MRI FINDINGS IN PATIENTS WITH HYPOGONADOTROPHIC HYPOGONADISM THAT ARE CHARACTERISTICS OF KALLMANN SYNDROME

Ali Hussein Albayati[1*], Nihad Abdallah Selman[1], Zaid Hadi Khadum[2]

[1.] College of medicine, University of Babylon, Iraq

[2.] AL-Hilla teaching hospital, Hilla, Iraq

***Corresponding author E-mail:ali75diabetologist@yahoo.com** (Albayati)

ABSTRACT

One of the congenital disorders that is characterized by reduced or even absent sense of smell, hyposmia or anosmia, is Kallmann syndrome. Actually, the principal problem is hypogonadism since this congenital disorder is characterized in addition to smell abnormality by hypogonadotrophic hypogonadism. In addition to hormonal assays, imaging techniques and mainly MRI plays an important role in establishing the diagnosis. In this Iraqi study, 20 patients with hypogonadotrophic hypogonadism have been examined by MRI in order to identify features that are caharcetristic of Kallmann syndrome contrasted to idiopathic hypogonadotrophic hypogonadism. The current study was carried out in the radiology unit at AL-Hilla Teaching Hospital, Babylon province, Iraq. The study was carried out in cooperation with urology unit. The study included a series of 20 patients who were referred by urology department for the assessment of cause of hypogonadotrophic hypogonadism following initial suggestion based on hormonal levels, FSH, LH and testosterone. The age range of those patients was form 20 to 27 years. The MRI imaging included coronal, sagital and axial T1 and T2 weighted images. The thickness of images was 3 mm and the interslice gap was 0.3 mm. Performance of MRI imaging was carried out using 1.5 T GE system. According to MRI examination, there were 5 patients with absent olfactory bulb accounting for 25 % and 3 with absent olfactory sulcus accounting for 15 %, as shown in figure 1. Twelve patients had no detectable MRI abnormality and therefore were considered to have idiopathic hypogonadotrphic hypogonadism; where those 8 patients with abnormal MRI findings were considered to have Kallman syndrome. Absent olfactory bulb was significantly asscoaited with anosmia. The principal findings in MRI that differentiate Kallman syndrome from idiopathic hypogonadotrophic hypogonadism are olfactory bulb and sulcus abnormalities that are best visualized using coronal MRI scanning.

Keywords: MRI, hypogonadotrophic hypogonadism, Kallmann syndrome

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INTRODUCTION

One of the congenital disorders that is characterized by reduced or even absent sense of smell, hyposmia or anosmia, is Kallmann syndrome[1]. Actually, the principal problem is hypogonadism since this congenital disorder is characterized in addition to smell abnormality by hypogonadotrophic hypogonadism[2]. Embryologically speaking, a subset of neuronal cells should migrate from olfactory region to reach the hypothalamus where they differentiate to take the function of secretion of gonadotrpin releasing hormone (GnRH). Due to failure of migration and or differentiation of such neuronal subset, the disease happens and manifests in the form of gonadal and olfactory dysfunction[3].When there is deficiency in GnRH, there will be inadequate amount of sex steroid leading to underdevelopment of secondary sexual characteristics and lack of sexual maturity[4, 5]. These principally included failure of menstruation in females and testicular underdevelopment in males; in addition to underdeveloped mammary glands and albescence of pubic hair. Some male patients may suffer undescended testes since birth or small size penis. These manifestations are the mirror image to low levels of testosterone in males and estrogen and progesterone in females due to low levels of both follicle stimulating hormone (FSH) and luteinizing hormone (LH) which are under direct stimulation by GnRH[4, 5].

The diagnosis of the condition is usually made when facing a child who failed to enter puberty[6]. The condition was initially recognized in 1856 by Maestre de San Juan; however, Franz Josef Kallmann was the first to describe the hereditary nature of the disease in 1944 (3). The disease is rare and is seen in one per 48,000 subjects[7]. Hypogonadotrophic hypogonadism and anosmia or hyposmia are the principal defining features of the disease; however, in a number of patients there are in addition other forms of congenital abnormalities such as unilateral renal agenesis, cleft lip or palate, hypodontia and color blindness [8-10].

In addition to hormonal assays, imaging techniques and mainly MRI plays an important role in establishing the diagnosis. The MRI findings have been previously described in a number of studies and they are indeed very characteristic[2]. In this Iraqi study, 20 patients with hypogonadotrophic hypogonadism have been examined by MRI and 8 of them were proved to have olfactory bulb and sulcus abnormalities.

