ETIOLOGICAL ASPECTS OF PRIMARY AMENORRHEA

ABDUL HAMID ZARGAR ● SHARIQ RASHID MOSOODI ● BASHIR AHMAD LAWAY ● NISSAR AHMAD SHAH ● FAYAZ AHMED SOFI ● MOHAMMAD SALAHUDDIN.

SUMMARY

We describe clinical and investigative data of 141 cases of primary amenorrhea, seen at Institute of Medical Sciences, Srinagar (Kashmir) over a period of nine years from 1986 to 1994. Average age at presentation of these patients was 21.17+5.39 years. Fifty eight patients (41.73%) had hypergonadotropic hypogonadism, 33(23.73%) had hypogonadotropic hypogonadism, 29(20.86%) had mullerian amomalies and 12 patients (8.63%) had delayed menarche. Of 58 patients with hypergonadotropic hypogonadism 46 cases had classical Turner's syndrome constituting singlemost common etilogic group. Of 33 cases with hypogonadotropic hypogonadism, 27 had isolated gonadotropin deficiency whereas 6 had pan-hypopituitarism. Among anatomic defects Mullerian agenesis was the commonest anomaly. Average height of patients with Turner's syndrome was 141cm and that of individuals with isolated gonadotropin deficiency was 163cm, compared to average height of 153cm in normal controls.

INTRODUCTION

Amenorrhea is a symptom of diverse etiologies. In contrast to earlier reports, amenorrhea during the reproductive years is not an uncommon occurrance (Schachter and Shoham 1994). It has been estimated that the prevalence of amenorrhea in the general female population during the reproductive years is 1.8% to 3% (Pettersson et al 1973), the prevalence in college-aged women is 2.6% to 5% (Bachmann and Kenmann 1982, Singh 1981). Amenorrhea occurs in 10-20% of patients complaining

Dept of Endocrino. and Immuno Inst. of Med. Sciences, Srinagar, Kashmir

Accepted for Publication 12.1.96

of infertility and is one of the commonest reasons for referral to gynaecological endocrine clinic (Franks 1987).

The differential diagnosis of primary amenorrhea continues to be an interesting intellectual exercise, an exercise that has become more fascinating with the unfolding knowledge of genetic and hormonal influences on phenotypic development. With proper diagnosis and management it should be possible for all these patients to lead a normal life, although many will be infertile (Shearman 1968). The present study is a retrospective analysis of data from 141 patients who presented with primary amenorrhea to the endocrine unit of Institute of Medical Sciences (IMS), Srinagar, Kashmir for evaluation. We discuss the etiological factors, modes of presentation and associated abnormalities.

MATERIAL AND METHODS

One hundred and fifty six patients were evaluated for primary amenorrhea during the nine year period (Jan. 1986 - Dec. 1994) under study. In 15 of these patients adequate data was not available and were therefore, excluded from the study. Only data from the remaining 141 patients were analysed further. These patients were referred by physicians and gynaecologists from all over the Valley and all were Kasnmiris. Primary amenorrhea was defined as failure of menarche by age 16 years, regardless of presence, or absence of secondary sexual characteristics (Carr 1992). Patients who had abnormalities in sequence and tempo of pubertal development, or secondary amenorrhea following an arbitary six cycles or less of menses after menarche were also included (Reindollar et al 1981). A few patients diagnosed during childhood as gonadal dysgenesis were subsequently referred for management and were included in this study. The initial evaluation included a detailed endocrine history, assessment of pubertal development by Tanner standards, ascertainment of genital and somatic anomalies and determination of estrogen status clinically and/or by progesterone challenge test. Progesterone challenge test (Hull et al 1979) was considered an adequate reflection of good estrogen status if it resulted in bleeding which approximated to that of spontaneous menses.

