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Endocrine and Cytogenetic Profile of Variations in Genital Development: Series of 9 Cases at the Mali Hospital

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Abstract

We carried out a retrospective and descriptive study in the Medicine and Endocrinology service of the Mali Hospital from January 2015 to December 2018. Nine cases of anomalies in sexual differentiation were referred for pubertal delay, growth retardation, gynecomastia, micropenis or infertility. **Outcomes:** The average age was 14 years; 5 patients were declared female at birth; 2 were married without children; 7 patients came from the region of Kayes; 8 patients consulted for pubertal delay; 1 patient presented with association of a blind vagina and 2 bilateral inguinal gonads. 3 of 4 patients declared male at birth had a micropenis; 2 patients had gynecomastia with a history of hypospadias. Ultrasound and biological data showed a clinical-hormonal picture of hypergonadotropic hypogonadism in 6 patients, 1 case of hypogonadotropic hypogonadism with hypercorticism and 2 cases with normal gonadotropic axis; two cases of azoospermia. Karyotypic analysis showed: 3 cases of SK, 2 cases of Klinefelter Syndrome, 2 cases of Androgen Insensitivity Syndrome and 2 cases of male 46 XX syndrome including one with sry negative. **Conclusion:** The precise diagnosis of anomalies in sexual differentiation remains complicated in Mali, due to the inadequacy of the technical platform. Diagnosis must be made at an early stage to allow normal growth, puberty and satisfactory fertility. Taking charge of the medical treatment possibly associated with plastic surgery could give good results.

Keywords

Variations in Genital Development, Endocrine Profile, Cytogenetics

1. Introduction

The disorders of sexual development formerly qualified as hermaphroditism, or sexual ambiguity have changed their name following societal advances and pressure from patient associations in the United States. It is now the Anglo-Saxon designation that prevails "Disorders of Sexual Development" (DSD) or French "Variations of Genital Development" (VDG) since the establishment of the new Chicago classification. These situations are relatively rare in the world and the prevalence varies according to the definition between 0.1% and 2% in the USA [1]. They share a singularly polymorphic clinical spectrum which ranges from the almost complete male phenotype to the female phenotype. Clinical, cytogenetic, hormonal and imaging data allow the karyotype to confirm the diagnosis so that early management can be undertaken.

In Mali, these pathologies are difficult to evoke because of modesty. Some cultures think that these situations are due to bad spells (pregnant having slept lying on the back, belly exposed to the moonlight, sexual intercourse during certain periods of the year …) and sometimes it is during certain rites (circumcision, excision …) that the problem is raised.

We proposed conducting a contributory study of VDG in the Medicine and Endocrinology service of the hospital of Mali, in order to study the parallel between the endocrine profile and the type of genetic anomaly involved. This work does not take into account the surgical aspect of VDG.

2. Methodology

We carried out a retrospective and descriptive study of the VDGs reported in the Medicine and Endocrinology department of the Mali Hospital, from January 2015 to November 2018. Due to the rarity of GBV, we were able to collect 9 cases in consultation. Included in this study were all patients received in endocrinological consultation for gynecomastia, micropenis or primary amenorrhea related to a disorder of sexual differentiation. The physical examination allowed measurement of height, weight, BP, palpation of gynecomastia and inspection of the external sexual organs. The serum follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), total testosterone (T2), fasting blood sugar (GJ), karyotype and sometimes cortisol have been systematically evaluated in each patient. cortisol, a minute brake test in a patient. Pelvic and testicular ultrasound assessed the internal genitalia and testicular volume. TSH has been evaluated in patients with Turner syndrome (ST). The spermogram was performed in the event of infertility. With the local inadequacy of the technical platform in Mali and the costs of the assessments requested at the patients' expense, some patients were not able to carry out all the assessments requested. Missing data and undetermined results were treated as such in the data collection. The data were collected by questionnaire established and coded by a number that did not allow the identification of patients when the results of the study were published.

All procedures used in the study confirmed to the tenets of the Declaration of Helsinki. The Ethics Committee of the Mali Hospital approved the protocols used. All participants have known to participate in the study. Written informed consents were obtained from all participants.

