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RESEARCH

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Cytogenetic evaluation of primary amenorrhea: a study of 100 cases at tertiary centre

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Abstract

Background: Amenorrhea is the absence of menstruation in women of reproductive age. The physiology of menstruation and reproduction has a strong correlation with the expression of the X chromosome. Early referral for cytogenetic evaluation is recommended for the identification of underlying chromosomal aberrations in amenorrhoea patients. This study aims to estimate the frequency and types of chromosomal abnormalities in primary amenorrhoea (PA) patients in western India and correlate their hormonal profile and sonographic findings with chromosomal reports.

Patients and methods: Clinical features of 100 patients along with their hormonal profile and sonographic findings were recorded. Karyotyping was done after taking informed consent from the patients. Molecular cytogenetic technique was used to confirm marker chromosomes and ring chromosomes.

Results: The results revealed 89% of PA with normal female karyotype (46,XX) and 11% with different abnormal karyotypes. Majority of females with normal karyotype were having Mullerian defects and among them most of them were categorized under Rokitansky syndrome. Among the abnormal karyotype constituents, 27.3% numerical abnormalities, all were Turner syndrome; pure and mosaic. Four cases (36.4%) showed male (XY) karyotype. The other four cases (36.4%) showed structural abnormalities, among which three cases showed X-associated structural abnormality and one case showed balanced translocation.

Conclusion: This study emphasizes the need for cytogenetic analysis as an integral part of the diagnostic protocol in the case of PA for precise identification of chromosomal abnormalities; and for appropriate reproductive management. Early detection of abnormalities is necessary for guidance to reproductive options and genetic counselling.

Keywords: Primary amenorrhea, Cytogenetic abnormality, Turner syndrome, Karyotype

Introduction

Primary amenorrhea (PA) refers to absence of spontaneous menarche by age 14 years with the absence of growth or development of secondary sexual characteristics or as absence of menses by age 16 years with normal development of secondary sexual characteristics [1]. Amenorrhea is caused due to failure of the hypothalamic–pituitary–gonadal axis which is responsible for inducing cyclic changes in the endometrium that usually results in menses. Amenorrhea may also result from the absence of end organs or from obstruction of the outflow tract. Gonadal dysfunction (50.4%) is known to be the leading cause followed by pituitary/hypothalamic (27.8%), and outflow tract abnormalities (21.8%) [2]. The cytogenetic studies have shown that the frequency of chromosomal abnormalities ranges from 15.9 to 63.3% in primary amenorrhea [3, 4]. Today, with advancements in cytogenetic

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techniques, the detection of chromosomal abnormalities is easier. Primary amenorrhea is also associated with sex reversal cases, i.e., patients with normal male chromosome complement but with female phenotype. The sex chromosome abnormalities may be numerical or structural, such as cases with mosaicism of X chromosome or abnormal small X chromosomes because of deletion or iso X chromosomes [5, 6]. Although newer genetic technologies like whole exome sequencing and chromosomal microarray have been used successfully to diagnose mendelian inheritance disorders and to detect gains and losses of DNA throughout the human genome, still to detect chromosomal abnormalities especially monosomies, larger structural abnormalities (isochromosome X, ring X etc.) and reversal of sex chromosome, conventional cytogenetic techniques are the gold standard and cost-effective method.

The objective of this study, which was conducted in western India, was to provide statistics and diagnosis of chromosomal abnormalities in patients with primary amenorrhea. Identifying these patients at an early age can be very helpful in accurately diagnosing and providing reproductive solutions to these individuals.

Materials and methods

Patient's sample collection

One hundred (100) cases of primary amenorrhea were studied for cytogenetic analysis during the period of 2014–2021. The age group of subjects ranged from 12 to 36 years, and mean age was 20.5 years. The clinical details like age, height, secondary sexual character, hormone profile and USG findings were recorded in the case record sheet. The study protocols were approved by the Institutional Ethics Committee.

At the initial visit, if the patient was diagnosed with PA, a physical examination was performed to identify secondary sexual characteristics or features of the syndrome. Informed consent was taken before sample collection.

