CASE REPORT

Functional Amenorrhea and Pituitary Microadenoma

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Abstract

Introduction: Functional hypothalamic amenorrhea is a diagnostic challenge, especially in association with structural pituitary changes. We present the case of a patient with functional amenorrhea and pituitary microadenoma, evaluated in multiple medical centres. **Case report:** A 27-year-old female was referred to our clinic for secondary amenorrhea installed 18 months prior, insomnia, polydipsia (around 4-6 l water intake/day) and polyuria. Clinical examination revealed an underweight patient, with BMI (Body Mass Index) of 17.5 kg/m², normal secondary sex characteristics, pallor of the skin and mucosa. The hormonal profile revealed normal FSH (Follicle Stimulating Hormone) levels, low LH - Luteinizing Hormone (of 0.15 U/L, normal: 1.20-12.8 U/L), estradiol (of 11.2 pg/mL, normal: 49-291 pg/mL) and progesterone (of 1.13 ng/mL, normal: 5.16-18.56 ng/mL). No pathological changes were recorded at somatotrophic, lactotropic, thyrotrophic and corticotrophic levels. The Diphereline stimulation test revealed functional integrity of the pituitary gland and ovaries. The progesterone with drawal test was negative. There were no pathological findings on biochemical workup and the water deprivation test excluded diabetes insipidus. Morphological exploration of the hypothalamic-pituitary region by contrast-enhanced MRI (Magnetic Resonance Imaging) scan revealed a left pituitary microadenoma measuring 5 mm in diameter. Adequate diet and oral contraceptive treatment were recommended. **Conclusion:** Functional hypothalamic amenorrhea (FHA) is the most common cause of neuroendocrine amenorrhea. Identifying the context and causative factors is essential for making an appropriate therapeutic decision.

Keywords: amenorrhea, polydipsia, diphereline.

Rezumat

Introducere: Amenoreea funcțională hipotalamică este o provocare diagnostică, în special în asociere cu modificările structurale ale hipofizei. Prezentăm cazul unui pacient cu amenoree funcțională și microadenom hipofizar, evaluat în mai multe centre medicale. **Prezentare de caz:** O femeie de 27 de ani a fost trimisă la clinica noastră pentru amenoree secundară instalată cu 18 luni înainte, insomnie, polidipsie (aproximativ 4-6 l aport de apă / zi) și poliurie. Examinarea clinică a evidențiat un pacient subponderal, cu IMC (indexul de masă corporală) de 17,5 kg / m², caracteristici sexuale secundare normale, paloare a pielii și mucoaselor. Profilul hormonal a evidențiat niveluri

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normale de FSH (hormon foliculostimulant), LH scăzut - hormon luteinizant (de 0,15 U / L, normal: 1,20-12,8 U / L), estradiol (de 11,2 pg / mL, normal: 49-291 pg / mL) și progesteron (de 1,13 ng / mL, normal: 5,16-18,56 ng / mL). Nu s-au înregistrat modificări patologice la niveluri somatotrope, lactotrope, tirotrope și corticotrope. Testul de stimulare cu diphereline a relevat integritatea funcțională a glandei hipofizare și a ovarelor. Testarea progesteronului a fost negativă. Nu au existat rezultate patologice privind testările biochimice și testul de deprivare a apei a exclus diabetul insipid. Explorarea morfologică a regiunii hipotalamice-hipofizare prin scanarea RMN (rezonanță magnetică nucleară) îmbunătățită prin contrast a scos la iveală un microadenom hipofizar stâng cu un diametru de 5 mm. S-au recomandat măsuri dietetice și un tratament contraceptiv oral adecvat. **Concluzie:** Amenoreea hipotalamică funcțională este cauza cea mai frecventă a amenoreei neuroendocrine. Identificarea contextului și a factorilor cauzali este esențială pentru luarea unei decizii terapeutice adecvate.

Cuvinte cheie: amenoree, polidipsie, diphereline.

INTRODUCTION

FHA is one of the most common causes of secondary amenorrhea, classified as hypogonadotropic hypogonadism due to an alteration of the pulsatile release of gonadotropin-releasing hormone (GnRH) from the hypothalamus¹⁻³. Disturbances in the hypothalamic-pituitary-ovarian axis may include a lower mean frequency of LH pulses, the complete absence of LH pulsatility, as well as a normal-appearing secretion pattern and higher mean frequency of LH pulses⁴. Consequently, production of estrogen in the ovary will be reduced. Depending on the causative factor, FHA is divided into three categories: weight loss-related, exercise-related and stress-related⁵. Secondary amenorrhea, defined as the absence of menses for 3 or more months, occurs in approximately 3-5% of adult women. According to the American Society of Reproductive Medicine, FHA is responsible for 20-35% of secondary amenorrhea cases and approximately 3% of primary amenorrhea cases⁶. Although the exact risk is unknown, patients with menstrual irregularity or secondary amenorrhea are at risk of hyperprolactinemia and pituitary adenomas. Pituitary adenomas may present during puberty in association with delayed or incomplete development of secondary sex characteristics. Primary or secondary

amenorrhea may be the most obvious clinical abnormality⁷.

