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CASE REPORT

STRESS-RELATED HYPOGONADOTROPHIC HYPOGONADISM AND ALOPECIA UNIVERSALIS IN A YOUNG WOMAN

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Summary

Introduction: Alopecia universalis is a severe form of alopecia areata, of unknown exact pathogenesis, frequently considered autoimmune. Hypogonadotrophic hypogonadism can occur in a number of conditions, including autoimmune syndromes.
Case report: We present the case of a young woman who presented with secondary amenorrhea and alopecia universalis, both developed in the first year after a significant stressful event. The personal and family history were clear, there was no abnormality at the clinical examination apart from complete alopecia. The laboratory examination diagnosed hypo-gonadotrophic hypogonadism and excluded hyperprolactinemia, hyperandrogenism, adrenal failure, hypothyroidism. During a 8 year follow-up the alopecia showed no sign of recovery but after 6-7 years the hypogonadism completely recover and the patient resumed normal menses. The final diagnosis was stress-induced hypothalamic amenorrhea associated with alopecia universalis of unknown origin.
Conclusion: hypogonadotrophic hypogonadism can occur in association with alopecia universalis and both can be triggered by severe stress. Affected cases should be strictly monitored for associated autoimmune conditions and longterm follow-up is usually needed. During long follow-up the hypogonadism can spontaneously recover.
Key words: alopecia universalis, hypogonadotrophic hypogonadism, stress, spontaneous recovery

Résumé

Hypogonadisme hypogonadotrophique lié au stress et Alopecia Universalis chez une jeune femme

Introduction: Alopecia Universalis est une forme sévère de la pelade, de pathogenèse exacte inconnue, considérée souvent comme auto-immune. L'hypogonadisme hypogonadotrophique peut survenir dans un certain nombre de conditions, y compris les syndromes auto-immuns.
Rapport de cas: Nous présentons le cas d'une jeune femme qui s'est présentée avec une aménorrhée secondaire et une alopécie universalis, les deux apparues dans la première année après un événement stressant significatif. L'histoire personnelle et familiale étaient claires, il n'y avait aucune anomalie à l'examen clinique à part l'alopécie complète. L'examen de laboratoire a mis le diagnostic d'hypogonadisme hypogonadotrophique et a exclu l'hyperprolactinémie, l'hyperandrogénie, l'insuffisance surrénalienne, l'hypothyroïdie. Pendant un suivi de 8 ans, l'alopécie n'a montré aucun signe de rémission, mais après 6-7 ans, l'hypogonadisme s'est complètement remis et la patiente a repris les règles normales. Le diagnostic final a été l'aménorrhée hypothalamique induite par le stress associée à alopecia universalis d'origine inconnue.
Conclusion: l'hypogonadisme hypogonadotrophique peut survenir en association avec alopecia universalis et les deux peuvent se déclencher par un stress sévère. Les cas affectés doivent être strictement surveillés pour des conditions auto-immunes associées et un suivi à long terme est d'habitude nécessaire. Pendant le suivi prolongé l'hypogonadisme peut se remettre spontanément.
Mots clefs: alopécie universalis, hypogonadisme hypo-gonadotrophique, stress, guérison spontanée

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INTRODUCTION

Secondary amenorrhea is frequent in women of reproductive age. The initial diagnostic workup leads to the more precise classification of the hypogonadism. Hypogonadotrophic hypogonadism can occur as a consequence of severe diseases (e.g. tumoral /inflammatory/autoimmune conditions affecting the hypothalamic-pituitary area, chronic medical conditions, genetic defects, chronic use of various medications) but also following severe stress, eating disorders (inducing a functional disorder called hypothalamic amenorrhea). (3)

Alopecia areata, with its most severe form, alopecia universalis (affecting the hair on the body, scalp, eyebrows, eyelashes) are considered to be of autoimmune origin and can also be frequently triggered by severe stress. (2)

CASE REPORT

We present the case of a 25 years old female, reffered for the first time to our department at the age of 18 years old for the investigation of secondary amenorrhea.

The patient had menarche at a normal age (13 years), initially had regular spontaneous menses but after 2 years she suffered a significant psychic stress followed by secondary amenorrhea. She was initially offered estroprogestatives (with recovery of normal menses), without a previous diagnostic workup.

At the time of her initial evaluation in our department she had been off estroprogestatives for almost a year and had no spontaneous menses since the interruption of the treatment. The clinical examination was unremarkable with the exception of complete alopecia (alopecia universalis, involving not only the scalp and body but also the eyebrows and eyelashes) – progressively developed over the course of one year following the severe stress. The patient had complete pubertal development. There were no clinical suspicious signs for thyroid or adrenal auto-immune failure. The medical history of the patient and family was clear. The laboratory tests (summarized in table 1) showed hypogonadotrophic hypogonadism and excluded hyperprolactinemia, hyperandrogenism, associated adrenal insufficiency. The results were stable over follow-up (see table 1).

Antimicrosomal antibodies (antithyroperoxidase) were negative. Routine laboratory panel of tests showed no evidence of pernicious anaemia or type 1 diabetes mellitus.

