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CYTOGENETIC STUDY OF CHRONIC MYELOID LEUKEMIA IN ERBIL CITY KURDISTAN REGION OF IRAQ

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ABSTRACT

Chronic myeloid leukemia is a rare form of cancer that affects blood cells and is characterized by a genetic mutation between chromosome (9) and chromosome (22) known by reciprocal t(9;22) (q34;q11) translocation, Which leads to composition of the chimerical fusion gene (BCR-ABL1) on chromosome (22), which is known after that by (Philadelphia chromosome). More than (90%) of chronic myeloid leukemia patients are diagnosed with presence of Philadelphia chromosome. The present study was carried out on (40) patients who were suffering from Chronic Myeloid Leukemia in Erbil city and (10) healthy individuals as a control group in both sex and different age groups. Blood samples were collected and chromosomal study was performed. The research concluded the effect of several factors, including that most cases were between the age group (41-50) and among males more than females. Also the percentage of illness in relation to the type of occupation was among most females who were housewives at (42%). As for the patients' living location, between inside and outside the city, the result was somewhat close to each other even when taking into consideration the proportion of males and females. As for the occurrence of types of chromosomal aberrations, the study showed that the highest value of chromosomal aberrations was in (Dicentric chromosome), specifically in females of the age group (41-50).

Keywords: Cytogenetic study, Chronic Myeloid Leukemia, Erbil City.

Introduction

Chronic myeloid leukemia is rare form and an uncommon type of cancer (the incidence is estimated at 10 to 15 cases per 1,000,000 people.) (Baccarani *et al*., 2019) Chronic Myeloid Leukemia affects white blood cells and it characterized by the existence of two fused genes (BCR-ABL1) in the patient's genetic material, this fused genes is a result of mutation known as: reciprocal translocation, which is occurs between chromosome (9) with (22), t (9; 22) (q34; q11), leads to composition of mutant fused gene (BCR-ABL1) in chromosome (22). The abnormal chromosome (22), called Philadelphia chromosome. The Philadelphia chromosome is the hallmark of CML, where it is found in more than 95% of the cases (Tang *et al*., 2020).

The Philadelphia chromosome's name, comes according to the Philadelphia city name, where was discovered and described first there , by David Hungerford, at the Institute for Cancer Research, and Peter Noel, at the University of Pennsylvania School of Medicine, in 1959 (Roberts *et al*., 2017). The presence of Philadelphia chromosome in the blood is considered as a cause of leukemogenesis, because when the ABL1 gene on chromosome (9), fused with BCR gene on chromosome (22), it will coding for a hybrid protein: a tyrosine kinase which is "always on" and causes the cell to divide uncontrollably by interrupting the stability of the genome and impairing various signaling pathways regulating the cell cycle (Kang *et al*., 2016).

This uncontrolled proliferation of cells of the myeloid series results to presence of many stages of differentiation of myeloid cells in the blood, that is why it also named an indolent myeloproliferative neoplasm, these uncontrolled proliferations, causes several specific symptoms and affects the body's immunity to fight infections, even against mild kinds of infections (Thoennissen *et al*., 2010).

Chronic myeloid leukemia is also divided into the fairly indolent, early phase known as the Chronic Phase (CP), and the more violent advanced phase, consisting of an initial Rapid Period, known as Accelerated Phase (AP) and a catastrophic Blast Crisis Period (BC), depending on the nature of the disease and clinical characteristics (Krishna Chandran *et al*., 2019).

Chronic myeloid leukemia appears among adults especially, with the average age at diagnosis being (45-55) years old, there are also rarer occurrence cases between children too (Suttorp and Millot, 2010).

The purpose of this research was to study several types of chromosomal aberrations in a number of Chronic Myeloid Leukemia patients. Many factors that contribute to the development of the disease have also been studied. Like the patient's gender, age, job, place of residence, and the relationship of kinship between the patient's parents and the history of illness in the family. The present research was conducted on (40) patients suffering from Chronic Myeloid Leukemia in Erbil city and (10) healthy individuals as a control group in both sexes and different age groups. Blood sampling and cell culturing was performed then the

chromosomal analysis was performed for both patients and healthy individuals.

