



Functional hypothalamic amenorrhea: case presentations and overview of literature

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Abstract

Functional hypothalamic amenorrhea is a form of chronic anovulation not due to identifiable organic causes with adverse health consequences. A thorough history is paramount in the identification of women with this disorder as it is usually associated with lifestyle factors such as stress, weight loss, and excessive exercise. In this paper, recently published clinical guidelines are reviewed and a series of cases is presented that highlights diagnostic and therapeutic challenges encountered.

Keywords Amenorrhea · Anorexia nervosa · Excessive exercise · Stress · Energy deficit · Hypercortisolemia

Introduction

Normal function of the female reproductive system is dependent on a cascade of events and hormonal actions involving the hypothalamus, pituitary, and ovary with response of the outflow tract to these hormonal changes. The system is finely regulated and both external factors, such as stress and starvation, and internal ones, such as systemic illness, can adversely affect the system, thereby compromising procreation.

The hypothalamic-pituitary-gonadal axis is quiescent during childhood and awakened at puberty. Increase in body weight, namely metabolic cues, as well as decrease in the exquisite sensitivity of the hypothalamus to sex steroid-negative feedback, leads to pulsatile release of gonadotropin-releasing hormone (GnRH) adequate to promote pituitary production of luteinizing hormone (LH); this occurs also in pulsatile fashion and initially nocturnally. This stimulates androgen secretion by theca cells of the ovarian follicular apparatus, while small amounts of progesterone are also produced. Progesterone slows down GnRH pulse generator frequency, thus allowing production of follicle-stimulating hormone

(FSH), which is also dependent on GnRH, in amounts sufficient to stimulate follicle growth and estradiol production. Ultimately, an advantaged follicle is selected and continues to grow with FSH stimulation, synergized by locally produced growth factors, leading to formation of the mature Graafian follicle. The high estradiol concentrations that are achieved and maintained in the late follicular phase promote release of a surge of LH (with smaller amounts of FSH), acting directly on the anterior pituitary. This is essential for oocyte maturation and release and corpus luteum formation, which produces progesterone in large amounts, as well as estradiol. These events have previously been summarized [1].

Meanwhile, with regard to the endometrium, it is first stimulated by estradiol and after ovulation by progesterone, preparing it for implantation. In the absence of pregnancy, the corpus luteum, which is dependent upon LH, becomes less responsive to LH over time. After 2 weeks, its hormone production ceases and the endometrium is no longer supported and is shed. Thus, menses ensue. This ovarian cycle is repeated time after time, unless it is interrupted by pregnancy or illness. It is in this context that normal function of the hypothalamic-pituitary axis is critical, the hypothalamus being very sensitive to both external and internal factors even when the pituitary and the ovary are able to function normally with appropriate stimulation [2].

The 2017 Endocrine Society Clinical Practice Guidelines on Functional Hypothalamic Amenorrhea (FHA), co-sponsored by the European Society of Endocrinology, the Pediatric Endocrine Society, and the American Society of Reproductive Medicine stress that FHA is a form of chronic anovulation, not due to

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identifiable organic causes but often associated with stress, weight loss, excessive exercise, or a combination thereof [3]. It is also underlined that FHA is a diagnosis of exclusion in which systemic and endocrinologic etiologies, including thyroid disease, pituitary disorders, adrenal hypo- and hyperfunction, ovarian failure, and hyperandrogenism, such as in polycystic ovary syndrome and vaginal and Müllerian anomalies, may be ruled out. Thus, the workup should include measurement of thyrotropin (TSH), free thyroxine, prolactin, LH, FSH, estradiol, and anti-Müllerian hormone. If there is clinical hyperandrogenism, testing should include testosterone, dehydroepiandrosterone sulfate, and also early-morning 17-hydroxyprogesterone if late-onset congenital adrenal hyperplasia is suspected. If there is a history of headaches, nausea, vomiting, or change in vision, magnetic resonance imaging (MRI) with contrast and pituitary cuts can be performed. The guidelines recommend a baseline bone mineral density test if the patient has had amenorrhea for over 6 months. In cases of primary amenorrhea, evaluation for Müllerian tract anomalies is recommended by physical exam, ultrasound, and if needed MRI. A progestin challenge, if positive, will also rule this out.