Extensive basal and dynamic laboratory testing as well as appropriate radiological and operative studies were carried out. The discretion of doing any particular investigation depended on the underlying cause suspected. These tests included hemogram, liver and renal function tests, urine analysis, buccal smear for Barr bodies, Karyotyping, endometrial biopsy, hysterosalpingography, skull roentgenography, pelvic ultrasonagraphy and laparoscopy. Hormonal estimation included that of serum luteinizing hormone (LH), follicle stimulating hormone (FSH), prolactin (PRL), triiodothyronine (T3), tetraiodothyronine (T4), thyroid stimulating hormone (TSH), growth hormone (GH) and cortisol. Gonadotropin estimations were done in all patients with suspected hypogonadism; Insulin tolerance test (with 0.1 - 0.15 units of soluble insulin/kg) for GH and cortisol was done in patients suspected to have pituitary disease, and thyroid function tests were done when thyroid dysfunction was suspected. Because of irregular availability of karyotyping during major part of the study period, buccal smears for Barr bodies

were used as the only cytogenetic evaluation in majority of the patients. Intravenous pyelography was performed in some patients with abnormal karyotype or Mullerian anomalies.

RESULTS

One hundred and forty one patients with presumptive diagnosis of primary amenorrhea were evaluated in the endocrine unit of IMS Srinagar from January 1986 to December 1994. Even though all the patients had amenorrhea, many patients presented with symptoms other than amenorrhea (Table I). Amenorrhea and/or underdeveloped secondary sexual characteristics (59.57%), growth retardation (18.44%) and infertility (7.8%) were common modes of presentation to the clinician. The age at the time of presentation ranged from 12 to 40 years (mean, 21.17±5.39; median, 21 yeats). 33.33% of patients were married at the time of presentation but none of them had ever conceived.

Analysis of the clinical and investigative data revealed that 58 patients (41.73%) had hypergonadotropic hypogonadism, 33 (23.74%) had hypogonadotropic hypogonadism, 29 (20.86%) had mullerian anomalies, and 12 (8.63%) had delayed menarche (Table II). In the remaining 2 patients no definite etiology could be ascertained. Table III shows the comparative heights in patients with primary amenorrhea of different categories. Patients with Turner's syndrome were significantly shorter ($P<0.01$) and those with hypogonadotropic hypogonadism were significantly taller ($P<0.01$) than the control population. Because of non-availability of karyotyping in most of the patients, buccal smear for Barr bodies was used for gross cytogenetic evaluation (Table IV). LH, FSH and PRL levels in patients with different categories of primary amenorrhea are given in Table V.

Fifty eight patients were found to have hypergonadotropic hypogonadism with mean

TABLE I
REFERRAL REASONS FOR 141 PATIENTS WITH PRIMARY AMENORRHEA

	No	%
Amenorrhea and/or underdeveloped secondary sexual characteristics	84	59.57
Growth retardation/short stature	26	18.44
Infertility	11	7.80
Hirsutism and/or masculine features	10	7.09
Dyspareunia	6	4.25
Features of cretinism	2	1.42
Pigmentation	2	1.42

TABLE II
ETIOLOGIC BREAKDOWN OF 139 PATIENTS PRESENTING WITH PRIMARY AMENORRHEA

	Group Total	No	Percentage
Hypergonadotropic hypogonadism:	58		41.73
Turner's syndrome		46	33.09
Non-Turner (Incomplete Turner's) Syndrome		12	8.63
Hypogonadotropic hypogonadism:	33		23.74
Isolated gonadotropin deficiency		27	19.42
Hypopituitarism		6	4.32
Anatomic defects (Mullerian anomalies)	29		20.86
Mullerian agenesis (Rokitansky syndrome)		15	10.79
Endometrial hypoplasia		7	5.04
Transverse vaginal septum		5	3.60
Imperforate hymen		2	1.44
Delayed menarche	12		8.63
Miscellaneous	7		5.04
True hermaphroditism		2	1.44
Congenital adrenal hyperplasia		2	1.44
Hypothalamic/weight loss amenorrhea		2	1.44
Testicular feminization sundrome		1	0.72

