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Clinicopathological features of premature ovarian insufficiency associated with chromosome abnormalities

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Purpose: The aim of this study was to investigate the clinicopathological features of premature ovarian insufficiency (POI) associated with chromosomal abnormalities.

Materials and Methods: This was a retrospective study of POI patients with chromosomal abnormalities diagnosed between January 2009 and December 2017. The definition of POI is based on hypergonadotropinism of 40 or greater in follicle stimulating hormone (FSH) measurements at age 40 years or less. FSH was measured twice at least 4 weeks apart. Karyotyping using peripheral blood for chromosomal testing was conducted in all patients diagnosed with POI. We analyzed the clinical characteristics and genetic causes of patients who were diagnosed with POI.

Results: Forty patients were diagnosed with POI including 9 (22.5%) with identified chromosomal abnormalities. The mean age at diagnosis was 23.1±7.8 years (ranging between 14 and 39). Three patients did not experience menarche. The presenting complaints were short stature in one case, one case of amenorrhea with ambiguous external genitals, one case of infertility, and six related to menstruation such as oligomenorrhea or irregular rhythm. Turner syndrome was diagnosed in four cases, Xq deletion in one case, trisomy X in two cases, and 46,XY disorder of sexual development in two other patients.

Conclusion: Patients diagnosed with POI carrying the same type of chromosomal abnormality manifest different phenotypes. The management protocol also needs to be changed depending on the diagnosis. A karyotype is indicated for accurate diagnosis and proper management of POI in patients, with or without stigmata of chromosomal abnormalities.

Key words: Premature ovarian insufficiency, Karyotype, Chromosome aberrations.

Introduction

Premature ovarian insufficiency (POI) is defined as ovarian failure with hypergonadotrophic hypogonadism (follicle stimulating hormone [FSH] level>40 IU/L and estradiol (E2) level<50 pmol/L) occurring before the age of 40 years [1]. The incidence of POI was reported to be 0.01% by the age of 20 years, 0.4% by the age of 35 years, and 1% by the age of 40 years [2]. Patho-

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physiological defects inducing ovarian dysfunction are of two types: acceleration of follicle depletion, and decreased steroid production with oocyte loss [3]. POI caused by genetic factor was associated with accelerated follicle depletion. The causes of primary POI including genetic factors, enzyme deficiency, defective gonadotropin structure or action are known. However, POI of unknown etiology accounts for approximately 75-90% of all cases [4]. About 10-15% of POI carry familial history [5,6], which suggests genetic predisposition. The most common presenting symptom in POI involves a change in menstrual cycle. Almost 10-28% of patients with primary amenorrhea and 4-18% with secondary amenorrhea are related to POI [7]. Early diagnosis is crucial for POI patients. Approximately 25% of patients are diagnosed after 5 years of symptoms [8]. Early diagnosis of POI prevents clinical events induced by estrogen deficiency such as osteoporosis. Diagnosis of chromosomal abnormalities in POI leads to different management options. Karyotyping is indicated for the diagnosis of POI.

The aim of this study was to investigate the clinicopathological features of POI in patients with chromosomal abnormalities.

Materials and Methods

We retrospectively analyzed 40 patients who were diagnosed with POI in the Obstetrics and Gynecology Department of Gyeongsang National University Hospital from January 2009 to December 2017. Because this study used data from patients that could not be personally identified, it was exempt from Institutional Review Board review according to the Korean Bioethics and Safety Act.

Diagnostic specification was based on the Korean Standard Classification of Diseases 7th edition, which is a modified version of the International Statistical Classification of Diseases and Related Health Problems 10th edition. In this study, the definition of POI was based on hypergonadotropinism (over 40 IU/L) and hypoestrogenism (E2 less than 50 pmol/L) at age 40 years or less among the diagnostic codes for primary amenorrhea (N910), secondary amenorrhea (N911), amenorrhea (N912), primary ovarian failure (E283), and delayed puberty (E300). FSH was measured twice at least 4 weeks apart. Also, we performed urine or serum human chorionic gonadotropin (hCG), thyroid stimulating hormone (TSH), prolactin. Karyotyping using peripheral blood for chromosomal analyses was performed in all patients diagnosed with POI. Anti-Müllerian hormone (AMH) was not measured in all patients with POI. Information pertaining to height (percentile) was based on data provided by the Korean Agency for Technology and Standards in 2010.