Material and Methods

During several visits to (Nanakli Hospital for blood diseases and cancer), (40) patients was provided with a special questionnaire form, which included some fields of information to be filled out about the patient like (name, address, gender, age, the date of disease diagnosis, occupation, location, presence of disease in Family history, smoking, alcohol habit, consanguinity between parents).

When the age groups of patients were arranged, seven age groups were obtained for those patients who underwent the study, where (A1, A2, A3, A4, A5, A6, A7) represented the age group (1-10), (11-20), (21-30), (31-40), (41-50), (51-60), (61~) respectively. Each group included the study of both males and females (S1 and S2) respectively too.

Blood Sampling

Five ml of blood was collected from (40) patients, and (10) healthy individuals, using sterile disposable syringes. Then, the blood was put in a special tube for chromosomal study (Lithium Heparin), Tube with a green cover.

Blood culture and Harvesting

About one ml of heparin-treated blood was cultured in (5) ml of Roswell Park Memorial Institute culture medium (RPMI-1640), and then supplemented with (0.25) ml phytohemaglutinin (PHA). Then the cell culturing tubes were incubated at (37 °C) for (72) hours, after (71) hours of incubation, (0.2) ml of colcemid was added to the cell culturing tube with light shaking, and then incubated at (37 ° C) for (1) another hour. Then a hypotonic solution Potassium chloride (KCL), was added to cell culturing tubes, then incubated and centrifuged. Finally, fresh prepared fixation solution was added, and the tubes were cooled, then the tubes were centrifuged. (This operation of fixation was repeated up to (3) times until the supernatant was completely clear, and cloudy pellet was mad. After the discard of the supernatant, and by using Pasteur pipette, (3) to (4) drops of cell suspension were dropped evenly from appropriate distance (typically 30 cm-1 m) on to a wet chilled and grease free slide, then the slide was dried at room temperature. The slide was stained with freshly prepared giemsa stain (Giemsa stain 1:4 Sorenson buffer solution) for 2-3 minutes. Then the slide was washed by Sorensone's buffer and left to dry at room temperature. Excess buffer was removed by slanting the slide on filter paper. Those steps were carried out according to the protocols of Iraqi Center for cancer and Medical Genetics Research. Microscopic examination was performed using Olympus Microscope with (10X) ocular lens and (100X) objective lens, for chromosomal examination.

Statistical Analysis

The Statistical analysis of the results of studying the types of chromosomal aberrations in chronic myeloid leukemia in male and female age groups was performed by using (SPSS version 22) application.

Results and Discussion

The study was conducted between specific age groups in both sexes of patients with chronic myeloid leukemia, to find out the types and incidence of chromosomal aberrations, as well as to find out whether there are disease-related factors that affect the state of disease stages, and the extent of the influence of those factors on the results of types and the amount of occurrence of those Chromosomal aberrations.

At first here the study of some Factors:

1. The distribution of patients with chronic myeloid leukemia according to their age and sex.

Figure (1) showed that most patients who were suffering from chronic myeloid leukemia are males, represent (52.5%), this because of their occupation and several other factors, while female represent (47.5%). There are differences in cancer incidence between males and females. The chronic myeloid leukemia is more common in males than in females (O'Brien *et al*., 2003).

The gender difference in cancer susceptibility is one of the most consistent findings in cancer epidemiology. Hematologic malignancies are generally more common in males (Dorak and Karpuzoglu, 2012). This can be attributed to the effect of sex hormones as showed in the published research (Androgen-induced immunosuppressant) by (Melanie R. Gubbels, 2018), which concluded that Androgens affects the rate of immune response, which in turn determines the difference in the incidence of diseases between males and females, especially cancers. The figure (1) also shows that most patients who were suffering from chronic myeloid leukemia are at age interval (41-50) years, represent (17.5%) who are males. While fewer of them are at age interval (1-20) years represent (3%) who are female. Similar result were obtained by (Radivoyevitch *et al*., 2014) who concluded from a study (Sex differences in the incidence of chronic myeloid leukemia) that; the rate of chronic myeloid leukemia's incidence which is caused by (BCR/ABL) chimeric oncogene formation in a pluripotent hematopoietic stem cell (HSC), increases with aging. This same conclusion is also found by (Jorge Cortes, 2007).