CASE REPORT

A 27-year-old female without significant medical history was admitted for evaluation due to the absence of menstrual cycles for more than 18 months, insomnia, polydipsia (around 4-6 l water intake/day) and polyuria. Clinical examination revealed weight of 42 kg, height of 167 cm, BMI (Body Mass Index) of 17.5 kg/m², normal blood pressure of 110/65 mmHg, heart rate of 74bpm, normal secondary sex characteristics, pallor of the skin and mucosa. The hormonal profile showed normal FSH (Follicle Stimulating Hormone) levels, low LH - Luteinizing Hormone (of 0.15 U/L, normal: 1.20-12.8 U/L), estradiol (of 11.2 pg/mL, normal: 49-291 pg/mL) and progesterone (of 1.13 ng/mL, normal: 5.16-18.56 ng/mL). No pathological changes were recorded at somatotropic, lactotropic, thyrotropic and corticotropic levels (Table 1). Diphereline (Triptorelin) stimulation test was performed: FSH, LH and estradiol were measured after administration of 0.1 mg dipherelines ©, at baseline, 4 hours and 24 hours, respectively. Increased levels of FSH and LH 4 hours after diphereline, as well as the adequate increase of es-

Table 1. Endocrine parameters of a 27-year-old female patient diagnosed with pituitary adenoma and secondary amenorrhea

Parameter	Value	Normal	Units
TSH	1.50	0.4-4	μUI/mL
FT4	0.58	0.61-1.35	ng/dL
antiTPO	0.65	<10	U/mL
antiTG	<1.0	<4	U/mL
PRL	7.33	3.3-26	ng/mL
Progesterone	1.13	5.16-18.56	ng/mL
Morningplasmacortisol	17.2	6-23	μg/dL

TSH=Thyroid Stimulating Hormone; FT4=FreeThyroxin; ATG =anti-thyroglobulinantibodies; ATPO = anti-thyroidperoxidaseantibodies; PRL = prolactin.

Table 2. Dipherelinetestperformedon a 27-year-old womanwithsecondaryamenorrhea.

Parameter	Value 0 hours	Value 4 hours	Value 24 hours	Units
FSH	3.14	20.7	9.05	mU/mL
LH	0.15 U/L	6.76	3.20	U/L
Estadiol	11.2	19.2	38.2	pg/mL

FSH= FollicleStimulatingHormone; LH=LuteinizingHormone.

tradiol levels after 24 hours confirmed the functional integrity of the pituitary and ovaries (Table 2). Pelvic ultrasound revealed a linear endometrium of approximately 3 mm, without pathological changes in ovarian morphology. The water deprivation test, carried out over a period of 6 hours, excluded diabetes insipidus. There were no pathological findings on biochemical workup. Morphological exploration of the hypothalamic-pituitary region by contrast-enhanced MRI showed a left pituitary microadenoma measuring 5 mm in diameter. Because no withdrawal bleeding appeared after oral progesterone administration, oral contraceptive treatment was initiated. Adequate diet was also recommended.

DISCUSSIONS

Functional hypothalamic amenorrhea should be differentiated from other forms of primary or secondary amenorrhea. In this case, the discovery of a pituitary adenoma on MRI raised the suspicion of hypogonadotropic hypogonadism caused by the pituitary tumor. At first sight, the presence of a polyuro-polydipsic syndrome was an argument in favor of a possible link between the adenoma and secondary amenorrhea.

The primary approach in determining the cause of secondary amenorrhea is the assessment of gonadotropin levels and identifying hypogonadotropic hypogonadism⁸. The diphereline test is a keytool in the diagnosis of FHA, showing a positive response of gonadotropins to exogenous GnRH stimulation. This test distinguishes between hypothalamic dysfunction and primary pituitary diseases, also characterized by hypogonadism⁹.

In this case the levels of FSH, LH and estradiol before and after diphereline administration were highly suggestive for FHA. The patient's history also advocates in favor of FHA: menarche occurred spontaneously at the age of 12, she had regular menstrual cycles up until the past 18 months, amenorrhea occurred in the context of weight loss, accompanied by repeated episodes of insomnia. The polyuro-polydipsic syndrome was

also interpreted as a reaction to stress after the water restriction test excluded diabetes insipidus.