3. Cases Observation

Case No. 1: 46 years old man, Single, childless, resident of Bamako, telecoms controller, with a personal history of hypertension since 2002 and asthma since childhood. He consulted for decreased libido, bilateral gynecomastia without galactorrhea since 1994-95 and erectile dysfunction. Upon weight examination: 106 Kg, T: 1.68 m, BMI: 37.55 kg/m^2, TA: 10/90mmHg, Android obesity with purple stretch marks (**Figure 1**), micropenis, (**Figure 2**) and small testicles, absence of beard. On the paraclinical level: FSH: 1.17 mIU/ml, LH: 0.628 mIU/ml, T: <0.025 ng/ml, Prolactin: 13 ng/ml (normal: 3 - 25), Cortisol 8 h post minute brake test: 472 nmol/l (Negative Test), Karyotype: 47, XXY/46, XY. Testicular ultrasound found two small testicles at the level of the bursa and the presence of a left adrenal adenoma on abdominal ultrasound. Diagnosis: Klinefelter syndrome (SK) likely associated with cushing syndrome.

Case No. 2: Adolescent girl 14 years old, third child in a family of 5 children, living in Sikasso consulted for stunted growth and puberty. Upon examination, stunting at (−3DS), Tanner 1; dysmorphic syndrome with widening of the base of the neck, a thorax with anterior convexity. On the paraclinical level: FSH: 117.6 mIU/ml, LH: 28 mui/l, E2 < 5 pg/ml, TSH: 2.8 iUI/ml; FT4: 14.89 pmol/l (normal: 9 - 20), Fasting blood sugar: 0.79 g/l. Bone age estimated at 9 years according to the Greulich and Pyle method. Unbalanced female karyotype with the presence in all cells examined for a normal X chromosome and an iso chromosome Xq, in favor of Turner's syndrome. Diagnosis: Turner's syndrome mosaic (ST).

Case No. 3: 23 years old woman, married with no children living in Kayes, pubarche between the ages of 14 and 15, consulted for primary amenorrhea, postural delay and dyspareunia. On examination, weight: 52 kg, height: 1.67 m, BMI: 18, 70 kg/m^2, hoarse voice, (P2, S2) (**Figure 3**), presence of inguinal gonads, blind vagina, 1.5 cm deep (**Figure 4**). On the paraclinical level, LH: 37.5 IU/ml, FSH: 52.2 IU/l, T: 2.1 ng/ml, karyotype 46, XY. Absence of internal genital organs during pelvic ultrasound. Diagnosis: complete androgen insensitivity syndrome.

Case No. 4: 20-years old woman, residing in Kayes, engaged, with no particular history, consulted for primary amenorrhea and weight-loss delay. On clinical examination: weight: 36 kg, Height: 1.43 m, BMI: 17.6 kg/m^2, dysmorphic syndrome (**Figure 5**), Puberty S1, P2 (**Figure 6**). Paraclinically FSH: 91.02 mIU/ml, LH: 9.51 mUI/ml, E2: 9 pg/ml, karyotype 45, X. Abdominopelvic ultrasound is in favor of internal genital organs of infantile type. Diagnosis mentioned: Turner's syndrome (ST). Treatment: Hormone replacement therapy.

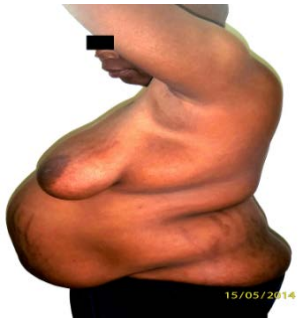

Figure 1. Case No. 1 with Gynecomastia, Android obesity and purple stretch marks - Lateral view.

Figure 2. Patient No. 1 with minimal hair growth and micropenis - Front view of EMBs.

Figure 3. Patient No. 3 with ambiguous phenotype Front view.

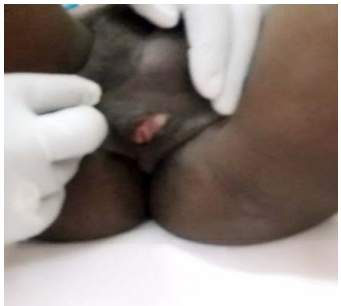

Figure 4. Patient No. 3 with terminal vagina - Front view of EMBs.

Figure 5. Patient No. 4 with Dysmorphic Syndrome - Front View.

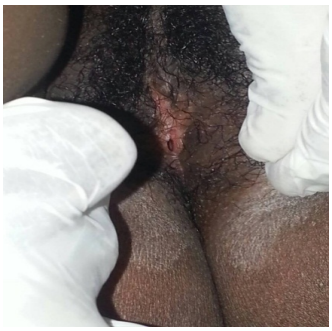

Figure 6. Patient No. 4 with small vaginal opening - Front view of EMBs.

