—Report on Experiments and Clinical Cases—

Re-evaluation of Secondary Amenorrheic Patients One Year after Initial Diagnosis: A Prospective Study

Joji Matsumoto[1] and Toshio Hata[2]

[1]Ogawa Red Cross Hospital
[2]Department of Obstetrics and Gynecology, Saitama Medical School

Abstract

Objectives: The aim of the study was to re-evaluate women with secondary amenorrhea one year after the first visit evaluation.

Study Methods: One hundred and seventy-five women with secondary amenorrhea were evaluated on the first visit. Their ages ranged from 18 to 29. Secondary amenorrhea was defined by the absence of menses for more than 3 months after excluding pregnancy. Women who were attempting to conceive were excluded from the study. 1) One hundred and two women were anovulatory (2) 36 had hypogonadotropic hypogonadism, 3) 11 had hypergonadotropic hypogonadism, and 4) 21 had hyperprolactinemia, 5) and five fell into other categories. The one hundred and forty-nine women in categories 1) to 3) were followed up for one year after the first diagnosis was made. A monthly progestational agent or HRT (hormone replacement therapy) was given to women with anovulation or hypogonadism, respectively.

Results: Of the 149 women in categories 1) to 3), 100 could be evaluated one year after the first diagnosis. There were 31 women whose diagnosis was changed. Anovulation changed to hypogonadotropic hypogonadism in 11 women, oligomenorrhea in four, and normal ovulatory cycle in two. Hypogonadotropic hypogonadism changed to anovulation in nine women, and to normal ovulatory cycle in one. Hypergonadotropic hypogonadism changed to normal ovulatory cycle in two women.

Conclusions: A significant finding is that approximately one third of the women initially diagnosed with secondary amenorrhea, upon re-evaluation within one year had their diagnosis changed. Therefore evaluation of amenorrhea at an appropriate time is critical for proper management.

(J Nippon Med Sch 2004; 71: 63–68)

Key words: secondary amenorrhea, prospective follow-up study

Introduction

One of the most difficult questions to answer from patients with secondary amenorrhea is how long the amenorrheic state is going to persist, especially when patients are relatively young. It appears that many patients are likely to think that amenorrhea is a temporary state that they can get over with short-term or even a single treatment. We are primarily

Correspondence to Joji Matsumoto, MD, Ogawa Red Cross Hospital, 1525 Ogawa, Ogawa-machi, Hiki, Saitama 355–0397, Japan
E-mail: jkrm@nms.ac.jp
Journal Website (http://www.nms.ac.jp/jnms/)

interested in how often the patient's condition changes from one amenorrheic state to another, or into an ovulatory cycle once the diagnosis for amenorrhea is made.

To evaluate this we prospectively monitored and looked at re-diagnosis of patients with amenorrhea, but who were not candidates for pregnancy one year after the first diagnosis of amenorrhea was made.

Subjects and Methods

One hundred and seventy five patients presenting with secondary amenorrhea who were not attempting to conceive from 1990 to 2002 were involved. Their ages ranged from 18 to 29.

Diagnosis of amenorrhea

Secondary amenorrhea is defined by the absence of menses for 3 months or more according to the definition of the Japan Society of Obstetrics and Gynecology[1]. Similarly oligomenorrhea is defined as menstrual cycles with intervals of 39 days or more. Evaluation of amenorrhea was performed according to the methods described by Speroff et al[2] with some modifications.

A careful history was taken and physical examination was done. The size or condition of the uterus, endometrium, ovaries, and follicles were evaluated by transvaginal ultrasound and were recorded. All subjects were asked to keep a basal body temperature chart. After excluding pregnancy, serum levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), thyroid-stimulating hormone (TSH), prolactin, estradiol, and testosterone were measured. Determination of hormone levels was performed at SRL (Tokyo) on a commercial basis using ELISA for TSH and RIA for other hormones.

A progestational challenge was started after the above mentioned blood test. If subjects bled with this progestational medication (medroxyprogesterone acetate, 10 mg daily for 5 days), a diagnosis of anovulation was made without further evaluation when subjects showed normal prolactin and TSH levels.

If a progestational medication did not produce withdrawal bleeding, 1.25 mg conjugated estrogen a day for 21 days and 10 mg medroxyprogesterone acetate per day for the last 5 of the 21 days were given. If subjects did not bleed after this medication the diagnosis of an end organ problem was made. Subjects who did not bleed with a progestational medication, but bled with estrogen and progestin cycle were diagnosed as having hypogonadotropic hypogonadism when the level of ganadotropin was either within the normal menstrual range or low. In addition, imaging evaluation of the pituitary gland was done using MRI, CT scan or plain x-ray for final localization to distinguish a pituitary or CNS-hypothalamic cause for the amenorrhea.

Subjects with high levels of gonadotropins were diagnosed as having hypergonadotropic hypoganadism. In all subjects in this category except subjects with hematological malignancy, a karyotype was determined and blood test for autoimmune disease[2] was performed.

