compliant with the assigned sex suggesting that appropriate follow-up and full involvement of parents in decision process represent a key point for long-term well-being in these females. The high androgen levels after the onset of puberty may affect gender identity and sexual orientation (30), as in our patient 5. In this adolescent, we firstly employed a therapeutic strategy suggested for mangement of adolescent transsexuals (31). The GnRH analog treatment, by blocking puberty, determines a prepubertal "peace of mind" and a regression of pubertal development (28), providing more time to explore the more appropriate choice regarding the definitive sex assignment without the distress of progressing secondary sexual characteristics (31).

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