Procedure of lymphocytes culture

Peripheral blood cultures were set up at 37 °C for 72 h according to standard procedure [7]. The cultures were stimulated with phytohemagglutinin (PHA) arrested with colchicine (50 ug/ml) and treated with hypotonic solution (KCL 0.56 g/100 ml). The cells were fixed in Carnoy's solution (methanol/glacial acetic acid; 3:1). The chromosomal preparations obtained were subjected to GTG banding [8].

Slide preparation and karyotyping

At least 20–30 metaphases were scored and karyotype (at 400–550 band resolution) according to International System of Chromosome Nomenclature 2020 (ISCN 2020) [9]. In the analysis stage, 50 or 100 metaphases were examined when mosaicism was suspected. Applied Spectral Imaging software systems (Israel) interfaced with Olympus BX61 microscope (Japan) were used for analysis. Fluorescence in situ hybridization (FISH) was done according to standard procedure using centromeric (CEP) probes for X and Y chromosomes (Vysis, Abbott Molecular Inc.).

Results

Among 100 PA cases studied, the chromosomal abnormality was detected in 11 (11%) cases. In our series, the frequency of the numerical chromosomal changes (27.3%) was found to be less compared to structural aberrations (36.4%) (Table1). The karyograms of different types of chromosomal abnormality observed are depicted in Fig. 1. The age of the patients at presentation ranged between 12 and 36 years, and the mean age of presentation in different categories of PA with cytogenetic

Table 1 Incidence and type of chromosomal abnormalities in PA

Sr. No	Cytogenetic category			Karyotype	Number (%)
1	Normal			46,XX	89 (89%)
2	Chromosomal abnormality				11(11%)
	1	Numerical abnormalities			03 (27.3%)
		a	Pure Turner	45,X	02(18.2%)
		b	Mosaicism of X	mos 45,X/46,XY	01(9.1%)
	2	Structural abnormalities			04 (36.4%)
		a	Deletion Xp	del(X)(p11.3)	01(9.1%)
		b	Translocation	46,XX,t(12;21)(q22;q22.3)	01(9.1%)
		c	Ring X	mos 45,X/46,X,r(X)	02(18.2%)
	3	Male karyotype		46,XY	04(36.4%)