Case No. 5: Adolescent 15 years old, residing in Ségou, seen in consultation for active bilateral gynecomastia (**Figure 7**) from the age of 12 without galactorrhea. On examination, Weight: 55 kg, Height: 169 cm, BMI: 19.26 kg/m^2, testicles measuring 3 ml on the left and 2 ml on the right, 6.3 cm penis at rest, penoscrotal hypospadias (**Figure 8**), pubic hair P4. On the paraclinical level, FSH: 22.2 IU/l, LH: 16.4 IU/l, T: 0.4 ng/ml, PRL: 11.1 µg/l, AMH: 1.3 ng/ml. Karyotype 46, XX SRY negative. Ultrasound: right testis 22 × 15 × 11 mm, carrying a 0.2 ml cyst and left 17 × 11 × 10 mm with the presence of a Müllerian derivative measuring 19 × 10 mm. Diagnosis used: Male 46, XX SRY negative.

Case No. 6: 17 years old girl, residing in Ségou, consulted for pubertal delay and primary amenorrhea. On general examination: weight: 54 kg, Height: 1.75 m, BMI: 17.53 kg/m^2, S1, P3. Gynecological examination, absence of the labia minora, presence of two masses in the pelvis, short vagina. On the para-clinical level: FSH: 69.62 mIU/ml, LH: 67.97 mIU/ml, E2: 26.39 pg/ml, T: 7.79 ng/ml. On abdominopelvic ultrasound, the uterus not seen, gonads visualized in inguinal measuring 33 × 23 × 11mm on the right and 30 × 22 × 13 mm on the left, no prostate. Karyotype 46, XY. Diagnosis: Complete androgen insensitivity syndrome.

Case No. 7: 17-years-old girl living in Bamako, with no particular history, consulted for absence of secondary sexual characteristics and primary amenorr-

hea. On general examination: Weight: 36 kg, Height: 1.32 m, BMI: 20 kg/m^2, absence of breast development, little hair present on the pubis (Figure 9), S1, P3, normal gynecological examination. LH: 15.15 IU/ml, FSH: 54.05 IU/l, E2: 35.08 pg/ml T < 0.025 ng/ml, TSH 7.5 micro IU/L, GAJ 18.77 mmol/l, HbA1c 8%, PRL: 20 ng/ml, karyotype: 46, X, del (X) 5q22). Uterine hypoplasia on pelvic ultrasound. Diagnosis: Turner's syndrome (ST). Treatment: Insulin, L-T4 75 µg/day, Hormone replacement therapy.

Figure 7. Patient No. 5 with bilateral micropenis gynecomastia - Front view.

Figure 8. Patient No. 5 with Hypospadias - Posterior view of the penis.

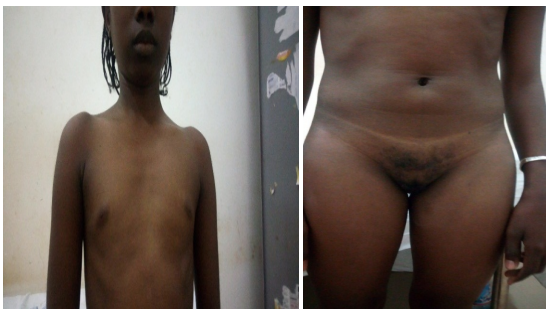

Figure 9. Patient No. 7 with puberty - Front view.

Case No. 8: 28-years-old man of Chadian origin, military, married without children, on a UN mission in Mali, evacuated from Tessalit for bilateral progressive gynecomastia for 6 years, erectile dysfunction, reduced libido. On examination: weight 65 kg, height: 1.71 m, BMI: 22 kg/m^2 slender appearance, dysmorphic syndrome with a cyphotic thorax, testicular hypotrophy, some pilosities in the armpits and pubis (P2). On the para-clinical level: FSH 44.49 mIU/ml, LH 29.37 mIU/ml, total T 1.86 ng/ml, AFP: 1.61 IU/ml, PRL 168.5 IU/ml, Spermocgram: azoospermia, hypospermia. Karyotype 47, XXY. On ultrasound, testicular atrophy of 18 × 7 × 13 on the right and 17 × 9 × 17 mm on the left. Diagnosis: Klinefelter syndrome (SK). Treatment: Testosterone enantate (Androtardy) 250 mg.