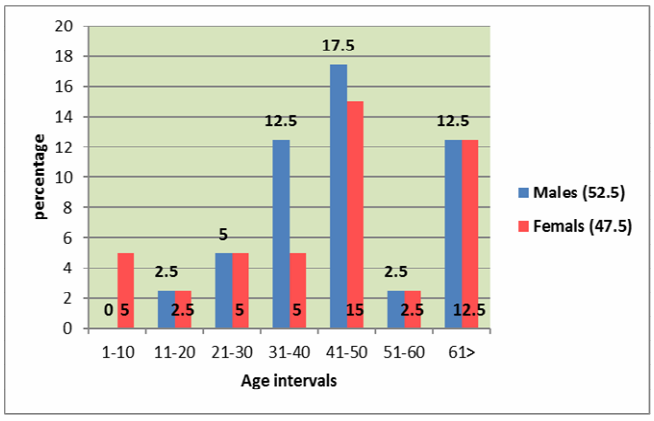

Fig. 1 : Distribution of patients with Chronic Myeloid Leukemia according to their age and sex.

2. The distribution of patients with Chronic Myeloid Leukemia according to their occupations.

Figure (2) shows that chronic myeloid leukemia was more common in housewives, with (42.5%), followed by men with free professions (25%).

Since the cancer is one of occupational-related disease, as (Park *et al*., 2014) concluded it in their study (A case of chronic myeloid leukemia in a diagnostic radiographer), also (Löffler *et al*., 2001) in the study (Reduced risk for chronic myelogenous leukemia in individuals with the cytochrome) concluded that; Most cancers can be attributed to the

environmental factors that act in conjunction with genetic readiness. As a result of the conclusions of these studies the development of chronic myeloid leukemia may correlate with exposure to many types of environmental agents according to the nature of the type of patient's occupation, for example: (Saberi Hosnijeh *et al*., 2013) concluded that exposure to radiation, inhalation of benzene, smoke of cars and generators are one of chronic myeloid leukemia risk factors.

Also (Knopper and Lean, 2010) in their study (carcinogenic and genotoxic potential of turf pesticides commonly used on golf courses) they listed the exposure to pesticides, herbicides as another risk factor of chronic myeloid leukemia.

On the other hand even the using with dishwashing liquids, and personal care products like cosmetics, can have a role in the development of chronic myeloid leukemia as (Carpenter and Bushkin-Bedient, 2013) concluded it in the study (Exposure to Chemicals and Radiation During Childhood and Risk for Cancer Later in Life).

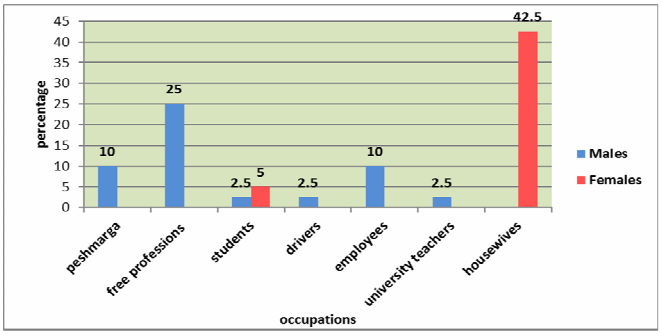

Fig. 2 : Distribution of patients with Chronic Myeloid Leukemia according to their occupations.

3. The Distribution of patients with Chronic Myeloid Leukemia according to their location.

Figure (3) shows that most patients with chronic myeloid Leukemia were living out of the city, represent by (52.5%), and the rate of females from this was (32.5%) higher than the males rate (20%), while the percentage of patients who were living inside the city was (42.5%), and the males rate from it was (32.5%) higher than females rate (15%). The slight difference between the proportion of patients living outside the city and those living within the city which is represent by (5%), can be attributed to the health culture, and the economic level.

Fig. 3 : Distribution of patients with Chronic Myeloid Leukemia according to their location.