As stated, the cause of the anovulation is a functional reduction in GnRH drive resulting in reduced LH pulse frequency and LH and FSH concentrations insufficient for full folliculogenesis [3]. Neuromodulatory signals that reduce GnRH function are many and include the following: activation of the hypothalamic-pituitary-adrenal axis resulting in hypercortisolemia, nutritional deprivation with reduced leptin from loss of body fat, excessive exercise especially when more calories are expended than consumed, and external stressors and stressful attitudes. A hypoestrogenic state incurs the risk of delayed puberty and long-term health consequences, with adverse effects on bone and possibly also the cardiovascular system, as well as the possibility of infertility, fetal loss, small-for-gestational age neonates, and preterm birth [3].

The following cases illustrate variations in presentation of FHA and some of the diagnostic and therapeutic challenges encountered.

Case 1

A 17-year-old patient presented with a 21-month history of secondary amenorrhea. Her menarche was at age 14 and she had regular cycles by age 15. However, by age 16, she was amenorrheic. Her weight at age 15 was 55 kg, with a body mass index (BMI) of 21 kg/m². She was unhappy about her weight and there was also a history of family conflict. She lost 23 kg of body weight.

Examination: Weight 32 kg, she had lanugo hair and atrophic breasts.

Laboratory tests: LH <0.5 IU/L, FSH 4.1 IU/L, estradiol 144 pmol/L (39 pg/mL); her TSH prolactin and cortisol responses to ACTH were all normal. However, her T3 was low.

This case is representative of classic anorexia nervosa with distorted body image, in the context of family conflict and stress. Her lanugo hair is a feature of anorexia and her atrophic breasts relate to severe loss of fat and her hypoestrogenic state. Her low T3, together with normal TSH, is reflective of the response of the thyroid axis to starvation. Of note, FSH secretion is relatively preserved, in part as a lower-frequency GnRH pulsatility is more favorable to FSH secretion and also because FSH is also governed by intraovarian factors such as inhibin.

Case 2

A 24-year-old patient presented with a 2-year history of severe oligomenorrhea; she had had three cycles in those 2 years. Her menarche was at age 13 and she had regular cycles until age 22. She had no history of weight loss.

Examination: Weight 61.4 kg and her BMI was almost 21 kg/m²; normal examination.

Laboratory tests available at visit: LH 3.5 IU/L, FSH 4.0 IU/L, normal TSH and prolactin.

This case is of a patient with amenorrhea and normal test results. The usual reflex reaction is to inform the patient of the normal results and encourage her to take a combined hormonal contraceptive pill (COC) to establish menses. However, this approach ignores the patient's problem, which needs to be explored further. The history is paramount. The patient had been involved in an intensive exercise program in the preceding 2 years involving 3 h of running and aerobics daily. Thus, despite her history of stable weight and her measurable gonadotropins, her intensive exercise had shut down her hypothalamic-pituitary-ovarian axis sufficiently to give her amenorrhea. Menstrual irregularities are common among female runners. In a survey of 184 runners at a marathon, 32% reported menstrual irregularity; both younger age and nulliparity were associated with menstrual irregularity [4].

Case 3

A 15-year-old patient presented with irregular menses. Her menarche was at age 9 with irregular cycles every 2½ to 5 weeks. She was otherwise in good health and had no history of weight loss or excessive gain. Prior labs had shown FSH 2.7 IU/L and normal TSH and prolactin.

Examination: Weight 57.3 kg, BMI 22.5 kg/m², normal examination.

Repeat laboratory tests: LH 3.0 IU/L, DHEAS 4.5 µmol/L (167 µg/dL), testosterone 0.21 nmol/L (6 ng/mL).