Case No. 9: 18 years old patient, student, coming from Koulikoro, declared male at birth, only boy in the family of 6, with no history. Consulted for hypogonadism with hypospadias and gynecomastia. On clinical examination, good general condition, left testicle not palpable, micropenis with hypospadias, gynecomastia. Pelvic ultrasound shows Müllerian derivatives, right ovarian follicular macro dystrophy and the right testicle in place, but the left testicle and left ovary are not visible. FSH: 17.6 mIU/ml, LH: 8 mIUi/ml, E2: <5 pg/ml, T 0.4 ng/ml, Prolactinaemia = 25.4 ng/ml N (3 - 20 ng/ml). The blood karyotype shows a chromosomal formula at 46, XX. Diagnosis: DSD ovotesticulaire 46, XX very likely. The patient having expressed the wish to be a boy, a wish supported by his family after the pre-anesthetic consultation, the father refused the intervention. The patient was not followed-up.

4. Results

Patients are represented in Table 1 (clinic, gender, Echo, FSH …, diagnosis).

Table 1. Distribution of patients according to their phenotype, hormonal profile and karyotype.

Patients		Distribution of patients according to phenotype, hormonal profile and karyotype						
N°	Phenotype	FSH	LH	TSH	Testostérone	Estradiol	F.B.S	Karyotype
1	Male	1.17	0.63	-	<0.025	-	-	47, XXY
2	Female	117.6	280	2.80	0.67	5	0.79	46X et Xq
3	Female	52	37	-	2.70	0,5	0.94	46XY
4	Female	91.02	9.51	-	0.43	9	1.17	46X0
5	Ambiguous	22.2	16.40	-	0.40	11.1	0.97	46 XX, SRY (-)
6	Female	69.04	67.97	-	4.79	26.39	-	46XY
7	Female	54.04	15.1	7.50	<0.025	25.08	3.37	46X dél(X)5q22
8	Male	44.9	29.37	-	1.86	4	-	47XXY
9	Ambiguous	17.6	8	-	0.4	5	0.82	46XX
Norms		**1.7 - 12.5**	**1.1 - 7**	**0.25 - 5**	**2.5 - 10**	**5.0 - 27**	**70 - 1.10**	
Units		**mUI/ml**	**mUI/ml**	**µUI/L**	**ng/ml**	**µg/l**	**g/l**	

5. Comments and Discussions

The mean age of diagnosis of GBV was 14 years, which is in adolescence, whereas Joel Hutcheson and Howard M Snyder suggest that the diagnosis should most often be made at birth [2]. In our case series, Turner syndrome (TS) is the most common diagnosis (3/9) [3].

The observed pubertal and growth retardation is consistent with the observations reported by Assié G *et al.* [4] and is thought to be due to premature ovarian failure and bone damage. The type 2 diabetes association reported in one patient is known: ST is associated with an increased risk of type 2 diabetes and is estimated to be 3 to 4 times more common in women with ST than in the population according to Bakalov V. K. *et al.* [5]. It is thought to be due to a decrease in insulin secretion in response to an increase in blood glucose levels. The hypothesis put forward to explain the mechanism is based on the haploinsufficiency of genes in the PAR 1 region [5]. The occurrence of dysthyroidism in ST is also known: the risk is more high as the karyotype presents an isochromosome 46, Xi(Xq) as reported according to lsheikh M. *et al.* [6].

2 patients were carriers of klinefelter syndrome (SK), the most common chromosomal abnormality in males, with an incidence of 1/400 to 600 male births according to Bojesen. A *et al.* [7]. Nos patients avaient tous un caryotype 47, XXY. The clinical diagnosis consists of palpation of the testicles in adults (5 of our patients had a testicular volume of less than 5.5 ml on ultrasound) [8]. The classic hormonal profile is that of hypergonadotropic hypogonadism, one of our patients presented hypogonadotropic hypogonadism by braking of the gonadotropins by cushing syndrome. SK is found in 11% of azoosperm patients and in 4% of infertile men according to Véronique K, *et al.* [9], which was confirmed in our 2 patients. Infertility during GBV remains a major problem. ST patients must resort to egg donation according to Chakhtoura Z. and Touraine P. [10] and SK patients to testicular biopsy or sperm donation, techniques which are not yet practiced in Mali.