TABLE III
COMPARATIVE HEIGHTS OF VARIOUS CATEGORIES IN PATIENTS WITH PRIMARY AMENORRHEA

	Height (Centimeters)		
Etiologic group	Mean	±SD	Range
Hypergonadotropic hypogonadism:			
Turner's syndrome	140.62	±11.95	114-158
Non Turner	160.87	±5.79	154-170
Hypogonadotropic hypogonadism:			
Isolated gonadotropin deficiency	162.89	±4.16	158-170
Panhypopituitarism	133.25	±8.13	127-133
Delayed menarche	152.71	±9.71	140-168
Mullerian anomalies	157.0	±6.03	146-168
Normal controls (general female population)	153.45	±5.79	134-168

TABLE IV
RESULTS OF CYTOGENETIC EVALUATION IN PATIENTS WITH PRIMARY AMENORRHEA

	Sex chromatin (% in buccal smear) Mean	±SD	Range
Hypergonadotropic hypogonadism			
Turner's Syndrome	10.65	±4.53	0-18
Non-Turner	22.17	±2.48	20-27*
Hypogonadotropic hypogonadism	20.44	±1.95	18-22*
Mullerian anomalies	20.57	±1.81	18-22*
Delayed menarche	21.75	±1.86	21-23*

* Minimum percentage of Barr bodies detected in buccal smears

TABLE V
SERUM GONADOTROPIN AND PROLACTIN LEVELS IN PATIENTS WITH PRIMARY AMENORRHEA

Hormone	Hypergonadotropic hypogonadism Turner's synd.	Non-Turner	hypogonadotropic hypogonadism	Mullerian anomalies	Delayed menarche
LH(IU/L)					
Mean	25.91	26.96	1.85	11.06	11.53
SD	±15.24	±11.83	±2.74	±11.54	±9.0
Range	3.3-57.7	21-50	UD-9.9	2.9-35.7	UD-34.2
FSH(IU/L)					
Mean	57.50	59.98	1.60	6.33	6.26
SD	±27.36	±12.12	±1.47	±4.91	±3.52
Range	27-103	30-74	UD-5.1	2.6-13.7	2.4-15.1
PRL(mU/L)					
Mean	380.97	398.82	247.65	333.90	373.60
SD	±173.17	±214.17	±128.64	±113.7	±197.33
Range	292-653	247-550	UD-553	234-599	240-490

UD= Undetectable
Normal lab value for LH, 3.0-12.0 (early follicular phase); Normal lab value for FSH, 2.0-6.6 (early follicular phase); and normal lab value for PRL; 0-520.

TABLE VI
CLINICAL DATA IN 46 PATIENTS WITH TURNER'S SYNDROME

	No*	%
Age at presentation (yr) (N=46)		
Mean ± SD (Range)	22.24±4.80	(13-29)
Married (N=37)	7	18.92
Evidence of gonadal function (N=42)		
Breast ≥ Tanner II	14	33.33
Menses 6 months	6	14.30
Height ≤ 150 cm (N=45)	34	75.55
Somatic anomalies other than short stature		
Webbing of neck (N=43)	13	30.23
Other Turner signs+ (N=43)	26	60.46

N : Number of patients in whom this data was available
* No. of patients affectd, except if otherwise indicated
+ These signs included low hair line, short 4th metacarpal bone, lymphedema, sheild chest, high arched palate and wide carrying angle.

LH and FSH of 26.09±14.54 IU/L and 58.05±25.39 IU/L respectively, suggesting significant ovarian failure. Forty six of these patients had various extragenital abnormalities associated with classical Turner's sundrome, most striking features being webbing of neck (Fig. 1), shortening of fourth meta-carpal bone, low hair line, lymphedema and widening of carrying angle. In these patients nuclear sex chromatin was usually of male type (mean percentage of sex chromatin in buccal smear: 10.65+4.53). Clinical details of this patient group are given in Table VI. Twelve patients with hypergonadotropic hypogonadism had normal sex chromatin in buccal smear (mean 22.17+2.48%), had attained normal height and did not have any overt somatic feature of Turner's syndrome except non-development of secondary sexual characteristics. This group, which we called non-Turner ovarian failure could be comprised of patients with incomplete Turner's syndrome (Henzl et al 1965), and some other forms of ovarian failure. These was no significant difference in the gonadotropin levels of the two groups.