The nature of cities in terms of large populations, and the large number of environmental pollutants, plays an important role in influencing the health of peoples. The high rate of disease diagnosis in males in the city can be due to the accumulation of environmental pollution factors as described in the published research (Lien *et al*., 2016), and also to the genetic readiness, as we discussed it previously. The low rate of diagnosis of patients living in the city, in the hospital where I collected the samples in it, can be due to psychological considerations resulting from the location, and the nature of the blood and cancer diseases hospital's atmosphere, This status concluded by (Spencer *et al*., 2010) in the study (Anxiety disorders in advanced concern patients) that: women patients when diagnosed with advanced cancer more likely to have an anxiety disorder.

4. The Distribution of patients with Chronic Myeloid Leukemia according to the presence of consanguinity between parents.

The Figure (4) illustrates the distribution of patients with Chronic Myeloid Leukemia according to the presence of consanguinity between parents.

Consanguineous marriage, define as a union between biologically associated individuals. This relationship has a set of factors that, if combined with each other, can show a certain percentage of either harmful or beneficial possibilities which affects the filial health. Since the main factor of chronic myeloid leukemia is the reciprocal mutation between the non-homologous chromosomes 9, 22, and the dominant risk factors which I observed in my study's patients was the age factor, exposure to chemicals, petrochemicals and pesticide, blood group, and socio-economic status, these factors play a major role of causing this type of mutation which is account as an important reason for the occurrence of the incidence.

It's clear in the chart figure the patients which there is no consanguinity between their parents have a great percentage (85%) while the patients which their parents were relatives of each other show a low percentage (15%), this result is similar with results were obtained by (Saadat, 2015) who concluded from the study (Age-standardized Incidence Rates for Leukemia Associated with Consanguineous Marriages in 68 Countries) that Leukemia rates are smaller in nations where consanguineous marriages are highly prevalent.

There is other studies approve opposite of this result like (Nasir *et al*., 2015), this is possible also if the issue is considered genetically, as explained above, at this case the possibilities role in combining of genetic factors are likely to be affect the results, this is what illustrating the disparity between the ratios of the two cases. The disparity between the ratios of the two cases shows that this factor does not have an accurate major role in the incidence of the disease.

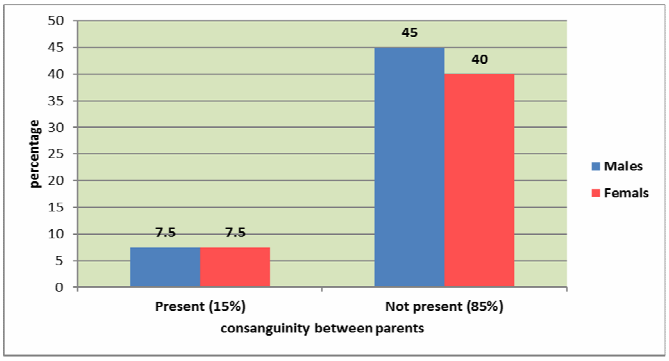

Fig. 4 : Distribution of patients with Chronic Myeloid Leukemia according to the presence of consanguinity between parents

As for studying the types of chromosomal aberrations in leukocyte of peripheral blood sample of chronic myeloid leukemia patients, in the different age groups for both sex, the blood samples of (40) patients, showed different types of chromosomal aberrations, showed in the table (1), while the other (10) blood samples for the ten healthy ones, who were representing the control group, all their karyotypes was normal, as Figure (5), without presence of any chromosomal aberrations. It is worth noting that this conclusion is also the same as what (Kaur *et al*., 2012) concluded in (Karyotypic findings in chronic myeloid leukemia cases undergoing treatment).

The values in table (1) represent the mean square, (F. value) and (P. value) of chromosomal aberrations, for both age and sex, also for the interaction between age and sex of patients.

The table (1) shows the highly significant effect at (P< 0.01) level of patients states on different chromosomal, as well as chromatid aberrations, like: (chromatid break without fragment, centromeric break, dicentric chromosome, quadriradial chromosome, and polyploidy), as were their images are shown in Figure (6) and Figure (7). It is noted from the table that, the age factor independently, also the two factors (sex*age) interaction had a high significant effect of (P <0.01) on all types of chromosomal aberrations.

