大韓不妊學會雜誌：第2卷 第2號 1975
Kor. J.Fertil. Steril., Vol.2, No.2, Dec.

AMENORRHEA (INTERMEDIATE)

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Virilizing adrenal hyperplasia may be classed into four groups. Group one is female hermaphroditism due to congenital adrenal hyperplasia. Group two comprises cases where the virilization doesn't seem to occur until about the time of puberty. That's considered pubertal virilization. The third category is post pubertal virilization due to the hyperplasia a very modest difficulty with respect to the external genitalia but a very common group as far as the gynecologist is concerned. These are patients with hirsutism, oligomenorrhea and infertility with elevated 17-ketosteroids. Finally there is another group that's exactly the same as the post pubertal group with elevated 17-ketosteroids except that ketosteroids aren't appreciably elevated but such patients are considered to be a variety of post pubertal hyperplasia without elevated 17-ketosteroids, because they respond to cortisone.

We seldom have an apportunity to see a patient with untreated virilizing adrenal hyperplasia-the consequences of that disorder. This is an individual who is primarily amenorrheic. She has no secondary sex development and her face and body show marked hirsutism. She has genitalia which can be considered to be ambiguous. A sagital section shows that the uterus is quite normal, consistent with the experiments of Jost which showed that it is impossible with any steroid hormone to inhibit the development of the Müllerian ducts, so that even though she is pouring out large quantities of androgenic steroid from her adrenal and has been doing so from early in embryonic life, the Müllerian ducts develop perfectly normally. There is a normal uterus, normal Fallopian tubes and normal ovaries in this particular situation even in the full-blown case.

The external genitalia in this disorder are masculinized to various degrees and, simply to give some order to this, they may be divided into six groups. Actually Group A represents the normal female situation. Then you can have a little disturbance by an enlargement of the phallus as in B. Then in Group C an enlargement of the phallus and some fusion of the scrotolabial folds. In D the phallus is still bigger and the fusion of the scrotolabial folds a bit more-still more in E and, finally, in F complete masculinization of the external genitalia as in normal male genitalia.

The intresting thing about this from a practical point of view is that, if one divides the cases according to the groups of external genitalia, the incidence of salt loss in the syndrome increases as the genitalia become more and more masculinized. From a practical point of view, salt loss is a serious problem because this is a lethal condition. If it is not identified, these patients often die in Addisonian crisis. As you can see, there is a very troublesome differential diagnosis involved. These patients are often missidentified at birth as to sex and are considered to be boys and many have been

operated upon with the mistaken diagnosis of pylorric stenosis due to their vomiting when they in reality were in Addisonian crisis. So that the more difficult sexual identity is, the more likely that the patient is to be a salt loser and one needs to be alert to this.

The normal adrenal cortex, as you remember from your histology days, is divided into three layers, an outer layer-the zona glomerulosa which in general has to do with the aldosterone part of the adrenal, the zona fasciculata which is the intermediate zone, having to do with the cortisol production of the adrenal, and finally the inner zone, the zona reticularis, making up about one-third of the normal adrenal cortex, which is the area having to do with the sex steroids. The estrogens and the androgens are produced primarily by that zone. In congenital virilizing adrenal hyperplasia, the problem is that the patient is unable to synthesize cortisol in normal amounts. There is a deficiency of the zona fasciculata. As a result of that deficiency, cortisol cannot feed back on the central mechanisms and ACTH is elevated in quantity. Increased ACTH then stimulates the portion of the adrenal which is best capable of responding, namely the zona reticularis. There is, therefore, great hyperplasia of the zona reticularis. If one searches the older literature before the treatment of this disorder with cortisone became available and reads the descriptions of these adrenals, as we have done in our own institution, the adrenal is often described as being as large at the kidney. Understanding this basic physiological problem allows one to understand the rationale of the treatment of this disorder with cortisone and its derivatives. There being a failure of cortisone production, one simply introduces cortisone into this system. This suppresses the overabundance of the secretion of ACTH which in turn allows the hyperplasia of the zona reticularis to recede to normal, and a homeostatic mechanism approaching normal is established.

Now the disturbances in cortisol synthesis are not due to one difficulty. It is necessary to recall the basic steps in the biosynthesis of cortisol. From $\triangle^5$ pregnenolone with the 3β-oldehydrogenase and isomerase, we get progesterone which is then hydroxylated at the 17 position with 17-α hydroxylase to form 17α-hydroxyprogesterone. This is then hydroxylated at the 21 position giving 11 desoxyhydrocortisone or compound S which then with the 11β-hydroxylation yields cortisol.