MATERIAL AND METHODS

The current study was carried out in the radiology unit at AL-Hilla Teaching Hospital, Babylon province, Iraq. The study was carried out in cooperation with urology unit. The study included a series of 20 patients who were referred by urology department for the assessment of cause of hypogonadotrophic hypogonadism following initial suggestion based on hormonal levels, FSH, LH and testosterone. The age range of those patients was form 20 to 27 years.

The MRI imaging included coronal, sagital and axial T1 and T2 weighted images. The thickness of images was 3 mm and the interslice gap was 0.3 mm. Performance of MRI imaging was carried out using 1.5 T GE system.

Variables included in the present study included age, olfactory manifestation such as anosmia and hyposmia, other congenital abnormalities, family history of hypogonadotrophic hypogonadism, family history of olfactory abnormalities, results of last hormonal assays including FSH, LH and testosterone. The main outcome was the MRI appearance of olfactory bulb and sulcus.

The study was approved by the institutional approval committee and verbal consent was obtained from all patients participating in the current study following full illustration of the aim and the procedures of the study. Data were then transformed into an SPSS, statistical package for social sciences, software (version 23). Categorical data were expressed as number and percentage, whereas, numeric data were expressed as mean, standard deviation and range. T-test was used to assess mean difference between two groups; whereas, chi-square test was used to assess differences in proportions. The level of significance was considered at $P \leq 0.05$.

RESULTS

The current study was based on the inclusion of 20 patients with clinical and biochemical evidences of hypogonadotrophic hypogonadism; their age ranged from 20 to 27 years and averaged 22.50 ±2.48 years. The clinical characteristics of enrolled patients are shown in table 1. All patients were males. Mean serum FSH was 0.95 ±0.26 IU/L and the range was 0.4 - 1.4 IU/l; all patients had serum FSH values below normal (< 1.5 IU/L). In addition, Mean serum LH was 0.94 ±0.24 IU/L and the range was 0.6 - 1.3 IU/l; all patients had serum LH values below normal (< 1.5 IU/L). Moreover, Mean serum testosterone was 10.65 ± 3.39 ng/dl and the range was 5 - 16 IU/l; all patients had serum testosterone values below normal (<20ng/dl), as shown in table (1).

Olfactory abnormalities were observed in the group of patients subjected to this study including anosmia in 4 (20 %) and hyposmia in 7 (35 %), (table 1).

According to MRI examination, there were 5 patients with absent olfactory bulb accounting for 25 % and 3 with absent olfactory sulcus accounting for 15 %, as shown in figure (1). Twelve patients had no detectable MRI abnormality and therefore were considered to have idiopathic hypogonadotrphic hypogonadism; where those 8 patients with abnormal MRI findings were considered to have Kallman syndrome. Paients, thus were categorized into tow group, idiopathic hypogonadotrphic hypogonadism (n = 12) and Kallmann syndrome (n = 8), for purpose of comparison, as shown in table (2).

There was no significant difference in mean age, serum FSH, serum LH and serum testosterone between the two groups. Anosmia was limited to patients with Kallman syndrome, 4 (20 %) versus 0 (0.0 %), respectively (P = 0.014). Hyposmia was more frequent in Kallman syndrome; howver, it was also seen in patients with idiopathic hypogonadotrphic hypogonadism, (table 2).

Table 1: Clinical characteristics of patients with hypogonadotrophic hypogonadism

Characteristic	Value
Age (years)	
Range	20 - 27
Mean ±SD	22.50 ±2.48
Gender	
Male, *n* (%)	20 (100 %)
FSH (IU/L)	
Range	0.4 - 1.4
Mean ±SD	0.95 ±0.26
< 1.5 IU /L, *n* (%)	20 (100 %)
LH (IU/L)	
Range	0.6 - 1.3
Mean ±SD	0.94 ±0.24
< 1.5 IU /L, *n* (%)	20 (100 %)
Testosterone	
Range	5 - 16
Mean ±SD	10.65 ± 3.39
< 20 ng /dl, *n* (%)	20 (100 %)
Anosmia, *n* (%)	4 (20 %)
Hyposmia,*n* (%)	7 (35 %)