In subjects presenting with galactorrhea, imaging evaluation of the pituitary was also performed in addition to measurement of serum levels of prolactin and TSH. Sequential pituitary testing[3] was recommended to subjects with a pituitary tumor using 1 μg/kg of CRH, 100 μg of Gn-RH, 1 μg/kg of GH-RH, and 200 μg of TRH. A measurement of bone mass density (BMD) was recommended to subjects with hypogonadism or subjects on medications other than sex steroids that may have an effect on BMD. Q-CT were used for this purpose for the first few years and later replaced by DEXA.

Treatments

Ten mg of medroxyprogesterone acetate daily for the first 10 days of each month was given to anovulatory subjects. Low-dose oral contraceptives have been available since 1999 in Japan. We recommended this to subjects who needed reliable contraception; however this is not covered by insurance in Japan. For subjects with hypergonadotropic hypoganadism or hypogonadotropic hypogonadism, 0.625 mg conjugated estrogen daily was prescribed, and 10 mg medroxyprogesterone acetate was added for the first 12 days of each month (HRT).

Table 1 Classification of subjects

Anovulation	102 (58.3%)
Hypogonadotropic hypogonadism	36 (20.1%)
Hypergonadotropic hypogonadism	11 (6.3%)
Hyperprolactinemia	21 (12.0%)
Others	5 (2.9%)
Total	175

Table 2 Complications or underlying diseases of amenorrheic subjects

Anovulation
Central neurocytoma: 1
Epilepsy: 2
Anorexia nervosa: 2
Crohn's disease: 1
Hypogonadotropic hypogonadism
Anorexia nervosa: 2
Schwannoma: 1
Germinomas of brain: 1
Ulcerative colitis: 1
Irritable bowel syndrome: 1
Hypergonadotropic hypogonadism
Unknown causes with 46XX: 7
Non-Hodgkin's lymphoma: 2
Acute lymphoid leukemia: 1
Acute myeloid leukemia: 1
Hyperprolactinemia
Microadenoma: 2
Macroadenoma: 1
Chronic renal failure: 2
Drug-induced hyperprolactinemia: 9
Others
Hyperthyroidism: 3
Hypothyroidism: 1
Cushing's syndrome: 1

Re-evaluation of amenorrhea

Anovulatory subjects and subjects with hypergonadotropic hypogonadism and hypogonadotropic hypogonadism as an initial diagnosis were re-evaluated one year later. For subject on HRT three weeks after stopping the medication and following the same blood tests as for initial diagnosis, a progestational agent alone was administered to determine whether subjects would bleed or not. If they did not bleed with this medication they were diagnosed with hypogonadism and placed back on HRT. For anovulatory subjects, monthly administration of progestational agent was stopped, and they were followed up for three months to see whether spontaneous ovulation would occur.

Data were analyzed by means of the χ^2 test, and a p value of less than 0.05 was considered significant.

Results

Of 175 subjects presenting with amenorrhea, 1) 102 subjects were anovulatory, 2) 36 had hypogonadotropic hypogonadism, 3) 11 had hypergonadotropic hypogonadism, 4) 21 had hyperprolactinemia, 5) and five fell into others (hyperthyroidism 3, hypothyroidism 1, Cushing syndrome 1) (**Table 1**). One subject with hypergonadotropic hypogonadism plus drug-induced prolactinemia was classified into the category of hypergonadotropic hypogonadism. Complications or underlying diseases of the amenorrheic subjects are listed in **Table 2**. One subject in the category of anovulation underwent brain surgery for central neurocytoma, after which amenorrhea started. In the category of hypogonadotropic hypogonadism, brain surgery was performed for Schwannomas in one patient, and for germinomas in another. The former had irradiation. The latter had both irradiation and chemotherapy and after that she needed to take glucocortiroids and levothyroxine sodium in addition to HRT due to panhypopituitarism. In these two subjects amenorrhea began after treatment. One subject with an irritable bowel syndrome suffered from persistent diarrhea. She could not take premarin tablets, and instead used transdermal estrogen. In the category of hypergonadotropic hypogonadism, seven subjects showed normal karyotype and normal results in autoimmune tests. One subject had chemotherapy for malignant lymphoma, another had chemotherapy and irradiation for malignant lymphoma with autologous bone marrow transplantation. One subject had chemotherapy for acute lymphoid leukemia and one subject had chemotherapy and irradiation for acute myeloid leukemia, with subsequent allogeneic bone marrow transplantation from a male donor.

One hundred and forty-nine subjects in categories 1) to 3) were followed. One year later, 100 subjects could be re-evaluated (**Table 3**). Of 59 subjects with

Table 3 Changes of diagnosis at one year

Initial diagnosis		Diagnosis at one year	
Anovulation	59	Anovulation	40
		Hypogonadotropic hypogonadism	13
		Oligomenorrhea	4
		Ovulatory cycle	2
Hypogonadotropic hypogonadism	31	Hypogonadotropic hypogonadism	21
		Anovulation	9
		Ovulatory cycle	1
Hypergonadotropic hypogonadism	10	Hypergonadotropic hypogonadism	8
		Ovulatory cycle	2

an initial diagnosis of anovulation, 40 subjects were anovuleic at re-evaluation at one year, 13 subjects were changed to hypogonadotropic hypogonadism, four to oligomenorrhea, and two to ovulatory cycle. Twenty one subjects initially diagnosed with hypogonadotropic hypogonadism remained in the same category as before, nine were moved to the category of anovulation and one was changed to ovulatory cycle. Two subjects who previously belonged to the category of hypergonadotropic hypogonadism were found to have ovulatory cycle. One of the two became a mother of two children later. Thus, 31 of the 100 subjects had their diagnosis changed within one year.