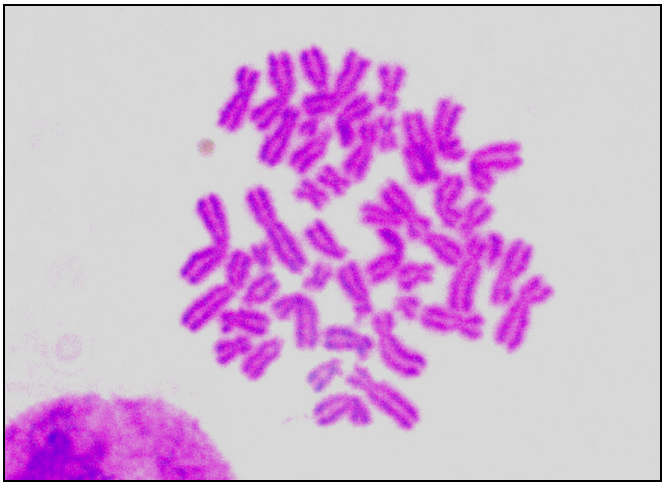

Fig. 6 : Normal human chromosomes from male (1000 X, Giemsa stain).

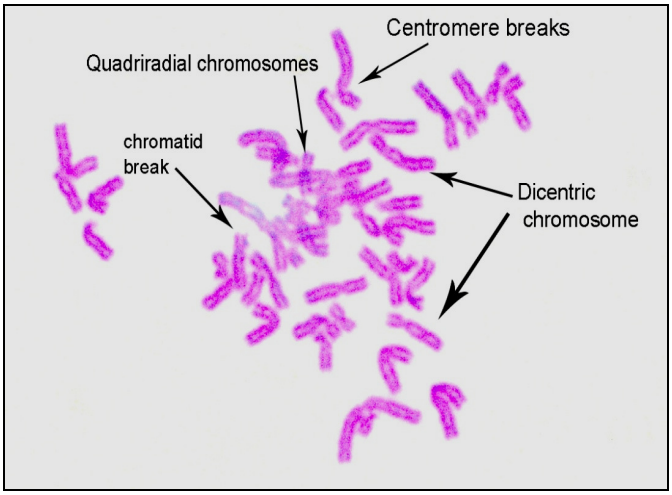

Fig. 6 : Some types of chromosome aberrations in a leukocyte of female patient who was suffering from chronic myeloid leukemia (1000 X, Giemsa stain).

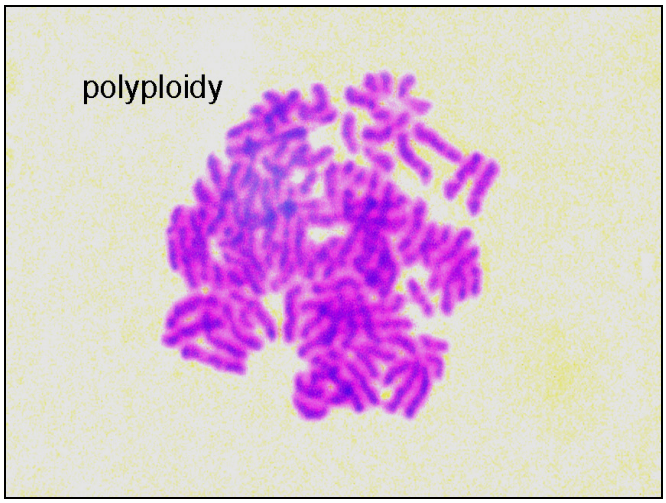

Fig. 7 : Polyploidy in human chromosome in a leukocyte of male patient who was suffering from chronic myeloid leukemia (1000 X, Giemsa stain).

While Table (2) shows the values of (mean ± SE) first for both sexes separately, then for all age groups, and finally for all interactions between the age groups, with both sexes separately, for all types of chromosomal aberrations that were observed and studied.