Of 33 patients with hypogonadotropic hypogonadism, 6 had panhypopituitarism while 27 had isolated gonadotropin deficiency including three sisters who had classical features of Kallmann's syndrome (Fig 2). Of 29 patients with mullerian anomalies, majority (15 patients) had congenital absence of the vagina and uterus, also known as Rokitansky-Kuster-Hauser

Fig. 1 A patient of Turner's syndrome with webbing of neck and incidental Grave's disease; B, a young lady with congenital webbing of neck but no features of Turner's sybdrome; C, Normal female nurse of comparable age.

Fig. 2 Three sisters with classical Kallmann's syndrome.

syndrome (Golditch 1969). Mean age of presentation of patients with mullerian anomalies was 23.68+6.14 years, higher than that of patients with hyper or hypogonadotropic hypogonadism but this age difference was not statistically significant. One patient with Rokitansky syndrome who was married for 2 years reported because of infertility even though she never had any sexual intercourse. Twelve patients were diagnosed to have delayed menarche on follow up. Their average age at presentation was 17.87 years. Two patients had true hermophroditism, 2 had female pseudohermaphroditism (congenital adrenal hyperplasia), one had testicular feminization syndrome and 2 had hypothalamic amenorrhea, one of whom was suspected to have anorexia nervosa. None of the patients with Turner's syndrome or mullerian anomalies (in whom this information was available) had any renal or cardiovascular anomaly.

DISCUSSION

The normal menarche requires a nice integration of hypothalamus, pituitary, ovary, uterus and a patent effluent canal for menstrual bleeding. Aberrations in any of these may result in failure of sexual maturation or absence of menarche (Sharman 1968). Amenorrhea is defined as the absence or cessation of menstrual bleeding and is a manifestation of a variety of pathophysi-

ological disorders. The criteria used to define the duration of absent periodic bleeding or the age at which menarche should appear are not uniform. The failure by the age of 16 years merits evaluation (Carr 1992).

The spectrum of pathologic conditions that we have reported is in agreement with that of most other series (Henzl et al 1965, Philip et al 1965, Shearman 1968, Carr 1992). In our series the single largest group of patients evaluated had hypergonadotropic hypogonadism, present in about 42% of the entire study (Table II). Most (79%) of these individuals has male type sex chromatin and well developed classical symptoms originally described by Turner, of which webbing of the neck was the most striking. Other somatic anomalies were present in varying proportions (Table VI). A small group of 12 patients had hypergonadotropic hypogonadism with positive sex chromatin. None of these patients had any clinical suggestion of a definite etiology. Redindollar et al (1981) found that 46, XX ovarian failure occured in majority of these patients but a well-defined etiology was elicited in only one patient who had recieved radiation for Wilm's tumor in childhood. The second largest group of patients with primary amenorrhea consisted of individuals with anatomic defects (21%). An almost equal number of patients had isolated gonadotropin deficiency (19%). These data confirm previous case series reports that the two largest groups of patients include those individuals with ovarian failure and Rokitansky syndrome (Carr 1992). Reindollar et al (1981) described 252 patients with primary (or pubertal amenorrhea) and found the most common etiologic factor to be ovarian failure, most commonly due to ovarian dysgenesis (43%), genital tract abnormalities (15%) and physiological delayed puberty (14%). About 23% of our patients had hypogonadotropic hypogonadism (19% having isolated gonadotropin deficiency and 4% having panhypopituitarism), suggesting a central cause i.e., hypothalamic and/or pituitary disease. Luteinizing hormone releasing hormone (LHRH) has been used to differentiate between hypothalamic and pituitary disease but, the variability in gonadotropin response limits the usefulness of LHRH test as a diagnostic tool to categorize individual patients (Soules et al 1979).