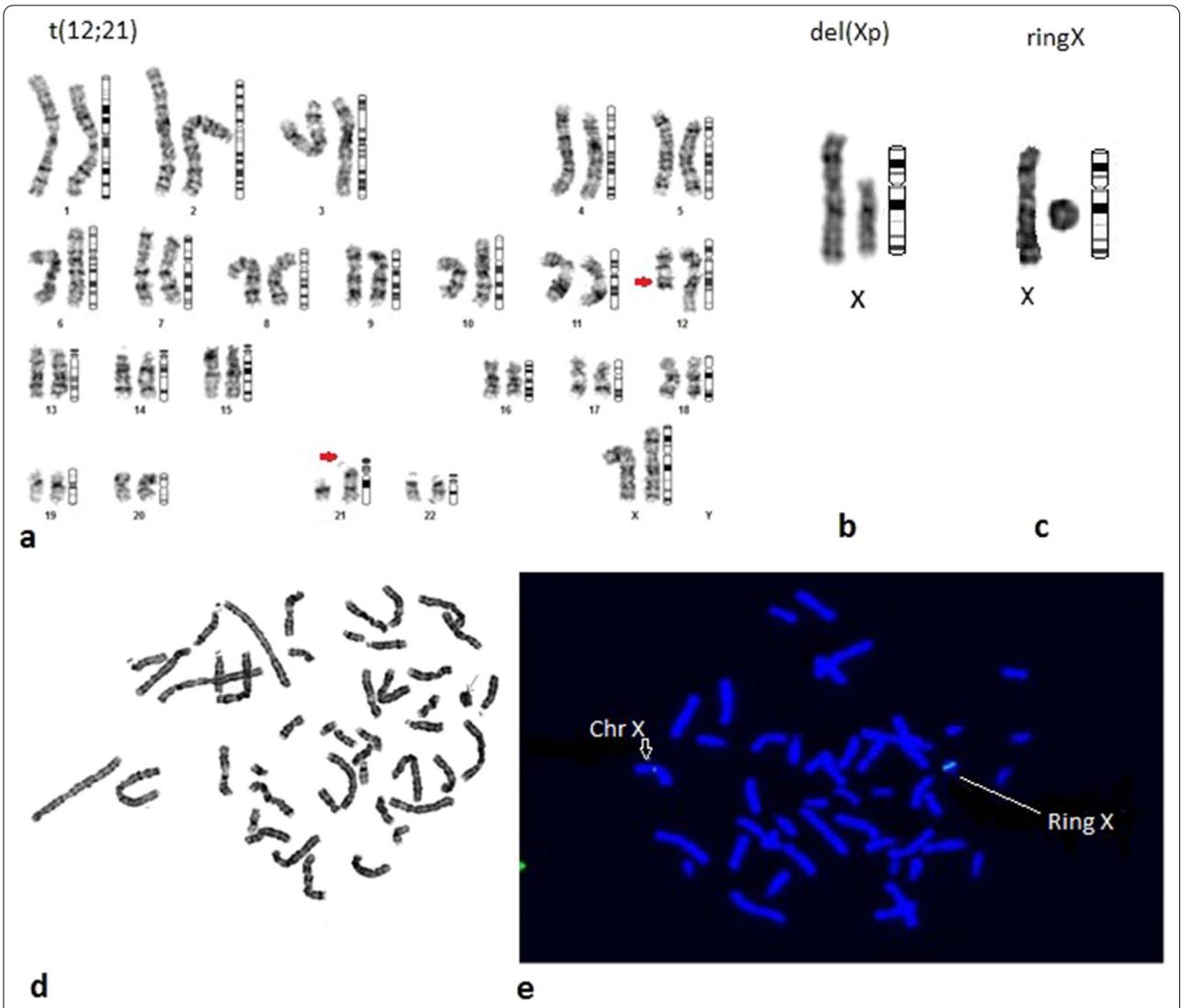

Fig. 1 Types of chromosomal abnormalities. **a** Karyotype of *t* (12;21), **b** partial karyotype of del (Xp), **c** Partial karyotype of ring (X), **d** metaphase showing ring X chromosome, **e** Fluorescence in situ hybridization (FISH) showing ring (marker) chromosome positive for centromeric X probe

abnormality is shown in Table 2. The reason for consultation was absence of menses or pain in the abdomen in the age group 12–17 years; among 18–25 years, it was mainly for vaginal reconstruction and 25 years above was mainly for infertility issues and for IVF. Distribution of cytogenetic abnormality, mean age of presentation and height

Table 2 Distribution of cytogenetic abnormality, age and height in primary amenorrhoea cases

Sr. No	Cytogenetic abnormality	Age (years) (Mean ± SD)	Height (cm)	
			< 150	150 and above
1	Pure Turner (2)	23.5 ± 7.77	2 (100%)	00
2	mos 45,X/46,XY (1)	14 ± 0.00	1 (100%)	00
3	Structural abnormalities (4)	25.25 ± 6.4177	2 (50%)	2(50%)
4	Male karyotype (4)	20.25 ± 5.1881	00	4(100%)
Total (11)			5(40%)	6(60%)

are presented in Table 2. It was observed that 40% cases of PA with cytogenetic abnormality had height less than 150 cm and 60% cases were of height more than 150 cm and above. Those with male genotype were taller, and all the pure Turner females ($n=2$) were less than 150 cm of height. Secondary sexual characters like pubic hairs and axillary hairs were correlated with cytogenetic abnormality (Table 3). Pure Turner cases showed poor breast development and absence of pubic and axillary hairs. Individuals with mosaic 9 ($n=1$) and structural abnormalities showed variable findings. Among individuals with male karyotype ($n=4$), 50% of them had no breast development. Correlation of cytogenetic abnormality, FSH and LH levels and ultrasonography findings in PA cases are shown in Table 4 and 5. In females with abnormal karyotype, a significantly high level of FSH was detected. On USG, ovaries were not visualized in patients with Turner syndrome (TS). Only females with translocation had normal ovaries. Among cases with male karyotype, no one had normal ovaries, either absent or streak. Overall, USG findings showed that the uterus was normal in 9.1%, hypoplastic in 54.5% and absent in 36.4%