This is a case where there is certainly a differential diagnosis. We can consider her irregular menses from age 9 to 12 to be pubertal anovulatory cycles but it is unclear why she remained irregular from age 12 to 15. Her early menarche and lack of establishment of regular cycles would certainly be consistent with polycystic ovary syndrome (PCOS). While no ultrasound was performed, it would likely have shown multicystic ovaries, as is common at this age in the absence of Graafian follicle development. She would have thus fit the Rotterdam definition of the normoandrogenic phenotype of PCOS. As it happens, she was intensively involved in gymnastics, dancing, and cheerleading from age 12 to 15. During a year of follow-up and with decreased physical activity, she established regular menses. In a recent review by Copp et al. entitled “Are expanding disease definitions unnecessarily labeling women with polycystic ovary syndrome,” this exact scenario was discussed [5]. In the absence of a detailed history, this is very likely to apply to many of the normoandrogenic patients with irregular menses and multicystic ovaries labeled as PCOS.

Case 4

A 33-year-old patient presented with secondary amenorrhea. Her menarche was at age 13 with regular cycles until age 31. She had had three menses from age 31 to 33.

Examination: Weight 63.4 kg and BMI of 21 kg/m², normal examination.

Laboratory tests: LH 5.0 IU/L, FSH 7.0 IU/L, estradiol 74 pmol/L (20 pg/mL), normal TSH and prolactin.

Prior imaging had shown the pituitary sella to be 60% empty.

An empty sella may be secondary to surgery, radiation, infarction as in Sheehan’s syndrome, and autoimmune as in lymphocytic hypophysitis, or it may be a primary process due to a defect in the diaphragm sella [6]. A minority of patients with an empty sella can have endocrine sequelae such as low gonadotropins and/or high prolactin. The differential diagnosis of her amenorrhea included empty sella syndrome. However, additional history revealed that she had lost 7–9 kg in the preceding 3 years and was also physically very active during this time, with a history of running 10–13 km per day and 5 h of other activities including aerobics. During follow-up, she had a stress fracture and stopped exercising for a few months. Her menses promptly resumed. Thus, her final diagnosis was FHA. It is sometimes easier to pin the cause of a problem on a structural abnormality, as in her case, but the real etiology may be quite different.

Case 5

A 21-year-old patient presented with a history of primary amenorrhea. Her pubarche was at age 11 but she had no ensuing breast

development or menses. She was evaluated at age 15 years 11 months for growth and pubertal delay. Records pertaining to this evaluation showed a weight of 40.5 kg, her LH and FSH were 4.8 and 8.8 IU/L, estradiol was 137 pmol/L (37 pg/mL), and TSH and prolactin were both normal. Her bone age at this time was between age 13 and 13½. At age 17, abdominal symptoms lead to a diagnosis of Crohn’s disease and she was treated with courses of prednisone (briefly) and later adalimumab, a tumor necrosis factor blocker, and mercaptopurine, with improvement. Records at age 17 revealed LH 11.4 IU/L, FSH 5.9 IU/L, and estradiol 30 pmol/L (8.2 pg/mL). Brain imaging had been normal. Over time, she attained a height of 165 cm and was given COC to induce menses.

She came off the COC pill at age 20 and had no ensuing menses, even despite progestin challenge. Her weight was stable as per her history. She ran 10 km per week.

Examination: Weight 54 kg, BMI 20 kg/m², and small Tanner 2–3 breasts.

Laboratory tests showed LH 5.9 IU/L, FSH 6.3 IU/L, estradiol 211 pmol/L (57 pg/mL), and normal testosterone and DHEAS. Repeat labs showed LH of 5.67 IU/L and estradiol of 100 pmol/L (27 pg/mL).

Prior to receiving her records, the differential diagnosis was primary hypothalamic amenorrhea versus pubertal delay related to systemic illness, low weight, and some running. However, her laboratory tests, especially at age 17 when her LH was 11.4 IU/L and FSH was 5.9 IU/L, eliminated the diagnosis of primary hypothalamic amenorrhea. Indeed, her LH was consistent with early puberty which is an LH-dominant state. She was treated with an estradiol patch of 0.1 mg weekly in an attempt to induce some breast development.