Results

During the past 9 years, 40 patients were diagnosed with POI including 9 (22.5%) with identified chromosome abnormalities. Table 1 displays characteristics of POI patients with chromosome abnormalities; age at diagnosis, height (cm), presenting complaints, FSH level (IU/L), E2 (pmol/L), AMH (ng/mL), and final diagnosis. All of FSH, E2, AMH value were obtained at diagnosis of POI. The mean age at diagnosis was 23.1±7.8 years (ranging between 14 and 39). Three patients did not experience men-

Table 1. Characteristics and genetic factors underlying premature ovarian insufficiency

No.	Age at diagnosis (yr)	Height (cm)	Parity	Age at menarche (yr)	Chief complaint	FSH (IU/L)[a]	E2 (pmol/L)	AMH (ng/mL)	Diagnosis	Additional information
1	16	168	0	14	Irregular	49.8/50.2	14.61		47,XXX	
2	16	167	0	(-)	Amenorrhea	51.45/80.2	16.82		46,XY	
3	18	164	0	14	Secondary amenorrhea	44.61/60.83	9.66		46,X,i(Xq) or 46,X,i(X)(q10)	
4	18	143	0	(-)	Short status	110.86/76.3	11		45,X[24]/46,X,+mar[6]	
5	19	164	0	(-)	Amenorrhea Delayed puberty Ambiguous genitalis	47.63/60.95	31.22		46, XY, inv(9)(p12q13)	Bilateral gonadectomy Penectomy
6	25	165	0	15	Oligomenorrhea Amenorrhea for 4 months	51.82/42.98	16.86		47,XXX	Hot flushing
7	27	156	0	15	Oligomenorrhea	52.41/78.6	5		45,X[18]/46,XX[22]	
8	30	151	0	15	Infertility Oligomenorrhea	79.48/47.23	<5	0.01	46,X,del(X)(q23)	
9	39	158	2	14	Secondary amenorrhea	65.37/43.4	25 17	0.01	45,X[4]/46,XX[96]	

[a]Value obtained at 2nd visit/value obtained at 1st visit.
FSH, follicle stimulating hormone; E2, estradiol; AMH, anti-Müllerian hormone.

arche. Presenting complaints included a case each of short stature, amenorrhea with ambiguous external genitals, and infertility, and 6 cases related to menstruation such as oligomenorrhea or irregularity of rhythm. Among 9 patients with chromosomal abnormality, Turner syndrome (TS), Xq deletion, trisomy X, and 46,XY disorder of sexual development (DSD) were diagnosed in four, one, two, and two cases, respectively.

Discussion

Premature ovarian failure is defined as ovarian failure with hypoestrogenism and hypergonadotropinism in women aged below 40 years. The etiology of POI remains unknown in approximately 75-90% of cases [4]. The genetic causes of POI include X-linked and autosomal dominant diseases. X-linked diseases are characterized by monosomy, trisomy, deletions, translocations, and fragile X syndromes. Autosomal dominant conditions associated with POI include FSH receptor gene polymorphism, inhibin B mutation, and so forth [9]. Chromosomal aberrations constitute nearly 14.71% of all causes underlying POI [10]. In this study, 9 (22.5%) out of 40 patients diagnosed with POI were associated with chromosomal abnormalities. No monosomy was detected; however, two cases of trisomy, three patients with mosaicism, one case of deletion, and one case of isochromosome were found. The remaining two patients manifested 46,XY DSD.

Four patients were diagnosed with TS in our study. TS, which is caused by total or partial loss of a second X chromosome, is one of the most common genetic causes of POI, with an incidence of approximately 1 in 2,000 to 2,500 live female births [10]. TS is associated with diverse chromosomal abnormalities including 45,X (monosomy X), 45,X mosaicism, X chromosome anomalies, and Y chromosome mosaicism [11]. Monosomy X is found in approximately 45% of TS. This type was not detected in this study. Monosomy X may manifest clinically as short stature, web neck, low hair line at the back of the neck, and lymphedema. In this study, two patients were diagnosed with TS and TS combined with mosaicism, at the age of 27 and 39 years, respectively. The karyotype of both patients was 45,X/46,XX. One patient (age, 39 years) experienced two deliveries, with the last one occurring 2 years before the hospital visit. The patient reported only a sudden onset of secondary amenorrhea that occurred 6 months ago. Another patient presented with only oligomenorrhea (five times per year) starting from menarche. Ultrasonography revealed no abnormal findings except a small uterus. TS caused by mosaicism was estimated at approximately 50% (e.g., 45,X/46,XX, 45,X/47,XXX or 45,X mosaic with X chromosome anomalies). The mechanism of mosaicism results from sex chromosome nondisjunction occurring during postzygotic cell division [12]. The clinical phenotype of patients with mosaicism depends on the tissues affected and the developmental timing of mosaicism. The clinical pathology of mosaicism is milder than that of monosomy X. Low degrees of mosaicism occur in phenotypically normal females. TS is induced by severe X chromosome anomalies such as isochomosome Xq [46,X,i(Xq)], ring chromosome [46, X,r(X)], and Xp or Xq deletion. Isochromosome is an abnormal structure composed of two long or two short arms. 46,X,i(Xq) is reported to constitute 7-17 % of the total TS [13]. It is reported that the clinical characteristics of this type are similar to those of classical TS. However, patients with an Xp deletion have short stature and congenital malformations. Those with deletions of Xq often only exhibit gonadal dysfunction. In this study, one patient was diagnosed with isochromosome Xq. Her height was 164 cm (75-95%). No distinguishing features except for secondary amenorrhea were observed. Among the patients diagnosed with POI in this study, only one patient had a short stature. She had a height of 143 cm (less than 1%). Her karyotype was 45,X/46,X, +mar type which is rare and is reported in approximately 1% of TS [13]. No additional information was available due to lack of follow-up observation. One patient presented with infertility. She was accompanied by oligomenorrhea that started at the age of 20. Her height was 151 cm (5-25%). She was diagnosed with a deleted Xq chromosome. In the case of deletion of the terminal portion in Xq, most of the symptoms were related to ovarian failure without other findings of TS. It was assumed that short stature was not related to chromosome abnormality. Rates of Xp-deletion TS and Xq-deletion TS were reported as 1.5% and 3%, respectively [14]. Ovarian function was preserved until nearly two-thirds of Xp chromosome is lost [15]. Two critical regions involved in normal ovarian function include Xq13-q21(CR1) and Xq23-q28 (CR2) [16]. The region between Xq26.2 and Xq28 is the most critical for POI [17].