These steps may not necessarily be in that order, but this is probably the primary pathway for the biosynthesis of cortisol. The excretion products are: from progesterone pregnanediol, from the 17-hydroxyprogesterone pregnanetriol, from compound S tetrahydro S and, finally, from the hydrocortisone tetrahydrocortisone. By studying the excretion products in the urine, it is usually possible to identify the particular enzymatic defect in a particular case of adrenal hyperplasia. With the defect in 21 hydroxylation, which is the most common disturbance, one has a buildup of the substrate, namely 17-hydroxyprogesterone and, therefore, pregnanetriol is excreted in excess. This accounts for the reason that a determination of pregnanetriol is sometimes advocated as a method for diagnosing virilizing adrenal hyperplasia. All four types of blocks have been described in various cases. The 11β-hydroxylase block is particularly interesting because, in the absence of the 11β-hydroxylase, 11 desoxycorticosterone, which is a potent mineral corticoid and a substrate for aldosterone, builds up in the pathway to aldosterone production and causes a certain amount of hypertension. This hypertensive form of adrenal hyperplasia is most often not associated

with very great virilization, and it is possible to have external genitalia that are not greatly deformed. The patients are amenorrheic or oligomenorrheic and have hypertension. It is exceedingly important to diagnose this particular type of disorder, because this is one of the few types of hypertension that can be cured if cortisone is used early enough, although we have had some patients whose hypertension did not respond because of the irreversible changes that had taken place in the cardiovascular system by the time the patients came under observation. 3β-ol-dehydrogenase deficiency is an exceedingly serious disorder. These children seldom live to adulthood so that the gynecologist does not ordinarily see such a patient. Such a patient is a problem of severe metabolic disturbances which is usually handled by the pediatrician and is usually fatal. More recently, there has been described a 17α-hydroxylase block. I think no more than a handful of female patients has been described. Within the last month, I have seen the description of a similar type of case in a male. Now this is an extremely interesting block, because it stops the biosynthesis of estrogens and androgens both of which have to go through the 17α-hydroxylase step. These patients, being unable to make estrogen and androgen would, of course, be primarily ame norrheic and have high gonadotrophins. Thus, the clinical picture is characterized by high gonadotrophins and no estrogens. So here is one more different problem in the syndrome of primary amenorrhea with elevated gonadotrophins, which a few years ago seemed like a simple situation in that it usually meant failure of gonadal development or gonadal agenesis. But now there are three conditions which may give primary amenorrhea and high gonadotrophins-there would be the 17β-hydroxylase deficiency, just mentioned, the gonadal agenesis probleme and a syndrome of ovarian insensitivity.

We as gynecologists are used to thinking about the feedback system between the ovary and the central mechanism. The same sort of feedback situation exists between the central mechanism and the adrenal cortex.

If there is a 21-hydroxylase deficiency of the simple variety, the problem is that the cortisol is normal in amount only by virtue of the fact that the ACTH is greatly increased, and it is able in the average case to whip up enough cortisol out of these deficient glands to have a balance but only at the expense of a great deal more ACTH than normal. The result of that increased ACTH is that there is a great overabundance of the androgens and estrogens, and for the first time we then have an important feedback to the central mechanism from the estrogens and androgens of the adrenal. The central mechanism can't tell where these estrogens and androgens are coming from and it, therefore, shuts off the gonadotrophins which are normally directed to the ovary. As a consepquence of that, aldosterone in the simple virilizing hyperplasia, has been found to be either normal or somewhat elevated. It has been an interesting question why these children and adults with this disorder do not exhibit more difficulty with hyperaldosteronism, but we will not take time to discuss that particular point.

In the salt losing variety of this disorder, there is apparently a severe 21-hydroxylase deficiency or, perhaps and more likely, two separate 21-hydroxylase deficiencies, one of which has to do with aldosterone biosynthesis which requires 21 hydroxylation in addition to all the other hydroxylation that it requires. In the salt losing variety, aldosterone is deficient and one has to give in addition to the cortisol,

DOCA-desoxycorticosterone acetate which serves as a substrate during the biosynthesis of aldosterone. The full-blown case of virilizing adrenal hyperplasia requires cortisone, as we have already said, and of course requires reconstruction of the external genitalia, where there have been deformities of the varieties mentioned above.

There are now 47 of our patients who were operated on in infancy with this disorder and have gotten old enough to have menstrual periods. Fifty percent of all normal girls at the age of 13 should have had their first menstrual period, while in the 47 girls with congenital virilizing adrenal hyperplasia, there is a shift in this curve to the right and actually many of the girls by the time they had reached 15 years of age still had not had their first period. We as gynecologists are going to see treated patients with some delay in their pubertal development, and I think this simply means that we are unable with our cortisol to quite exactly replase the normal cortisol produced by the normal adrenal. The practical point is that one need not get too excited about working up a patient with congenital virilizing adrenal hyperplasia because of pubertal delay, because most of these girls finally will come around, although we have a couple of worrisome patients in the 17 to 18 year old range, and I don't know whether or not they will have their puberty spontaneously.