Average age at presentation of our patients was 21 years, higher than that (17.5 years) reported by Reindollar et al (1981). Delay in seeking medical advice by our patients cound be because of lack of awareness in the population under discussion. Majority of females seem to hesitate in seeking medical advice for poor development of secondary sexual characteristics and are often shy to discuss their menstrual history.

Table III depicts the significance of height in differential diagnosis of primary amenorrhea. All patients with Turner's syndrome were less than 159 centimeters in height while many patients with hypogonadotropic hypogonadism were short or normal in height. However, the mean height of individuals with Turner's syndrome was significantly shorter, and that of individuals with hypogonadotropic hypogonadism was significantly taller than the mean height of general female population. The height of patients with mullerian anomalies and delayed puberty was comparable with that of normal controls.

Reindollar et al (1981) found that all patients with Turner's syndrome were less than 63 inches (160cm) in height. Some authors tend to incriminate deletion of short arm X material for short stature, others suggest that deletion of any X material compromises height (McDonough, 1977). Buccal smears were used as the only cytogenetic evaluation in most of the patients because of irregular availability of karyotyping. Buccal smears need to be used along with karyotyping as ancillary data in determination of the presence or absence of Y cell lines and mosaicism. Gonadal tumors have been diagnosed in individuals with dysgenetic gonads associated with a Y chromosome (Reindollar et al, 1981). However, none of the patients in this series had a gonadal tumor.

Reproductive potential is significantly altered in patients with primary amenorrhea. Thirty-three percent of individuals with primary amenorrhea who were married, were all infertile. One patient with imperforate hymen and hematocolpos who was operated in time, has prospects of having a good reproductive potential.

With availability of chromosomal analysis, gonadotropin assays, pelvic sonagraphy and laparoscopic expertise the diagnosis of primary amenorrhea and its management has been simplified. Data regarding the aberrations of menstrual pattern relevant to whole population cannot be extracted from hospital records of a tertiary centre, where more or less selected groups of women turn up; instead such data must be collected from population surveys.

ACKNOWLEDGEMENT

We are thankful to Mrs. Sharnagat Kour, Senior Resident, Immunology and Mr. Mohd. Shafi Bhat, Senior Technologist, Immunology for their assistant in data collection; and Mr. Farooq Ahmed Nadaf for his help in preparation of this manuscript.

REFERENCES

1. *Bachmann Ga, Kenmann E Am J Obstet Gynec. 144:98; 1982.*
2. *Carr BR Disorders of the Ovary and female reproductive tract. In: William's Text book of Endocrinology (8th ed) Wilson JD and Foster DW editors. Saunders, Philadephia, 733. 1992.*
3. *Franks S. B. Med. J. 294: 815; 1987.*
4. *Golditch IM Surg. Gynec. Obstet, 129: 361; 1969.*
5. *Henzl M, Presl J, Horsky J Am Obstet. Gynec. 93: 79; 1965.*
6. *Hull MGR, Knuth UA, Murray MAF, Jacobs HS. Brit. J Obstet Gynec. 86: 799; 1979.*
7. *McDonough PG, Byrd JR and Tho PT Fertil steril, 28:638; 1977.*
8. *Pettersson F, Fries H, Nillius SJ Am J Obstet. Gynec. 117:80; 1973.*
9. *Philip J, Sele Vand Trolle D Fertil Steril, 16: 795; 1965.*
10. *Reindollar RH, Byrd Jr, McDonough PG Am J Obstet. Gynec. 140: 371; 1981.*
11. *Schachter M, Shoham Z Fertil. steril. 62: 1; 1994.*
12. *Shearman RP Obstet. Gynaecol. Brit C'Wealth 75:1101; 1968.*
13. *Singh KB Am J Obstet. Gynec. 140:299; 1981.*
14. *Soules MR, Jwlovsek FR, Wiebe RH et al. Am J Obstet. Gynec. 135:651; 1979.*