To test the integrity of the hypothalamic-pituitary-ovarian (H-P-O) axis, she was later withdrawn from the estradiol patch and given clomiphene 100 mg daily for 5 days. Her LH increased from 4.26 to 7.65 IU/L, her FSH from 6.0 to 7.6 IU/L, and her estradiol from 127 to 2002 pmol/L (34.2 to 541 pg/mL). This tremendous estradiol response confirmed the integrity of the H-P-O axis and, as expected, she had withdrawal bleeding after the progestin withdrawal challenge. Clomiphene has anti-estrogenic as well as estrogenic activity and its anti-estrogenic effect stimulates the GnRH pulse generator into improved production, hence the response of the pituitary and in turn the ovary. In cases of more profound shutdown of GnRH, the challenge test may not result in a positive result, as in this case, but such a response confirms the integrity of the H-P-O axis.

Unfortunately, she had no further menses, despite the fact that her Crohn’s disease was under control. It may be that her relatively low weight, exercise history, and prolonged shutdown of GnRH are hindering her recovery. She was placed back on an estradiol patch and given cyclic progesterone. She was also told she had to gain about 4–5 kg and/or stop running before it was reasonable to withdraw her from hormonal treatment.

Case 6

A 27-year-old patient attended with essentially primary amenorrhea. Breast development had occurred at age 11 and her only episode of spontaneous bleeding had been 1 day of vaginal spotting at age 14. She was given COC at age 16, with menses following, and took them on and off, with no menses when off. In addition, she had had no withdrawal menses to previous progestin challenge. Her weight was 66 kg at age 18. While she was a vegetarian and “ate no fat,” she had no history of an eating disorder, such as anorexia. Additional history revealed that she bicycled 128–192 km per week from age 13–25 and had reduced her cycling to 48 km, and “walked a lot” from age 25–27.

Examination: Weight 62 kg, BMI 21 kg/m², and normal examination.

Laboratory tests: LH 1.06 IU/L, FSH 2.6 IU/L, estradiol 94 pmol/L (25.5 pg/mL), normal TSH and prolactin, and normal pituitary imaging.

She was given a diagnosis of FHA, related to her exercise history, and stopped bicycling after her visit. Two months later, she had some spotting after progestin challenge, but no menses. Over the course of the subsequent 2 years, she had two clomiphene challenge tests with 100 mg clomiphene given for 5 days. While her LH increased to 8 and 9.5 IU/L in the first and second tests, her estradiol remained low after clomiphene at 103 and 122 pmol/L, respectively (27.9 and 33 pg/mL). Over these 2 years, she had two further episodes of spotting, one lasting 3 days.

Was FHA the wrong diagnosis? That is unlikely. An Internet search revealed that cycling about 8 km per h for 6 h (= 48 km, which was her prior exercise habit before she stopped it) burns 1250 calories. Thus, at this rate, she would have burnt about 3750 calories every 3 weeks with such exercise. Consultation with an expert in nutrition revealed that on average, 3800 extra calories would lead to half a kilogram gain in weight. Thus, if she were eating the same amount, as she professed, she should have gained about 8 kg per year. However, she had only gained about 2 kg in 2 years, hence, perhaps, her lack of recovery. She was treated with an estradiol patch and cyclic progesterone.

Case 7

A 39-year-old patient was attended for secondary amenorrhea. Her menarche was at age 12, with regular cycles, interrupted by two pregnancies. She remained regular until age 38 when her menses stopped. She had no history of an eating disorder or excessive exercise and no symptoms to suggest perimenopause. However, at age 38, she had developed a painful autoimmune polyneuropathy and lost 22.5 kg within a year, dropping her weight to 60 kg and a BMI of 20.7. Her neuropathy was treated

with steroids, briefly, and analgesics and later intravenous immune globulin were added with response over time.

Examination: Weight 60 kg, BMI 20.7 kg/m², normal general examination.

Laboratory tests: LH 5.44 IU/L, FSH 6.0 IU/L, estradiol 574 pmol/L (155 pg/mL) which is consistent with a mid-follicular phase level. Her TSH and prolactin were normal.

The etiology of her FHA was explained to her, and after her laboratory tests, she was told she may be recovering, as her estradiol was normal. She was given a progestin, with withdrawal bleeding as expected. Within 2 months of her visit, she reestablished regular menses. What information was she given as regards the etiology of her FHA? Was it her weight loss alone and had she gained enough weight to allow for recovery? Not exactly, as her weight had fluctuated between 59.5 and 60.9 kg from 5 months before her visit to 5 months after. So why did she recover from her FHA within 2 months of her visit? It was because another factor was involved in her case, namely exogenous opiates.