This disorder is a genetic problem. It is not a cytogenetic problem. Cytogenetically these individuals are quite normal. It is an autosomal recessive disorder and inherited according to strict Mendelian laws. The gene frequency is somewhat different, depending upon where it is studied. Dr. Barton Childs has studied it in the Baltimore population, where it seems to occur about 1 in 67,000 births Dr. Prader, on the other hand, studied it in Switzerland and found 1 in 18,000 births. This gives in round numbers an incidence of the heterczygotes of about 1 in 100.

One of the things that the patient with a child with virilizing adrenal hyperplasia wants to know is what are her probabilities of having another child with the same disorder. An individual who is a known heterozygote with a known heterozygote husband, is going to have one chance in four. She will have two heterozygote carriers, one unaffected and one affected homozygote, according to strict Mendelian laws. We are increasing ever so slowly the gene pool of people with this disorder by the use of cortisone, so that what we're doing is making patients to be treated by the next generation of gynecologists.

Now perhaps of more importance to the gynecologist, is the patient who has her puberty at the expected time, with normal breast development. However, she has some excess hair and might be considered as a patient with the Stein-Leventhal Syndrome, because the history is exactly the same, namely one of hirsutism, oligomenorrhea and infertility. An examination of her ketosteroids, however, showed a mild elevation and, with the dexamethasone suppression test, these ketosteroids would drop to at least 2.5mg/24 hrs., so that she must be considered as an example of the postpubertal form of virilizing adrenal hyperplasia with hirsutism, oligomenorrhea and infertility with slightly elevated 17-ketosteroids. Furthermore, on physical examination, her ovaries are entirely normal in size, or perhaps even smaller than normal, in contrast to a patient with a Stein-Leventhal Syndrome. We might view such a patient as having her primary defect in the adrenal glands whereby she has an inadequate biosynthesis of cortisol with normal amount of ACTH secretion. However, because of this defect, there is less than normal feedback on

the central mechanism with the result that ACTH secretion is elevated. This brings the cortisol production to normal, so that there is no sign of cortisol deficiency but in the process of doing so, increased amounts of adrenal secretions from the zona reticularis are produced, i.e., estrogens and androgens, and these in turn partially inhibit the proper gonadotrophin secretion with the result that the patient has inadequate and abnormal menstrual function. Just as is the case with individuals with the more severe form of the classical virilizing adrenal hyperplasia, the therapeutic use of cortisone, but in this instance in more modest doses, will result in the resumption of normal ovarian cycles and in pregnancy.

A postpubertal patient with normal 17-ketosteroid excretion may be encountered with oligomenorrhea, hirsutism and infertility. In order to be considered a patient within this classification, it is necessary to respond satisfactorily to cortisone. When this result occurs, we believe that it is reasonable to suppose that there is a mild adrenal defect or an allied disorder, but that the difficulty is so subtle that it cannot be measured by the rather crude examination of the urinary 17-ketosteroid excretion. If such a patient does not respond to cortisone she must be considered to have some other type of difficulty. It is, therefore, worth trying cortisone in this situation. It must also be mentioned that patients with the classical Stein-Leventhal Polycystic Ovary Syndrome will sometimes ovulate at least once with cortisone, the reason being that the use of cortisone by the mechanism already described will result in at least an initial surge of gonadotrophin, so that an occasional ovulation even in the classic Stein-Leventhal Syndrome is possible with cortisone. Patients with this latter classical syndrome fail to ovulate more than once or twice which is in marked contrast to patients with adrenal disorders who continue to ovulate with some regularity with the administration of a small dose of 50 mg. of cortisone a day for one month, dropping to 25 mg. as a maintenance dose although the dose must be adjusted to the individual patient, the goal being to have the 17-ketosteroid excretion in the neighborhood of 3 to 5 mg/24 hrs.

So much for virilizing adrenal hyperplasia and especially for its moderate form which is of much more interest as a daily problem to the gynecologist than the full-blown female hermaphrodite. However, a complete understanding of the latter is very helpful in the treatment of the former.

AMENORRHEA (CENTRAL)

CLASSIFICATION

Amenorrhea and oligomenorrhea are symptoms which may be caused by a variety of etiological factors. A single individual with a constant etiological background may show at various times any or all of the pathological manifestations of menstruction, including dysfunctional uterine bleeding, oligomenorrhea, amenorrhea, infertility, and habitual abortion. It is most satisfactory, therefore, whenever possible to make the classification of these symptom complexes on the basis of the underlying etiological disturbance. The following outline shows the etiological classification of amenorrhea to be used in the discussion with the inclusion of the most common syndromes.