Two patients presented with a 46, XX karyotype (a 46, XX male SRY negative and an ovotesticular DSD). Males 46, XX SRY negative are rare, the incidence varies from 1 in 9000 or 2 in 20,000 births according to Abusheikha N *et al.* [11]. As described in the literature, most 46, XX male patients with atypical genitals are SRY negative according to Falth. Y Dorsey *et al.* [12] and Jimenex AL *et al.* [13]. The SRY gene is located in chromosome Y and encodes a high mobility group domain (HMG) in DNA, which regulates testicular differentiation [14] [15]. Some phenotypic similarities between males 46, XX and ovotesticular DSDs 46, XX are reported [16]. The phenotypic variability between males 46, XX and ovotesticular DSDs 46, XX, cannot be explained solely by the presence or absence of SRY, other genes such as SOX9, DAX-1, WT1 WNT4, FGF9 and RSPO1 are involved in the gonadal differentiation process [17].

The diagnosis of complete androgen insensitivity syndrome (CAIS) was mentioned in 2 of our patients, with a normal gonadotropic axis, a female phenotype

with female genital organs and a male karyotype (karyotype 46, XY) [18]. CAIS is secondary to mutations in the RA gene [19]. The RA gene invalidation models have been an excellent model to understand the regulation of male sexual differentiation by androgens [20]. They are associated with a mutation in the RA gene in 90% to 95%, while molecular confirmation in the context of PAIS is found only in 15% to 20% of cases [21]. In the case of somatic mutations, the patient has 2 cell populations, one carrying the mutation, the other normal [22]. When none of these anomalies are found, prenatal contamination by environmental endocrine pollutants could be discussed [23] [24]. The management of CAIS covers both psychological support and the question of the choice of sexual orientation, the risk of degeneration and, therefore, the need or not for a gonadectomy, hormone replacement therapy, treatment of gynecomastia in the event of PAIS and family genetic counseling [18].

6. Conclusion

The precise diagnosis of variations in genital development remains complicated in Mali, due to the inadequacy of the technical platform. Diagnosis must be made early to allow normal growth, puberty and satisfactory fertility. Funding medical treatments associated with plastic surgery could give good results. In a society where the inheritance is often based on gender, it would be necessary to regulate the law, the constitution for people with GBV, in order to assert their civil rights.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Vorona, E., Zitzmann, M., Gromoll, J., *et al.* (2007) Clinical, Endocrinological, and Epigenetic Features of the 46, XX Male Syndrome, Compared with 47, XXY Klinefelter Patients. *The Journal of Clinical Endocrinology et Métabolism*, **92**, 3458-3465. https://doi.org/10.1210/jc.2007-0447

[2] Hutcheson, J., Sneyder, H.M., *et al.* (2019) Ambiguous Genital and Intersexuality; Com/PED/Topic 1492; HTM (15/10/2019).

[3] Akbas, E., Altintas, Z.M., *et al.* (2015) Karyotype and Variables in Turner Syndrome: A Case. *International Journal of Scientific Study*, **3**, 171-175.

[4] Assie, G., Rosenberg, D., Clauser, E., *et al.* (2004) Biochimie des hormones et leurs mecanismes d'action: Recepteurs membranaires. EMC—Endocrinologie-Nutrition, Article 10-001-C-10, 1-22. https://doi.org/10.1016/S1155-1941(04)25922-4

[5] Bakalov, V.K., Cheng, C., Zhou, J., *et al.* (2009) X-Chromosome Gene Dosage and the Risk of Diabetes in Turner Syndrome. *The Journal of Clinical Endocrinology & Metabolism*, **94**, 3289-3296. https://doi.org/10.1210/jc.2009-0384

[6] lsheikh, M., Dunger, D.B., *et al.* (2002) Turner's Syndrome in Adulthood. *Endocrine Reviews*, **23**, 120-140. https://doi.org/10.1210/edrv.23.1.0457

[7] Bojesen, A., Juul, S., Gravholt, C.H., *et al.* (2003) Prenatal and Postnatal Prevalence

of Klinefelter Syndrome: A National Registry Study. *The Journal of Clinical Endocrinology & Metabolism*, **88**, 622-626. https://doi.org/10.1210/jc.2002-021491

[8] Lanfranco, F., Kamischke, A., *et al.* (2004) Klinefelter's Syndrome. *The Lancet*, **364**, 273. https://doi.org/10.1016/S0140-6736(04)16678-6

[9] Véronique, K., *et al.* (2014) Le syndrome de klinefelter à l'âge pédiatrique et l'âge adulte. *MCED*, **68**, 48-53.