She had been treated with hydrocodone with acetaminophen 10/325 mg every 4–6 h for many months. In addition, she was on a fentanyl patch for breakthrough pain during this time. The gradual withdrawal from opiates, coinciding with her visit, allowed menses to resume despite lack of significant weight gain. Thus, the etiology of her amenorrhea was weight loss in the context of systemic illness, compounded by narcotics. Narcotic analgesics shut off the GnRH pulse generator and the pituitary-ovarian axis is also thus shut off [7], a finding that was illustrated many years ago [8]. Using electrodes implanted in the mediobasal hypothalamus of the ovariectomized rhesus monkey to record multiunit activity, with simultaneous measurement of serum LH, it was shown that a single 2-min intravenous infusion of morphine (2 mg per kg body weight) shuts down multiunit electrical activity of the pulse generator and the corresponding LH pulses, this effect lasting at least 4 h. The outcome is the same as that of endogenous opioids such as β -endorphin that are produced in response to stress and exercise. While the Endocrine Society guidelines mention opiates, along with other drugs that may affect the H-P-O axis, the influence of opiates needs to be more strongly emphasized [3]. This is especially so in the current climate of liberal use (and also abuse) for the relief of pain in reproductive age women and also men.

Case 8

A 16-year-old patient was seen for oligomenorrhea. Her menarche was at age 13 and she had irregular cycles for a year. She then established regular cycles and these remained regular for 6 months before becoming irregular again. Her last menstrual cycle was 4 months prior to her visit. She had lost 13.5 kg in the preceding year by changing her eating habits and was also running 8 km per week during this time.

Examination: Weight 48.6 kg, BMI 19 kg/m², mild abdominal hirsutism.

Laboratory tests: Her LH was 0.3 IU/L, FSH 3.6 IU/L, normal prolactin, TSH, and T4. Her T3 was low at 1.1 nmol/L (74 ng/dL), her testosterone was < 1.4 nmol/L (< 20 ng/dL), and DHEAS was 2.8 μmol/L (105 μg/dL).

After some discussion, she agreed to regain some weight and returned 3 months later. She had gained 12.5 kg (BMI now 24 kg/m²) and her exercise remained unchanged. No menses had ensued.

Repeat laboratory tests at second visit: LH 16.8 IU/L. With the possibility of this high LH being her LH surge, no action was taken. However, she had no menses and a repeat LH several weeks later was 21.3 IU/L with FSH of 5.1 IU/L. Her testosterone was now high at 3.0 nmol/L (92 ng/dL) and her DHEAS was 3.3 μmol/L (124 μg/dL). Late-onset congenital adrenal hyperplasia was ruled out and PCOS was diagnosed.

Follow-up over the subsequent 9 years: She has remained anovulatory with further weight gain and has taken COC on and off during this time for acne and also metformin.

This patient clearly had FHA upon initial presentation, with low LH, a relatively normal FSH, and low T3 commensurate with significant weight loss. However, since her initial and also subsequent further weight gain, she has remained anovulatory. Her anovulation and hyperandrogenism, manifesting clinically as acne, are consistent with PCOS. The Endocrine Society guidelines discuss the metabolic cues that in a normal female allow normal functioning of the H-P-O axis [3]. Effects of excess weight on this system, with insulin resistance and hyperandrogenism, are also well known. What is interesting in the case presented above is that it seems that the metabolic cue window for normal functioning of the H-P-O axis may be quite narrow in some women and possibly difficult to maintain.