FHA should not be considered only as a symptom, such as amenorrhea. This disorder has a more profound clinical picture³⁻⁵. The final endocrine consequence of GnRH and gonadotropin pulsatile secretion impairment is profound hypoestrogenism. Hypoestrogenic status has a negative impact on different aspects of female health, not just in menopausal women but also in younger ones³⁻⁵. Normal estrogen levels and metabolic homeostasis have a major importance for the cardiovascular system, normal bone metabolism and mental health, especially in younger women¹⁰⁻¹⁴. Therefore, prolonged hypoestrogenism that occurs in young women may have critical significance in the years to come. For this reason, in our patient's case we decided to initiate oral contraceptives. At the same time, we recommended limiting water intake, avoiding stressful situations and adequate food intake in order to reach a normal BMI. Periodic monitoring of the pituitary adenoma is required.

Pituitary incidentaloma is most frequently an incidental finding without a pattern related to age¹⁵⁻¹⁷. Whether in this case it might represent a hallmark of a genetic late onset central hypogonadism is still challenging to confirm at this point.

CONCLUSION

Functional hypothalamic amenorrhea is an underestimated clinical problem. FHA patients should be carefully diagnosed and appropriately treated in order to prevent both short-term and, particularly, long-term medical consequences.

Compliance with ethics requirements: The authors declare no conflict of interest regarding this article. The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study.

References

1. Meczekalski B, Katulski K, Czyzyk A, Podfigurna-Stopa A, Maciejewska-Jeske M. Functional hypothalamic amenorrhea and its influence on women's health, *Journal of Endocrinological Investigation* 2014;37(11):1049-1056. doi:10.1007/s40618-014-0169-3.
2. Berga SL, Mortola JF, Gorton L, Suh B, Laughlin G, Pham P, Yen SS. Neuroendocrine aberrations in women with functional hypothalamic amenorrhea, *J Clin Endocrinol Metab* 1989;68:301–308.
3. Gordon MC. Functional hypothalamic amenorrhea, *N Engl J Med* 2010; 363:365–371.
4. Genazzani AD. Neuroendocrine aspects of amenorrhea related to stress, *Pediatr Endocrinol Rev* 2005; 2:661–668.
5. Meczekalski B, Podfigurna-Stopa A, Warenik-Szymankiewicz A, Genazzani AR. Functional hypothalamic amenorrhea: current view on neuroendocrine aberrations, *Gynecol Endocrinol* 2008; 24:4–11.
6. Harlow SD. Menstruation and menstrual disorders: the epidemiology of menstruation and menstrual dysfunction. In Goldman MB, Katch M (eds): *Women and Health 2000*, Academic Press, San Diego, 99–113.
7. Elwyn M Grimes. Pituitary Microadenomas: Diagnostic and Therapeutic Trends, *J Natl Med Assoc* 1984; 76(10): 997–1004.
8. De Souza MJ, Toombs RJ, Scheid JL, O'Donnell E, et al. High prevalence of subtle and severe menstrual disturbances in exercising women: confirmation using daily hormone measures, *Hum Reprod* 2009; 25:491–503.
9. Practice Committee of the American Society for Reproductive Medicine. Current evaluation of amenorrhea, *Fertil Steril* 2006; 86:S148.
10. Stanescu AMA, Grajdeanu IV, Serban B, Bratu OG, Socea B, Diaconu CC. Sexual dysfunction in patients with psoriasis. *Arch Balk Med Union* 2019; 54(2):339-344. doi.org/10.31688/ABMU 2019.54.2.19.
11. O'Donnell E, Goodman JM, Harvey PJ. Clinical review: cardiovascular consequences of ovarian disruption: a focus on functional hypothalamic amenorrhea in physically active women, *J Clin Endocrinol Metab* 2011; 96:3638–3648.
12. Misra M. What is the best strategy to combat low bone mineral density in functional hypothalamic amenorrhea? *Nat Clin Pract Endocrinol Metab* 2008; 4:542–543.
13. Giles DE, Berga SL. Cognitive and psychiatric correlates of functional hypothalamic amenorrhea: a controlled comparison, *Fertil Steril* 1993; 60:486–492.
14. Carsote M, Valea A. Insights of peak bone mass, *Acta Medica Transilvanica* 2016; 21(2):82-85.
15. Poiană C, Chiriță C, Carsote M, Hortopan D, Ioachim D, Corneci CM, Stănescu B. Adrenal and pituitary incidentalomas in a case of Cushing's syndrome. *Chirurgia (Bucur)*. 2013 Nov-Dec; 108(6):886-91.
16. Carsote M, Chirita C, Dumitrascu A, Hortopan D, Fica S, Poiana C. Pituitary incidentalomas - how often is too often? *J Med Life* 2009 Jan-Mar; 2(1):92-7.
17. Gheorghisan-Galateanu AA, Carsote M, Valea A. Incidentaloma: from general practice to specific endocrine frame. *J Pak Med Assoc* 2017 Jun; 67(6):917-922.