[10] Chakhtoura, Z. and Touraine, P. (2013) Fertilite chez les femmes ayant un syndrome de Turner. *La Presse Médicale*, **42**, 1508-1512. https://doi.org/10.1016/j.lpm.2013.03.016

[11] Abusheikha, N., Lass, A., *et al.* (2001) XX Males without SRY Gene and with Infertility: Case Report. *Human Reproduction*, **16**, 717-718. https://doi.org/10.1093/humrep/16.4.717

[12] Falth, Y., Dorsey, *et al.* (2009) 46xx, sry-Négative à propos de 2 cas. *Pédiatrie Urology*, **73**, 529-531. https://doi.org/10.1016/j.urology.2008.09.050

[13] Jimenex, A.L., Kofman-Alfaro, S., *et al.* (2000) Partially Deleted SRY Gene Confined to Testicular Tissue in a 46, XX True Hermaphrodite without SRY in Leukocytic DNA. *American Journal of Medical Genetics*, **93**, 417-420. https://doi.org/10.1002/1096-8628(20000828)93:5<417::AID-AJMG13>3.0.CO;2-S

[14] Jiang, T., Hou, C.C., She, Z.Y. and Yang, W.X. (2013) The SOX Gene Family: Function and Regulation in Testis Determination and Male Fertility Maintenance. *Molecular Biology Reports*, **40**, 2187-2194. https://doi.org/10.1007/s11033-012-2279-3

[15] Zhao, L. and Koopman, P. (2012) SRY Protein Function in Sex Determination: Thinking outside the Box. *Chromosome Research*, **20**, 153-162. https://doi.org/10.1007/s10577-011-9256-x

[16] Wu, Q.-Y., *et al.* (2014) Clinical, Molecular and Cytogenetic Analysis of 46, XX Testicular Disorder of Sex Development with SRY-Positive. *BMC Urology*, **14**, 70. https://doi.org/10.1186/1471-2490-14-70

[17] Ergun-Longmire, B., Vinci, G., *et al.* (2005) Clinical, Hormonal and Cytogenetic Evaluation of 46, XX Males and Review of the Literature. *The Journal of Clinical Endocrinology & Metabolism*, **18**, 739-748. https://doi.org/10.1515/JPEM.2005.18.8.739

[18] Mongan, N.P., Tadokoro-Cuccaro, R., Bunch, T. and Hughes, I.A. (2015) Androgen Insensitivity Syndrome. *Best Practice & Research Clinical Endocrinology & Metabolism*, **29**, 569-580. https://doi.org/10.1016/j.beem.2015.04.005

[19] Françoise, P., Pascal, P., *et al.* (2016) Syndrome d'Insensibilité aux androgènes. *Correspondances en Métabolismes Hormones Diabètes et Nutrition*, **20**, 28-46.

[20] Zhou, X. (2010) Roles of Androgen Receptor in Male and Female Reproduction: Lessons from Global and Cell-Specific Androgen Receptor Knockout (ARKO) Mice. *Journal of Andrology*, **31**, 235-243. https://doi.org/10.2164/jandrol.109.009266

[21] Sultan, C., Philibert, P., Gaspari, L., *et al.* (2014) Androgen Insensitivity Syndrome. In: New, M.I., Ed., *Genetic Steroid Disorders*, Elsevier, San Diego, 225-237. https://doi.org/10.1016/B978-0-12-416006-4.00016-8

[22] Kohler, B., Lumbroso, S., Leger, J., *et al.* (2005) Androgen Insensitivity Syndrome: Somatic Mosaicism of the Androgen Receptor in Seven Families and Consequences for Sex Assignment and Genetic Counseling. *The Journal of Clinical Endocrinology & Metabolism*, **90**, 106-111. https://doi.org/10.1210/jc.2004-0462

[23] Gaspari, L., Paris, F., Philibert, P., *et al.* (2011) "Idiopathic" Partial Androgen Insen-

sitivity Syndrome in 28 Newborn and Infant Males: Impact of Prenatal Exposure to Environmental Endocrine Disruptor Chemicals? *European Journal of Endocrinology*, **165**, 579-587. https://doi.org/10.1530/EJE-11-0580

[24] Gaspari, L., Sampaio, D.R., Paris, F., *et al.* (2012) High Prevalence of Micropenis in 2710 Male Newborns from an Intensive-Use Pesticide Area of Northeastern Brazil. *International Journal of Andrology*, **35**, 253-264. https://doi.org/10.1111/j.1365-2605.2011.01241.x