Additional comments and overview

Appropriate metabolic cues are necessary for normal function of the H-P-O axis and, given the energy requirement of reproduction, female athletes with an energy deficit (expending more energy than they eat) often have FHA, as do those with anorexia who also have decreased leptin [3]. Neurons within the arcuate nucleus secrete kisspeptin and this stimulates GnRH and may be the final common pathway that integrates other neuromodulatory signaling systems. Thus, lack of kisspeptin can lead to decreased GnRH. A longer duration of insult is typically associated with a longer time to reversal to normal menses. Inability to achieve an adequate peak bone mass is a significant long-term risk of FHA, especially in those with restrictive eating habits and low weight. Stress fractures are common in those with low bone mass but the low energy state may also lead to decreased bone formation and bone

turnover, favoring a resorptive state. This uncoupling of bone turnover is more typical of nutritional deficiency as opposed to estrogen loss [3]. Activation of the H-P-Adrenal axis is also tightly linked to reduction of GnRH, hence the increased cortisol that is seen in patients with FHA, as related to stress and eating disorders and exercise [3].

The primary intervention should be behavioral change with increased calorie intake, improved nutrition, and/or decreased exercise, as well as psychological support. Often, weight gain is required. While replacement of estrogen is frequently accomplished by the use of COC, the Endocrine Society guidelines advise against their use, in part because they may mask return of menses and also because bone loss may continue despite their use. In addition, COC (and oral estrogen) downregulates IGF-1, a bone trophic hormone [3]. Thus, if hormone therapy is given because of lack of return of menses after a reasonable trial of behavioral changes, including better nutrition and decreased exercise, short-term use of transdermal estrogen with cyclic oral progestin is appropriate. Transdermal estrogen does not affect IGF-1 secretion [3]. In a study of anorectic female adolescents randomized to transdermal estrogen and cyclic oral progestin versus placebo patches and placebo cyclic pills for 18 months, there were significant improvements in lumbar bone density and also improvement in hip bone density in that timeframe, versus placebo [9]. However, bone health may not be protected with estrogen replacement if energy deficit continues. Whether FHA has adverse cardiovascular consequences in the long term is also a potential concern.

In those who wish to conceive, the guidelines recommend ovulation induction only in those with a body mass index (BMI) of at least 18.5 kg/m² after attempts to normalize energy deficit. There is a higher risk of adverse pregnancy outcomes if the BMI is < 18.5 kg/m² [3]. Pulsatile GnRH, if available, is recommended as first-line treatment, followed by gonadotropin therapy with some caution to avoid multiple gestation and severe ovarian hyperstimulation syndrome. In patients with sufficient endogenous estrogen, clomiphene citrate (or letrozole) may induce follicular development, as in case 5. The guidelines recommend against the use of kisspeptin and leptin therapy for the treatment of infertility [3].

Compliance with ethical standards

Conflict of interest The author declares that she has no conflict of interest.

References

1. Nader S (2013) Hyperandrogenism during puberty in the development of polycystic ovary syndrome. *Fertil Steril* 100:39–42

2. Navarro VM, Kaiser UB (2013) Metabolic influences on neuroendocrine regulation of reproduction. *Curr Opin Endocrinol Diabetes Obes* 20:335–341
3. Gordon CM, Ackerman KE, Berga SL et al (2017) Functional hypothalamic amenorrhea: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* 102:1413
4. Hampton SL, Promecent PA, Mastrobattista J, Nader S (2005) Characteristics of menstrual irregularities in female athletes. *Obstet Gynecol* 105(supp 4):19S
5. Copp T, Jansen J, Doust J, Mol BWJ, Dokras A, McAffery K (2017) Are expanding disease definitions unnecessarily labelling women with polycystic ovarian syndrome? *BMJ* 358:3694–3703
6. Chiloiro S, Giampietro A, Bianchi A et al (2017) Primary empty sella: a comprehensive review. *Eur J Endocrinol* 177:R275–R285
7. Bottcher B, Seeker B, Leydendecker G, Wildt L (2017) Impact of the opioid system on the reproductive axis. *Fertil Steril* 108:207–213
8. Hotchkiss J, Knobil E (1994) The menstrual cycle and its neuroendocrine control. In: Knobil E, Neill JD (eds) *The physiology of reproduction*. Raven Press, New York; ch 48, vol 2, pp 711–749
9. Misra M, Katzman D, Miller KK et al (2011) Physiologic estrogen replacement increases bone density in adolescent girls with anorexia nervosa. *J Bone Miner Res* 26:2430–2438