It is noted from Table (2) that the highest value of the types of chromosomal aberration was dicentric chromosome, as it was (10.761 ± 1.811) for females in general, followed by the value (7.523 ± 1.635) for males in general, and when determining the age group, it was noted that the fifth age group, Represented by (50-41) its value was (23.666 ± 1.452), which is the highest value among all age groups for all types of chromosomal aberrations. When determining the state of interaction between sex and age in this group, I mean the fifth group (50-41), the highest value was in females, with a value of (25.333 ± 2.333). Leukemia as a type of cancers results from somatic mutations in the genes that promote oncogenes or deactivate tumor suppressor genes, and it hamper the control of cell division and its differentiation, also its death. (Pascual *et al*., 2018)

In patients with chronic myeloid leukemia, the presence of many other chromosomal aberrations is associated with the presence of the (Philadelphia) chromosome, which is known to have the fused gene (BCR-ABL1) and which is formed as a result of the occurrence of the reciprocal translocation mutation between chromosome (9) and chromosome (22), which known by: t (9; 22) (q34; q11) and which proved to be the reason behind the occurrence of the chronic myeloid leukemia disease.

It is believed that, the occurrence of these chromosomal aberrations, is due to the fact that; the genome of patients with advanced stage of the disease, is very unstable, and this genetic instability is responsible for the high incidence of these additional aberrations, as concluded by (Krishna Chandran *et al*., 2019) in the published research titled (Impact of Additional Chromosomal Aberrations on the Disease Progression of Chronic Myelogenous Leukemia). Also (Syed *et al*., 2008) in their research (Additional chromosomal abnormalities in Philadelphia-positive chronic myeloid leukemia) concluded that a group of chromosomal aberrations has proven its existence in many age groups, and at different stages of the disease

Table 1 : Analysis of variance to study the chromosomal aberrations in patients were suffering from chronic myeloid leukemia in Erbil City (in both sexes at different age groups).

		source of variance	Age	Sex	Age * Sex	Error	Total
		df.	6	1	6	28	42
1	chromatid break without fragment	mean square	123.762**	1.524	11.524**	1.262	
		F-value	98.075	1.208	9.132		
		sig. /P.value	0.000	0.281	0.000		
2	centromeric break	mean square	41.540**	20.024**	5.968**	0.714	
		F-value	58.156	28.033	8.356		
		sig. /P.value	0.000	0.000	0.000		
3	dicentric chromosome	mean square	376.190**	110.095**	25.873**	3.167	
		F-value	118.797	34.767	8.170		
		sig. /P.value	0.000	0.000	0.000		
4	quadriradial chromosome	mean square	0.278**	0.024	0.468**	0.048	
		F-value	5.833	0.500	9.833		
		sig. /P.value	0.000	0.485	0.000		
5	polyploidy	mean square	152.635**	10.500	18.778**	2.024	
		F-value	75.420	5.188	9.278		
		sig. /P.value	0.000	0.031	0.000		

Table 2: (Mean±S.E) and (Duncan's Multiple Range Test) to study chromosomal aberrations in patients who were suffering from chronic myeloid leukemia in Erbil City (in both sexes at different age groups).