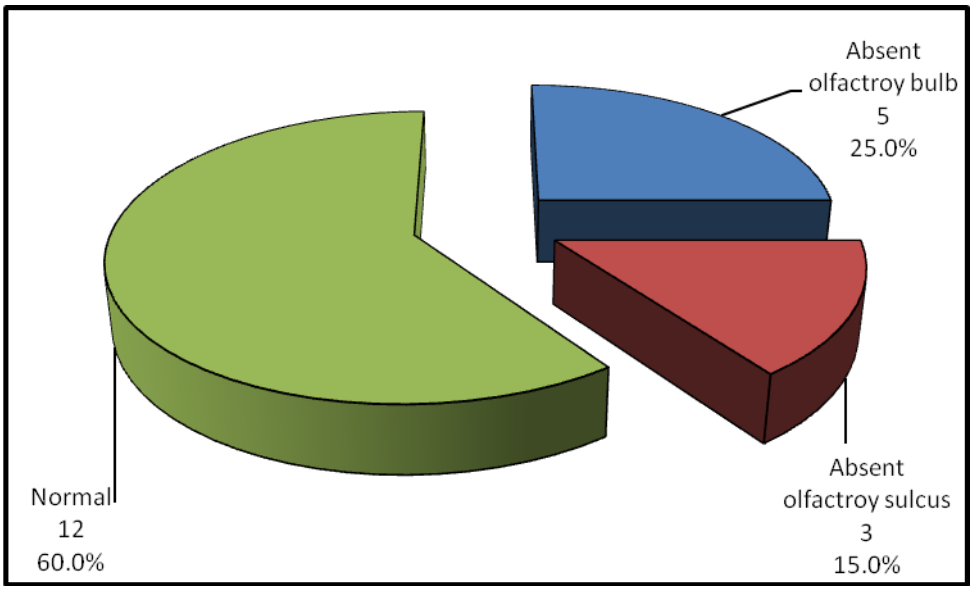

Figure 1: Pie chart showingresults of MRI examination

Table 2: Correlations of Kalmman syndrome to clinical characteristics of patients

Characteristic	Kallmann syndrome *n* = 8	Idiopathic hypogonadotrophic hypogonadism *n* = 12	*P*
Age (years), Mean ±SD	23.38 ±3.02	21.92 ±1.98	0.206 † NS
FSH (IL/L), Mean ±SD	1.00 ±0.29	0.91 ±0.25	0.463 † NS
LH (IU/L), Mean ±SD	0.85 ±0.19	0.99 ±0.26	0.211 † NS
Testosterone (ng/dl), Mean ±SD	10.75 ±2.49	10.58 ±3.99	0.918 † NS
Anosmia, *n*(%)	4 (20.0 %)	0 (0.0 %)	0.014¥ S
Hyposmia, *n*(%)	4 (20.0 %)	3 (15.0 %)	0.365 ¥ NS

n: number of cases; SD: standard error; †: independent samples t-test; ¥: Chi-square test; NS: not significant at $P \leq 0.05$; S: significant at $P \leq 0.05$

DISCUSSION

For the best of our knowledge this is one of the first Iraqi studies dealing with MRI characteristics of Kallman syndrome. We included 20 patients with clinical evidence of hypogonadotrophic hypogonadism that was supported by biochemical estimation of follicle stimulating hormone, luteinizing hormone and testosterone. The aim of the study was to do MRI examination suggesting that those patients may have evidence of Kallman syndrome based on the presence of anosmia and hyposmia in some of them. Actually, the main findings in our study were in the form of absence of either the olfactory bulb or the olfactory sulcus.

Zaghouani *et al*., assessed the MRI findings is a series of 5 patients [(2)]; they found also olfactory bulb and sulcus abnormalities which were described as hypoplastic or absent. These findings are consistent with our findings; in addition, Zaghouani et al. found correlation between anosmia and olfactory bulb absence and this fading is also in line with ours. In another study, the most frequent findings in patients with Kallman syndrome were olfactory bulb and sulcus aplasia [(11)], these are again in line with our findings. In another study, olfactory bulb and tract was absent in 17 out of 18 patients with Kallman syndrome, again in accordance with our findings [(12)]. In a further study, the olfactory bulb and tract were hypoplastic or absent [(13)], in support for our findings.

Indeed, the assessment of olfactory bulb abnormalities were difficult radiologically in the era before MRI; however, introduction of MRI more 30 years ago has made this mission more easy and fine details of olfactory bulb disorders becomes amenable for radiologic evaluation[(13, 14)].For better visualization of the

olfactory bulb, the best way is to perform coronal scanning with little interslice gap and wide matrix size. Indeed, this is the best way for visualization of olfactory tract anatomy and to make volume calculations [(2)].Other scanning planes, sagital and axial provide less sensitivity than coronal plane [(15)]. The best sequences for evaluation of olfactory bulb are the high resolution coronal fast spin echo T2 and T1 weighted images [(16)].Olfactory bulbs are usually observed as well categorized objects over the cribriform plate; whereas, olfactory sulci are usually observed between medial orbital gyrus and gyrus rectus[(2)].