Discussion

A single physician adhering to the methods described by Speroff et al[2] could evaluate all subjects presenting with amenorrhea. In our study, the subjects came from six institutions and not at the same period of the time. In other words, the data are presented from the experience of one physician in different institutions at different periods of time. The frequency of various categories of secondary amenorrhea in our data did not vary from institution to institution though the sample size was too small for further breakdown by categories. Reindollar et al[4] reported a study of 262 patients with adult-onset amenorrhea. Their criteria for inclusion into the study consisted of secondary amenorrhea of 6 months' duration or more, which occurred before age 39 years. When our data on 175 subjects were compared with theirs, there was a significant difference in the diagnostic frequency ($p<0.0001$). The difference may depend partly on age; when our present data in the 18 to 29 age range were compared with another set of data on 24 subjects with secondary amenorrhea in their 30s, the diagnostic frequency differed ($p<0.0001$). The one-year period prevalence of secondary amenorrhea in the general population has been reported to be 4.6 percent, of which only 39 percent seek medical advice[5]. For this reason, the selection bias in a hospital-based study might be high.

In a follow-up study we dealt with subjects with hypogonadotropic hypogonadism, hypergonadotropic hypogonadism, and anovulation with normal TSH and prolactin levels. A subject with hyperprolactinemia might belong to one of the three categories. An 18-year-old subject was enrolled because of amenorrhea. She had chronic renal failure, and showed elevated prolactin levels. Her amenorrheic condition was diagnosed as anovulatory, and she still remained so after a normal level of prolactin was obtained with bromocriptine that was used because elevated prolactin itself might cause amenorrhea. Approximately two years later, she had a renal transplantation from her father. Her blood level of prolactin was then normal, but she was diagnosed as still having anovulation.

How far do we have to examine patients to obtain a precise etiology? Do we have to think about it at the DNA levels[6-9]? Not only is it impossible, but also it is usually unnecessary to define the precise etiology of amenorrhea as is described by Speroff et al[10]. We agree with them. However, we need to be aware of a progressive underlying disease, if any, such as

brain tumor, which is usually under surveillance of a neurosurgeon. The diagnosis of amenorrhea is simple and falls into the three categories described above.

Management seems simple too; however, we may encounter interesting cases. Response to medication may vary even when the patient remains in the same category. The following two are examples. A 25-year-old patient with hypogonadotropic hypoganadism was on HRT. In the meantime, she was found to have pulmonary tuberculosis, and medication for it was started. With this medication, uterine bleeding did not occur. Culture of discharge for tuberculosis was negative, and biopsy from the endometrium was not suggestive of a pathologic condition. Uterine bleeding by HRT was regained after treatment for tuberculosis was over. We have to be aware of medication that has an effect on the metabolism of sex steroids. An 18-year-old subject with hypergonadotropic hypogonadism was referred, who had the vagina but no detectable uterus by CT. She was excluded from the present data because her problem was primary amenorrhea with normal karyotype. We could not depict the uterus by rectal ultrasound on her first visit. She had no pubic or axillary hair at that point of time. She was placed on HRT. She experienced uterine bleeding for the first time in her life after more than two months had passed, at which time we recognized with certainty the presence of the uterus and endometrium by ultrasound. She also gained pubic and axillary hair and six centimeters in height in a few years from the age of 18 with HRT. It seems to us that each patient has her own story with HRT. HRT, however, has been reported not to be beneficial to the cardiovascular system in postmenopausal women, as was previously thought[11].

The prognosis of amenorrhea may differ in different etiologies[4, 12–14]. We usually give the patient a possible explanation for etiology with known data. We have to manage, and so long as management depends on the three categories, we, as mentioned above, usually do not bother to pursue the etiology unless it is associated with immediate threats to patients' health. Diagnosis of amenorrhea can change in approximately one-third of subjects within one year, as shown in our results. Any bleeding other than expected bleeding or delayed onset of expected bleeding might be good news. No response to hormonal medication indicates re-evaluation. We usually recommend the measurement of BMD to subjects with hypogonadism or subjects on medications other than sex steroids that may have an effect on BMD. We have two subjects who had been anovuleic at the initial diagnosis who were changed to hypogonadotropic hypogonadism in a short time and measurement of BMD revealed relatively low density. Although there are many factors that have effects on BMD, it would be possible to assume they were in the state of hypogonadism for a long period of time before. Management of subjects with amenorrhea according to the category is all right. However, we should keep in mind that the initial diagnosis can change over time and that subjects might belong to a different category than in the past.

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(Received, April 28, 2003)
(Accepted, June 25, 2003)