HYPOGONADOTROPIC HYPOGONADISM – CLINICAL SPECTRUM: FROM SPORADIC TO FAMILIAR FORMS

ANA SAAVEDRA[1,2,3], ELISABETE RODRIGUES[1,2,3], MANUEL LEMOS[4], DAVIDE CARVALHO[1,2,3]

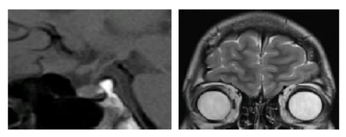
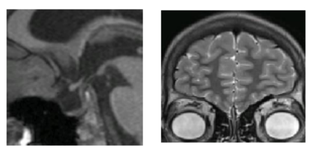
1-Department of Endocrinology Diabetes and Metabolism, Centro Hospitalar de São João, Porto - Portugal; 2-Faculty of Medicine, University of Porto, Portugal; 3-Instituto de Investigação e Inovação em Saúde, University of Porto, Portugal; 4-Health Sciences Research Centre, Faculty of Health Sciences, University of Beira Interior, Covilhã – Portugal

TOPIC: MALE HYPOGONADISM

INTRODUCTION

Congenital hypogonadotropic hypogonadism (CHH) is a rare disorder. It can be sporadic or familial and is divided into anosmic hypogonadotropic hypogonadism (Kallmann syndrome - KS) and congenital normosmic isolated hypogonadotropic hypogonadism (idiopathic hypogonadotropic hypogonadism - IHH). A growing number of genes are involved in its etiology, suggesting the heterogeneity and complexity of this condition.

CASE REPORTS

	PATIENT 1	PATIENT 2	PATIENT 3	PATIENT 4	PATIENT 5	PATIENT 6
	Kallmann Syndrome			Normosmic isolated hypogonadtropic hypogonadism		
				Familial		Sporadic (Acquired?)
SEX	Male	Male	Male	Male	Female	Male
AGE AT DIAGNOSIS	18y	18y	13y	22y	18y	28y
CLINICAL MANIFESTATIONS	**Delayed Puberty** • Sparse body hair • Small testis (R 9x10x11mm, L 10x11x12mm at ultrassonography) • Small penis (45mm) **Cryptorchidism** (orchidopexy at 5 years old).	**Delayed Puberty** • Sparse body hair • Small testis (R13mm, L12mm at ultrassonography) • Small penis for age **Gynecomastia** Other medical conditions†	**Delayed Puberty** • Sparse body hair • Small testis (R 12x5x11mm, L 15x7x9mm at ultrassonography) • Small penis for age **Cryptorchidism** (right orchidopexy in 2008)	**Delayed Puberty** • Sparse body hair • Small testis (R=L 5mL) • Penis: 70 mm	**Primary amenorrhea** → **Patient 4 Sister**	**Gynecomastia** • Since 14 years old (stable) • No other symptoms
SMELL	Anosmia	Hyposmia	Anosmia	Normal	Normal	Normal
LAB TESTS	• **Total Testosterone** 0.20 (2.8-8.0) ng/mL • **FSH** 0,80 (1,5-12,4) µUI/m • **LH** <0,10 (1,7-8,6) µUI/mL • **LHRH stimulation test** FSH (mUI/mL): 0' 0.73; Peak 3.44 LH (mUI/mL): 0' <0.10; Peak 2.0	• **Total Testosterone** 0.30 (2.8-8.0 ng/mL) • **FSH** 0,32 (1,5-12,4) µUI/mL • **LH** <0,10 (1,7-8,6) µUI/mL	• **Total Testosterone** 0.14 (2.8-8.0) ng/mL • **FSH** 0,94 (1,5-12,4)µUI/mL • **LH** <0,10 (1,7-8,6) µUI/mL • **LHRH stimulation test** FSH (mUI/mL): 0' 0.23; Peak 0,96 LH (mUI/mL): 0' <0.10; Peak 0,69	• **Total Testosterone** 0.33 (2.8-8.0) ng/mL • **FSH** 2.35 (2.5-10.2) mUI/mL • **LH** <0,10 (1,9-2.5) mUI/mL • **LHRH stimulation test** FSH (mUI/mL): 0' 2.81; Peak 8.2 LH (mUI/mL): 0' 1.06; Peak 18,66	• **Estradiol** 15 (11-69) pg/mL • **FSH** 2.2 (2.5-10.2) mUI/mL • **LH** <0,9 (1,9-2.5) mUI/mL • **LHRH stimulation test** FSH (mUI/mL): 0' 3.81; Peak 8,84 LH (mUI/mL): 0' 1,41; Peak 18.34	• **Total Testosterone** 1.83 (2.8-8.0) ng/mL • **FSH** 3.02 (1,5-12,4) µUI/m • **LH** 2.54 (1,7-8,6) µUI/mL • **LHRH stimulation test** FSH (mUI/mL): 0' 3.30; Peak 4.56 LH (mUI/mL): 0' 4.06; Peak 12.94 • **Human chorionic gonadotrophin stimulation test:** normal
CEREBRAL CT/MRI	**MRI:** Absent olfactory bulbs 	**CT:** vermis hypoplasia and enlarged sixth ventricle	**MRI:** Absent olfactory bulbs 	**MRI:** Normal	**MRI:** Normal	**MRI:** does not exclude pituitary microadenoma 
GENETIC TEST	Negative*	Negative*	Negative*	*GNRHR* gene mutations: c317A>G8 (exon 1) and c.937_947delTTTTTAAACCC(exon 3)		Negative*
TREATMENT	**Testosterone Enanthate** (250mg i.m. monthly)	**Testosterone Enanthate** (250mg i.m. 3 in 3 weeks)	**Testosterone Enanthate** (250mg i.m. 3 in 3 weeks)	**Testosterone Enanthate** (250mg i.m. monthly)	**Estradiol Valerate + Norgestrel** (2mg/0,5mg)	**Testosterone Enanthate** (250mg i.m. monthly)
FOLLOW-UP	**Improvement of sexual characters** (6-12 months after starting treatment)	**Improvement of sexual characters**	**Complete virilization**	**Patient had one child during treatment with testosterone** (HH reversal)	**Referenced for infertility consultation:** planning pregnancy	**↑ muscle strength** **Family History of Breast Cancer** • Genetic screening: positive‡ • Prophylactic bilateral mastectomy (histology: no malignancy)

† Other medical conditions: bilateral deafness, congenital cardiomyopathy, cognitive impairment, thyroid papillary carcinoma.
*Genetic test performed for *KAL1, FGFR1* and *GNRHR* genes.
‡Mutation carrier in heterozygosity of *BRCA2* gene mutation: c4808delA (p.Asn1603ThrfsTerm14) in exon 11.

CONCLUSION

Although the cases presented share the main manifestations of CHH, each one has specific characteristics demonstrating the heterogeneity of this condition. They also highlight how diagnosis can be challenging, sometimes delayed to adult age, because distinction from constitutional delay of puberty may be difficult.

REFERENCES: 1 – Shin SJ et al. Clinical, endocrinological, and molecular characterization of Kallmann syndrome and normosmic idiopathic hypogonadotropic hypogonadism: a single center experience. Ann Pediatr Endocrinol Metab 2015; 20:27-33. 2 – Silveira L, Latronico A. Approach to the patient with hypogonadotropic hypogonadism. J Clin Endocrinol Metab, 2013; 98(5):1781-1788.