In conclusion, the principal findings in MRI that differentiate Kallman syndrome from idiopathic hypogonadotrophic hypogonadism are olfactory bulb and sulcus abnormalities that are best visualized using coronal MRI scanning.

CONCLUSION

The principal findings in MRI that differentiate Kallman syndrome from idiopathic hypogonadotrophic hypogonadism are olfactory bulb and sulcus abnormalities that are best visualized using coronal MRI scanning.

ETHICAL CLEARANCE

The Research Ethical Committee at scientific research by ethical approval of both environmental and health and higher education and scientific research ministries in Iraq

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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REFERENCES

1 Stamou MI, Georgopoulos NA. Kallmann syndrome: phenotype and genotype of hypogonadotropic hypogonadism. *Metabolism*. 2018;86:124–134.

2 Zaghouani H, Slim I, Zina NB, Mallat N, Tajouri H, Kraiem C. Kallmann syndrome: MRI findings. *Indian J Endocrinol Metab*. 2013;17(Suppl 1):S142–S145.

3 Arkoncel ML, Arkoncel FR, Lantion-Ang FL. A case of Kallmann syndrome. BMJ Case Rep. 2011:2011

4 Fraietta R, Zylberstejn DS, Esteves SC. Hypogonadotropic hypogonadism revisited. *Clinics (Sao Paulo)*. 2013;68 Suppl 1(Suppl 1):81–88. doi:10.6061/clinics/2013(sup01)09

5 Kumar P, Kumar N, Thakur DS, Patidar A. Male hypogonadism: Symptoms and treatment. *J Adv Pharm Technol Res*. 2010;1(3):297–301. doi:10.4103/0110-5558.72420

6 Lenzi A, Balercia G, Bellastella A, Colao A, Fabbri A, Foresta C, et al.. Epidemiology, diagnosis, and treatment of male hypogonadotropic hypogonadism. J Endocrinol Invest. (2009) 32:934–38.

7 Laitinen EM, Vaaralahti K, Tommiska J, Eklund E, Tervaniemi M, Valanne L, Raivio T. Incidence, phenotypic features and molecular genetics of Kallmann syndrome in Finland. Orphanet J Rare Dis. 2011 Jun 17;6:41.

8 Balasubramanian R, Crowley WF.Isolated Gonadotropin-Releasing Hormone (GnRH) Deficiency. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Stephens K, Amemiya A, editors. GeneReviews® [Internet].University of Washington, Seattle; Seattle (WA): May 23, 2007.

9 Kim SH. Congenital Hypogonadotropic Hypogonadism and Kallmann Syndrome: Past, Present, and Future. Endocrinol Metab (Seoul). 2015 Dec;30(4):456-66.

10 Lima Amato LG, Latronico AC, Gontijo Silveira LF. Molecular and Genetic Aspects of Congenital Isolated Hypogonadotropic Hypogonadism. Endocrinol.Metab.Clin. North Am. 2017 Jun;46(2):283-303.

11 Koenigkam-Santos M, Santos AC, Versiani BR, Diniz PR, Junior JE, De Castro M. Quantitative magnetic resonance imaging evaluation of the olfactory system in Kallmann syndrome: correlation with a clinical smell test. Neuroendocrinology. 2011;94:209–17.

12 Vogl TJ, Stemmler J, Heye B, Schopohl J, Danek A, Bergman C, et al. Kallman syndrome versus idiopathic hypogonadotropic hypogonadism at MR imaging. Radiology. 1994;191:53–7

13 Yousem DM, Turner WJ, Li C, Snyder PJ, Doty RL. Kallmann syndrome: MR evaluation of olfactory system. AJNR Am J Neuroradiol. 1993;14:839–43.

14 Duprez TP, Rombaux P. Imaging the olfactory tract. Eur J Radiol. 2010;74:288–98.

15 De M Freitas P, Carvalho S, Ribeiro F, Marnoto D, Martins F. Neuroradiology of Kallmann's syndrome. Acta Med Port. 2001;14:123–6.

16 Munoz A, Dieguez E. A plea for proper recognition: The syndrome of Maestre de San Juan-Kallman. AJNR Am J Neuroradiol. 1997; 18:1395–6.