The hypothalamic-pituitary imaging revealed no abnormalities. Barr test was positive, caryotype was 46XX.

The pelvic ultrasonography was consistent with the clinical and hormonal picture showing small uterus and ovaries, thin endometrial lining (see table 1).

The estroprogestative therapy was resumed but inconsistently administered by the patient. During the following 3 years the patient had normal menses under continuous estroprogestative treatment. In this time interval she was reevaluated twice in our department (after 2 months interruption of treatment) and the results were similar to the initial evaluation.

In 2015 the patient returned for evaluation. She had interrupted the estroprogestatives one and a half year previously. In the last year she had normal, spontaneous menses. The clinical examination was normal apart from alopecia universalis. The hormonal profile of day 5 of the menstrual cycle was normal- see table 2.

The patient remained under our close supervision, without any treatment. Her spontaneous menses remained regular, she developed no further symptoms.

DISCUSSION

Alopecia universalis is a severe form of alopecia areata, thought to have an autoimmune pathogenesis with genetic predisposition (20% of affected cases have a similarly affected family member). Spontaneous remission and/or recurrence are frequent, especially in alopecia areata, with no more than 10% of the cases with alopecia totalis or universalis showing spontaneous recovery (2).

In our case, the association of hypogonadotrophic hypogonadism and alopecia universalis was initially interpreted as of possible autoimmune origin. This prompted the initial evaluation and further monitoring for associated autoimmune conditions, such as those described in polyglandular autoimmune syndromes (PAS). PAS were initially described in 1908 (12); the best described variants are PAS type I and II (both including autoimmune adrenalitis with adrenal insufficiency, as well as a constellation of other autoimmune conditions). Another later described variant is PAS type III not associating adrenal insufficiency. PAS type III is further divided into three variants (A, B and C) with type IIIC including autoimmune thyroiditis and other autoimmune conditions (including hypogonadism, vitiligo and/or alopecia). (13) However, in our case the clinical and laboratory data

Table 1 - Results of the laboratory tests performed during follow-up

	Estradiol (pg/ml)	LH (mUI/ml)	FSH (mUI/ml)	Testosterone (ng/ml)	DHEAS (mcg/ml)	Basal cortisol (mcg/dl)	PRL (ng/dl)	Transvaginal pelvic ultrasonography
2008	15.33	42.75	12.79	0.41 (0.14-0.76)		17.8	3.4	Small uterus, thin endometrial lining, both ovaries of normal volume with few millimetric cystic images
2009		13.97	13.02	0.18	135	18.61	6.31	Similar aspect
2010	49.8	20.9	13.73	0.2	161		7.9	

Table 2 - Laboratory tests at the last visit (after resumption of normal menses)

Estradiol (pg/ml)	LH (mUI/ml)	FSH (mUI/ml)	Testosterone (ng/ml)	DHEAS (mcg/ml)	Basal cortisol (mcg/dl)	PRL (ng/dl)	Transvaginal pelvic ultrasonography
25	14.13	13.99	< 0.1 (0.14-0.76)	106.2	18.62	6.58	normal uterus, trilaminar endometrium, cystic image in the right ovary

consistently suggested that hypogonadotropism was the only hormonal defect so we did not have enough data to diagnose PAS type III.

The lack of other affected family members argued against familial associations of alopecia universalis and hypogonadism described in the literature (with hypogonadism of either hypogonadotrophic (16) or hyper-gonadotrophic variant (11, 17). Furthermore, in these poorly understood conditions, frequently other syndromic features are found (1, 5, 7,8,9).

Our patient did not display any syndromic components (such as diabetes mellitus, mental retardation, deafness also); also the family history was negative. Together with the spontaneous remission of hypogonadism, the clinical picture suggests a stress-induced hypothalamic amenorrhea.

Hypothalamic amenorrhea is a frequent cause of secondary amenorrhea, especially in young women and frequently occurs related to an eating disorder, significant stress or weight loss.(14) Recovery of spontaneous menses during long follow-up is common, especially in the cases with a specific, reversible precipitant factor (83 % recovery in one study during longterm follow-up). (14)

In our case, the major stressful event appears to have precipitated both the menstrual disorder and universal alopecia. Just as in the case of hypogonadotrophic hypogonadism, a very stressful stimulus is frequently recorded in relation to the onset and development of alopecia. Experimental evidences are accumulating in relation to the mechanisms involved in stress-related telogen effluvium and alopecia areata. (15) Predictors of poor prognosis are early onset, extent and duration of involvement, positive family history and association of other autoimmune conditions.(2,4,6,10) Despite the apparent lack of these poor predictors, alopecia showed no sign of spontaneous recovery in our case during 8 years-follow-up.

CONCLUSIONS

In conclusion, hypogonadotrophic hypogonadism can occur together with alopecia universalis not only as part of definite syndromes such as polyglandular autoimmune syndromes but also as a consequence of severe stress. Affected cases should be strictly monitored for other associated conditions (especially autoimmune) and dysmorphic features. Careful follow-up is needed and during longterm monitorisation hypogonadism (and sometimes alopecia) can show spontaneous recovery.

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