			chromosomal aberrations									
			Chromatid break with out fragment		Centromeric break		Dicentric chromosome		quadriradial chromosome		Polyploidy	
			(Mean±SE) and (Duncan's Multiple Range Test)									
Sex	S1	M	5.476 ± 1.101	b	3.476 ± 0.748	b	7.523 ± 1.635	a	0.190 ± 0.087	b	5.857 ± 1.306	b
	S2	F	5.095 ± 0.896	a	2.095 ± 0.407	a	10.761 ± 1.811	b	0.142 ± 0.078	a	4.857 ± 0.936	a
Age	1_10	A1	0.000 ± 0.000	a	0.000 ± 0.000	a	1.000 ± 0.447	a	0.000 ± 0.000	a	1.333 ± 0.614	a
	11_20	A2	0.666 ± 0.210	a	0.833 ± 0.1666	a	2.166 ± 0.307	a	0.000 ± 0.000	a	1.500 ± 0.836	a
	21_30	A3	5.00 ± 0.258	b-c	2.666 ± 0.210	b	7.500 ± 0.885	b-c	0.333 ± 0.210	a-b	2.667 ± 0.494	a-b
	31_40	A4	5.500 ± 1.056	c	3.333 ± 0.802	b-c	9.166 ± 1.249	c	0.333 ± 0.210	a-b	5.000 ± 1.505	b
	41_50	A5	12.166 ± 1.108	e	7.500 ± 1.258	d	23.666 ± 1.452	e	0.500 ± 0.223	b	14.833 ± 1.046	d
	51_60	A6	3.500 ± 0.846	b	0.666 ± 0.210	a	5.500 ± 1.802	b	0.000 ± 0.000	a	2.666 ± 0.802	a-b
	61~	A7	10.166 ± 0.600	d	4.500 ± 0.425	c	15.000 ± 1.949	d	0.000 ± 0.000	a	9.500 ± 1.118	c
Age* Sex	1	A1M	0.000 ± 0.000	a	0.000 ± 0.000	a	0.000 ± 0.000	a	0.000 ± 0.000	a	0.000 ± 0.000	a
	2	A1F	0.000 ± 0.000	a	0.000 ± 0.000	a	2.000 ± 0.000	a	0.000 ± 0.000	a	2.666 ± 0.333	a
	3	A2M	0.666 ± 0.333	a-b	1.000 ± 0.000	a-b	1.666 ± 0.333	a-b	0.000 ± 0.000	a	2.000 ± 0.000	a
	4	A2F	0.666 ± 0.333	a-b	0.666 ± 0.333	a-b	2.666 ± 0.333	a-b	0.000 ± 0.000	a	1.000 ± 0.577	a
	5	A3M	4.666 ± 0.333	c	2.666 ± 0.333	b-c	5.666 ± 0.333	b-c	0.666 ± 0.333	b	1.666 ± 0.333	a
	6	A3F	5.333 ± 0.333	c-d	2.666 ± 0.333	b-c	9.333 ± 0.666	c-d	0.000 ± 0.000	a	3.666 ± 0.333	a
	7	A4M	7.666 ± 0.881	d-e	5.000 ± 0.577	d	11.000 ± 2.081	d	0.666 ± 0.333	b	8.333 ± 0.333	b
	8	A4F	3.333 ± 0.333	b-c	1.666 ± 0.333	a-b	7.333 ± 0.333	c-d	0.000 ± 0.000	a	1.666 ± 0.333	a
	9	A5M	14.00 ± 1.154	g	10.000 ± 1.154	e	22.000 ± 1.527	e-f	0.000 ± 0.000	a	17.000 ± 0.577	d
	10	A5F	10.333 ± 1.201	f	5.000 ± 0.577	d	25.333 ± 2.333	f	1.000 ± 0.000	b	12.666 ± 0.666	c
	11	A6M	1.666 ± 0.333	a-b	0.666 ± 0.333	a-b	1.666 ± 0.333	a-b	0.000 ± 0.000	a	1.666 ± 0.333	a
	12	A6F	5.333 ± 0.333	c-d	0.666 ± 0.333	a-b	9.333 ± 1.201	c-d	0.000 ± 0.000	a	3.666 ± 1..452	a
	13	A7M	9.666 ± 0.881	e-f	5.000 ± 0.577	d	10.666 ± 0.333	d	0.000 ± 0.000	a	10.333 ± 1.201	b-c
	14	A7F	10.666 ± 0.881	f	4.000 ± 0.577	c-d	19.333 ± 0.333	e	0.000 ± 0.000	a	8.666 ± 2.027	b

Conclusions

We conclude from the results of this study that types of Chromosome aberrations have been observed in patients who were suffering from chronic myeloid leukemia, like (chromatid break without fragment, centromeric break, dicentric chromosome, quadriradial chromosome, and polyploidy), and the highest value of chromosomal aberration was (Dicentric chromosome), which occurred most in females at age group (41-50). And most patients who were suffering from chronic myeloid leukemia was males at age group (41-50), and according to occupations, most of the patient were housewives, and (% 85) of patients there was not consanguinity between their parents.

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