Table 3 Distribution of cytogenetic abnormality, Breast development and secondary sexual characters in PA

Sr. No	Cytogenetic abnormality	Breast development			Pubic hair		Axillary hair	
		Normal	Poor development	Absent	Scanty	Absent	Scanty	Absent
1	Pure Turner (2)		2 (100%)			2 (100%)		2 (100%)
2	mos 45,X/46,XY (1)	1 (100%)				1 (100)		1 (100%)
3	Structural abnormalities (4)	2 (50%)	2 (50%)		2 (50%)	2 (50%)	2 (50%)	2 (50%)
4	Male karyotype (4)		2 (50%)	2 (50%)	1 (25%)	3 (75%)	1 (25%)	3 (75%)
Total (11)		3 (27.3%)	6 (54.5%)	2 (18.2%)	3 (27.3%)	8 (72.7%)	3 (27.3%)	8 (72.7%)

Table 4 Distribution of cytogenetic abnormality, FSH, LH levels and USG findings in PA

Sr. No	Cytogenetic abnormality	FSH Mean ± SD	LH Mean ± SD	USG findings (Uterus)			USG findings (Ovary)		
				Normal	Hypoplastic	Absent	Normal	Absent/not visualized	Streak
1	Pure Turner (2)	69 ± 82.02	21.935 ± 26.49		2 (100%)			2 (100%)	
2	mos 45,X/46,XY (1)	127.08 ± 0.00	15.03 ± 0.00		1 (100%)			1 (100%)	
3	Structural abnormalities (4)	31.92 ± 24.74	14.18 ± 3.06	1 (25%)	2 (50%)	1 (25%)	1 (25%)	3 (75%)	
4	Male karyotype (4)	90.127 ± 2.5884	29.215 ± 5.4977		1 (25%)	3 (75%)		3 (75%)	1(25%)
Total (11)				1 (9.1%)	6 (54.5%)	4 (36.4%)	1 (9.1%)	9 (81.8%)	1 (9.1%)

Table 5 Case-wise FSH, LH levels and USG findings in PA according to cytogenetic abnormality

Sr. No	Karyotype	FSH	LH	USG findings(uterus)			USG findings(ovary)		
				Normal	Hypoplastic	Absent	Normal	Absent	Streak
1	46,XY	93.71	28.19		√				√
2	46,XY	98	25.3			√		√	
3	46,XY	89.6	28			√		√	
4	46,XY	97.2	27.9			√		√	
5	45,X	11	3.2		√		Left ovary	Right ovary	
6	45,X	127	40.67		√			√	
7	mos 45,X/46,X,r(X)	17.02	15.33		√		Left ovary	Right ovary	
8	mos 45,X/46,X,r(X)	69.7	15.29		√			√	
9	mos 45,X/46,XY	127.08	15.03		√			√	
10	del(X)(p11.3)	36.99	9.03	√				√	
11	46,XX,t(12;21)(q22;q22.3)	4.1	17.1			√	√		

cases and ovaries were normal in 9.1%, absent in 54.5% and small/streak in 36.4% cases.

Discussion

The PA occurs due to various factors including hormonal imbalance, anatomical abnormalities, genetic factors and environmental factors [2]. Genetic factors could be chromosomal or single gene disorders or multifactorial. Recently, with the advent of next generation sequencing, multiple genes have been attributed to the cause of primary amenorrhea. However, in majority it is chromosomes and their abnormalities, contributing to the constitutional etiology of amenorrhea. Among the chromosomal abnormalities are the numerical chromosomal anomalies like monosomy and mosaicism, whereas the structural abnormalities include translocation, isochromosome, deletion, duplication and ring chromosomal anomalies [10].