In this study, two patients were diagnosed with trisomy X (47,XXX), which is a sex chromosome aneuploidy associated with an extra X chromosome. The incidence of this condition is approximately 1/1,000 female births [18]. Trisomy X is caused by chromosomal nondisjunction during gametogenesis (resulting in a trisomic conceptus) or after conceptus (and known as postzygotic nondisjunction) [19]. Only approximately 10% of patients were identified clinically due to significant phenotypic variation [18]. Although most cases of trisomy X involve 47,XXX, approximately 10% is characterized by mosaicism such as 47,

XXX/48,XXXX or 46,XX/47,XXX [20]. Significant facial and physical features associated with trisomy X are rare, and include tall stature, epicanthal folds, clinodactyly, hypotonia in infancy, and hypertelorism, with tall stature being the most common manifestation. Nearly 80-89% of cases reported a height above 75th percentile [21]. Two patients measured 168 cm (above 95%) and 165 cm (above 95%) in height, respectively. No other physical features were shared by such patients.

Two patients were diagnosed with 46,XY DSD in this study including one with androgen insensitive syndrome (AIS), and another with mixed gonadal dysgenesis. In the former case, the patient's sister and aunt were diagnosed with AIS and were treated appropriately. AIS is an X-linked recessive disorder. The patient's height was 167 cm (above 95%). Ultrasonography revealed no uterus or ovary. However, no further information was available due to loss of follow-up observations. In another patient, physical examination showed normal external female genitals except for clitomegaly. The uterus and ovaries were not observed on magnetic resonance imaging; however, laparoscopic examination revealed both streak gonads in the pelvic cavity. Bilateral gonadectomy with penectomy was done. Histopathology revealed a penile shaft in clitomegaly and testicular atrophy in both streak gonads. DSD is defined as a clinical condition of discordance between sexual phenotype and genotype. It is classified into three groups based on chromosomal components; 46,XX DSD, 46,XY DSD, and sex chromosomal DSD. 46,XY DSD is divided into two groups based on etiology: abnormal testicular development and defective androgen action [22]. The first group included conditions such as gonadal dysgenesis (Swyer syndrome), and the second group was characterized by AIS (Morris syndrome). Gonadal dysgenesis manifests three different phenotypes: simple gonadal dysgenesis, mixed gonadal dysgenesis (asymmetrical gonadal development, and external female genitalia) and partial gonadal dysgenesis (bilateral dysgenetic testis, and mixture of male and female external genitalia) [23]. The incidence of gonadal tumors is higher in XY females. It is reported that seminoma occurs in AIS and gonadoblastoma, whereas gonadal dysgerminoma is found in gonadal dysgenesis [23]. The streak gonads should be removed promptly after early diagnosis. In most cases, fallopian tubes are also removed in gonads with a wide margin.

This study has several limitations. First, a selection bias can arise from studies conducted at a single tertiary hospital. Second, a small number of patients participated in the study. Third, because this study involved a retrospective design, it was hard to determine the clinical characteristics of POI patients.

In conclusion, most of POI is of unknown etiology. However, a few cases of POI are caused by genetic factors such as chromosome anomalies. In this study, 9 (22.5%) patients were diagnosed with POI caused by chromosome anomalies. Four cases of TS, one case of Xq deletion, two trisomy X and two 46,XY females were diagnosed. Patients with POI carrying similar chromosomal abnormality manifest phenotypes differently, and the method of management depends on the diagnosis. Karyotyping is recommended for accurate diagnosis and management of POI patients, with or without chromosomal abnormalities.

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