ETIOLOGICAL CLASSIFICATION OF AMENORRHEA

I. Lesions of central origin
  A. Neurogenic
    1. Organic, destructive lesions, tumors or scars
    2. Idiopathic hypothalamic dysfunction

(Stein syndrome)

3. Inhibition of the prolactin inhibition factor (Chiari-Frommel syndrome)
4. Iatrogenic
   a. Steroids
   b. Drugs

B. Pituitary disturbances
1. Insufficiency
   a. Destructive processes (Sheehan's and Simmonds' disease)
2. Tumors
   a. Chromophobe adenoma (Ahumada-del Castillo)
   b. Acidophilic adenoma(acromegaly)
   c. Basophilic adenoma (Cushing's disease)
3. Congenital defects (?)
   a. Hypogonadotrophic eunuchoidism

C. Psychogenic amenorrhea
1. Major and minor psychosis
2. Emotional shock
3. Pseudocyesis
4. Anorexia nervosa

Ⅱ. Lesions of intermediate orgin
A. Chronic illnesses
B. Metabolic diseases
1. Thyroid
   a. Hypothyroidism and hyperthyroidism
2. Pancreas
   a. Diabetes mellitus
3. Adrenal
   a. Congenital adrenal hyperplasia, adrenogenital syndrome, and related disturbances
   b. Cushing's disease and "stress obesity"
   c. Tumors

C. Nutritional disturbances
1. Malnutrition
2. Exogenous obesity

D. Excretory and metabolic disease
1. Liver cirrhosis
2. Chronic nephritis (?)

Ⅲ. Lesions of peripheral origin
A. Ovarian amenorrhea
1. Insufficiency
   a. Congenital developmental defects-hermaphroditism and related conditions
      (1) Gonadal dysgenesis (Turner's syndrome)
      (2) True hermaphroditism
      (3) Male hermaphroditism
      (4) Testicular feminization syndrome
   b. Premature menopause (autoimmune disease)
   c. Destructive lesions abscesses, neoplasms, irradiation, and surgical trauma
2. The insensitive ovary
3. Tumors
   a. Arrhenoblastoma, hilus cell, adreral rest
   b. Granulosa cell, thecoma
   c. Nonspecific with steroidogenic steroma

B. End organ cryptomenorrhea
1. Congenital defects
   a. Imperforate hymen
   b. Absence or atresia of vagina
   c. Septum of vagina
   d. Absence of uterus (congenital absence of Mullerian ducts)
2. Traumatic
   a. Stenosis of vagina
   b. Stenosis of cervix
   c. Sclerosis of uterine cavity (Asherman's disease)

Ⅳ. Physiological amenorrhea
A. Delayed puberty

B. Pregnancy
C. Postpartum amenorrhea
D. Menopause

V. Etiology undetermined

DIAGNOSIS AND TREATMENT OF AMENORRHEA OF CENTRAL ORIGIN

Problems of central origin responsible for menstrual irregularities can be divided into psychogenic, neurogenic and specific pituitary problems. Psychogenic factors are represented by depressive reactions and some of the specific syndromes such as anorexia neurosa, pseudocyesis, acute psychic stress. Neurogenic problems can be the result of scars from trauma or infection or tumors and are usually associated with other signs of neurological disease. Hypothalamic disease can be the result of iatrogenic factors, heritable disease, scars or tumors. Pituitary lesions can be categorized under the heading of destructive lesions, tumors or congenital deficiencies such as specific defects in the gonadotrophin producing cells.

The most helpful diagnostic tests for amenorrhea of central origin are the pituitary gonadotrophin assays, either total urinary gonadotrophins by bioassay, or radioimmunoassay in the serum for FSH and LH. With few exceptions, specifically the Stein-Leventhal syndrome, all patients having amenorrhea of central origin show gonadotrophin values below normal or in the very lowest normal levels. Under these circumstances, it is then necessary to have an X-ray of the sella turcica to exclude pituitary tumors. The visual fields are also helpful, as well as neurological examinations. An electroence phalogram is unfortunately usually not sufficiently sensitive to pick up early neurological lesions. An hematocrit has been said to be the poor man's diagnostic tool for investigating destructive lesions of the pituitary, as pituitary destruction is associated with unexplained anemia.

From this point, the slide review will illustrate clinical examples of the categories described with a discussion of diagnostic criteria and therapy.

(本演題는 1975. 5. 19. ~5. 24에 있었던 존스·홉프킨스大學校 國際產婦人科 韓國敎育硏究院(JHPIEGO/KOREA)의 第1次學術大會時에 講演하였든 것이며 著者의 承認을 얻어서 本誌에 게재함).