The chromosomal aberration frequency has been reported to be ranging from 14 to 60% (Table 6) [11–16]. In the present study, chromosome aberrations were identified in 11 (11%) out of 100 PA cases studied. The frequency of chromosome aberrations in our study is lesser as compared to studies reported from different parts of the world (Table 6). This could be attributed to the regional difference or selection bias as our centre is also a tertiary centre for vaginal reconstruction. This too explains why the majority of our PA cases fall under the category of Mullerian defects.

Interesting observation in our cohort is that the structural chromosomal aberrations (36.4%) and male genotype (36.4%) were more compared to numerical aberrations of X chromosome (27.3%). Females who present with PA with karyotype 46, XY are phenotypically female since the abnormal gonadal tissue in these cases fails to produce Mullerian inhibiting factor and testosterone. Gonadal tumours are seen in 25% of women with a Y chromosome and should be removed at the time of diagnosis [17].

They mainly consulted during 13–17 years of age. The primary motive for their visit was either to get treated for absence of menses or to get vaginal reconstruction done. One of them was diagnosed as Swyer syndrome, and the other three as testicular feminization syndrome. These cases need to be further assessed for any mutation of SRY gene, SF1 gene and other gene responsible for reversal of sex. We carried out a mutation study in the Swyer syndrome case, but no mutation was detected.

Structural abnormalities of X chromosome such as Xq deletions, isoXq and isodicentric X are equally associated with PA. An abnormality such as the ring X chromosome is relatively uncommon. However, in our study we observed two cases (18.2%) with ring X chromosome. The molecular cytogenetic technique, FISH, is an important technique used to delineate the nature and origin of marker chromosomes in primary amenorrhea patients, which is difficult by conventional cytogenetics. Similar to that, in the present study, the presence of deletion of short arm of chromosome X in 1 patient and ring chromosome in two patients were confirmed, using FISH (Fig. 1). In some TS patients, the karyotype shows both a normal X and a structurally rearranged X chromosome. Structural abnormalities, such as deletions, duplications, inversions, translocations, and rings, are usually associated with chromosome breaks which in turn can result in significant imbalance of gene content of the X chromosome. However, such abnormalities are generally well tolerated because of the preferential inactivation of the abnormal X. Thus, at least in part, a balanced genetic makeup can be restored. This preferential inactivation of X results in a mild phenotype in most patients with structural abnormalities of the X, and clinically they resemble TS patients with a 45,X karyotype [18, 19].

Genes essential for gonadal function are located on the proximal part of Xp, the long arm of X proximal to Xq13 and/or the long arm of X distal to Xq26. Deletion of Xp results in primary amenorrhea and all the features of Turner syndrome which explains the findings in one of our cases with Xp deletion. Patients with deletion of

Table 6 Scenario of genetic abnormalities reported in earlier studies of PA cases worldwide

Sr. No	Study	Study population	Study period/year	No. of cases	Normal karyotype	Abnormal karyotype
1	Present study	India	2014–2021	100	88 (88%)	12 (12%)
2	Seema Korgaonkar et al. [11]	India	2000–2015	490	369 (75.3%)	121 (24.7%)
3	Sapna Amin et al. [12]	India	2006–2012	98	78 (79.5%)	20 (20.5%)
4	Faeza EL Dahoty. [13]	Egypt	2008–2010	223	177 (79.37%)	46 (20.63%)
5	Tanmahasamut et al. [14]	Thailand	1992–2009	295	236 (80%)	59 (20%)
6	Vijayalaksmi et al. [15]	India	1998–2006	140	101 (72.15%)	39 (27.85%)
7	Cortes et al. [16]	Mexico	1995–2003	187	109 (58.28%)	78 (41.72%)

Xq have primary amenorrhea, but lack features of TS. In contrast to 46, X, i(X)(q10) females, 50% of females with 46,XX,del(X)(p11) karyotype menstruate or develop breasts [20]. Therefore, it can be concluded that Xp deletion has a milder phenotype compared to isoXq and Xq deletion.

Translocation is another unique chromosomal alteration observed in one of the subjects of our study. The female's karyotype was 46,XX,t(12;21)(q22;q22.3). Ultrasonography report of the patient revealed uterine agenesis with rudimentary fallopian tube and normal ovaries. X-autosome translocations have been reported [15, 21] in PA cases, while other studies at isolated places have reported autosome–autosome translocations [22]. Besides, Tupler et al. [23] have reported two unrelated women with gonadal dysgenesis who were found to have balanced autosomal translocations, i.e. t(6;15)(p21.3;q15) and t(8;9)(p11.2;q12), respectively. Gonadal dysgenesis in such cases could possibly be attributed to the disruption of autosomal gene(s) playing a role in the normal gonadal development [24]. However, the possibility that autosomal translocation could be an incidental finding and not related to the primary amenorrhea cannot be ruled out. In our study, the patient could simply be a case of Mullerian defect with incidental finding of balanced translocation without any associated manifestation.

The chromosomal abnormalities associated with X and Y chromosomes have direct influence on stature and pubertal development. Sexual development is the result of interplay of numerous genes on the X chromosome and mutation in any of these genes can result in partial or complete failure of stature and pubertal development. The clinical evaluation including height and secondary sexual characters is important in diagnosis of PA. The short stature and poor development of secondary sexual characters may be indication for the diagnosis of PA as in our study the chromosomally abnormal PA cases had short stature (< 150 cm) and poor development of secondary sexual characters. In the present study, out of 11 cases of PA with chromosomal abnormality, 6 (54.5%) cases had poor breast development, which suggests that underdeveloped breasts might be one of the clinical features in PA (Table 4). In our series, hypoplastic uterus (54.5%), absence of uterus (36.4%), absence of ovaries (81.8%) and streak gonads (9.1%) were found to be the major anatomical abnormalities and similar abnormalities also have been reported in earlier studies [17, 25, 26].

Most of the Turner syndrome cases are diagnosed in pubertal years due to stunted growth; hence, it is essential to diagnose these cases during the neonatal period to develop appropriate hormonal therapy for development, growth, and pubertal induction. It is also important to diagnose TS early so that screening for congenital heart disease, horseshoe kidney, and hypothyroidism associated with TS can be detected before the presentation of symptoms and timely intervention could be possible. The presence of a short 4th toe, which was present in one of our ring TS patients, can be used as a marker for early cytogenetic study. Early hormone therapy especially in girls will lead to proper development of secondary sexual characters and female reproductive organs. With early treatment in such cases, normal uterine size could be achieved which will enable them to bear the child naturally or through assisted reproductive techniques in the case of ovarian failure.

Conclusion

In summary, the women who couldn't attain menarche and have poorly developed to absent secondary sexual characters should be investigated for chromosomal abnormality. Cytogenetic investigation is crucial in classifying these patients as extreme variability has been observed in terms of clinical signs and symptoms in such cases. After exclusion of non-genetic causes, patients with PA should be considered for genetic and molecular study. The risk of premature menopause for patients with Turner's syndrome, possibility of pregnancy in cases with X mosaicism and the use of hormone replacement therapy, the risk of gonadal malignancy for patients with male karyotype and the possibility of infertility in patients with other chromosomal aberrations should be explained as a part of genetic counselling.

Abbreviations

PA: Primary amenorrhea; TS: Turner syndrome; IVF: In vitro fertilization; USG: Ultrasonogram; FSH: Follicle-stimulating hormone; LH: Luteinizing hormone; FISH: Fluorescence in situ hybridization.

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None.

Author contributions

KP and VM conceived of the presented idea and designed the study. SC and RA performed the examination, evaluated the reports, and verified the analytical methods. VM encouraged KP to investigate and supervised the findings of this work. HP and KP processed the samples, performed the karyotyping, and designed the figures and tables. KP, VM, SC and RA aided in interpreting the results and worked on the manuscript. All authors discussed the results and contributed to the writing of the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

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Declarations

Ethics approval and consent to participate
Ethical clearance for this study was obtained from the local ethical committee of Institute of Kidney Diseases and Research Centre and Institute of Transplantation Sciences (IKDRC-ITS), Ethical approval no: (IKDRC-ITS)EC/APP/22oct21/04.

Consent for publication
All consent for publications is taken before submission of manuscript.

Competing interests
The authors declare no conflict of interest.

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