INTRODUCTION

Retinoblastoma is a rare form of cancer that rapidly develops from the immature cells of a retina, the light-detecting tissue of the eye. It is the most common malignant cancer of the eye in children. Though most children survive this cancer, they may lose their vision in the affected eye(s) or need to have the eye removed ***(Yun et al., 2011, Zage et al., 2008).***

About 1 out of 3 retinoblastomas is caused by a mutation in the retinoblastoma 1 (RB1) gene (long arm of chromosome 13 band 13q14) that is present in all the cells of the child's body. But of these cases, only about 1 in 4 is inherited from one of the child's parents. In the rest, the gene mutation is not inherited, but occurs during early development in the womb. Most of the remaining 2 out of 3 retinoblastomas occur as a result of a random RB1 gene mutation that occurs only in one cell of one eye ***(Castera et al., 2010).***

Intraocularly, it exhibits a variety of growth patterns, Endophytic growth occurs when the tumor breaks through the internal limiting membrane and has an ophthalmic appearance of a white-to-cream mass showing either no surface vessels or small irregular tumor vessels, Exophytic growth occurs in the subretinal space and is often associated with subretinal fluid accumulation and retinal detachment, Diffuse infiltrating growth is a rare subtype comprising 1.5% of all retinoblastomas

characterized by a relatively flat infiltration of the retina by tumor cells but without a discrete tumor mass ***(Palazzi et al., 1990, Shields et al., 2008).***

Leukocoria (white pupillary reflex or cat's eye reflex) is the most common presenting sign, accounting for about 56.1% of cases. Strabismus, which occurs as a result of visual loss, is the second most common mode of presentation. Thus, funduscopic examination through a well-dilated pupil must be performed in all cases of childhood strabismus. Other less common signs and symptoms of retinoblastoma include: Vision problems, Red painful eye with glaucoma, Hyphema, Bulging of the eye, Anisocoria, Heterochromia iridis, Orbital cellulitis & Nystagmus ***(Abramson et al., 1998a).***

Patients noted to have signs of retinoblastoma should undergo complete eye examination including an estimation of the patient's visual acuity for both eyes. A dilated fundus examination with indirect ophthalmoscopy should be completed since ancillary diagnostic studies play only a secondary role when the fundus can be visualized clearly. Imaging tests (Imaging tests use x-rays, sound waves, magnetic fields, or radioactive substances to create pictures of the inside of the body) will be done to help confirm it and to find out how far it may have spread within the eye and possibly to other parts of the body ***(Apushkin et al., 2005b).***

The outlook (prognosis) for children with retinoblastoma depends, to some extent, on the cancer's stage. The stage is also an important factor in choosing treatment. The International Classification for Intraocular Retinoblastoma (ICRB) is the newer retinoblastoma staging system. In this staging system, intraocular retinoblastoma is differentiated into 5 groups, from A to E. A indicates a better prognosis, and E indicates a poorer prognosis using existing treatment modalities. According to the ICRB, patients within groups A, B, and C had a significant chance of ocular salvage and avoidance of EBRT while those within group D had a much higher rate of treatment failure, with approximately one half requiring external beam radiation therapy (EBRT) or enucleation. Group E eyes were intended to be managed with primary enucleation ***(Linn Murphree, 2005a, Shields et al., 2006a, Novetsky et al., 2009).***

Prior to the International Classification for Intraocular Retinoblastoma, the Reese-Ellsworth classification system was the most useful system when (EBRT) was the standard of treatment for eye salvage. However, now that chemotherapy has supplanted radiation, this classification system is not as predictive of outcome and survival ***(Shields et al., 2006a, Linn Murphree, 2005a).***

The goals of treatment for retinoblastoma are to preserve the patient's life and salvage the affected globe, to preserve as much vision as possible and to limit the risk of second cancers

later in life, which can be caused by treatment, particularly in children with hereditary retinoblastoma ***(Chintagumpala et al., 2007, Abramson et al., 2015).***

Overall, more than 9 in 10 children with retinoblastoma are cured. The chances of long-term survival are much better if the tumor has not spread outside the eye ***(Tamboli et al., 2015).***

The main types of treatment for retinoblastoma are chemotherapy, thermotherapy (using a type of laser to apply heat to kill small tumors), photocoagulation (using lasers to kill small tumors or the blood vessels that feed them), Cryotherapy (using cold to freeze and kill small tumors), radiation therapy and surgery (enucleation).

Sometimes more than one type of treatment may be used. The treatment options are based on the extent of the cancer and other factors ***(El-Barbary et al., 2018).***

Patients with treated retinoblastoma should be monitored with examination under anesthesia every 3-4 months until age 3-4 years, after which they are examined under anesthesia every 6 months until age 5-6 years and then annually thereafter. At about age 8 years, most patients can tolerate a dilated fundus examination in the office without anesthesia and can be examined annually in the office thereafter ***(Rothschild et al., 2011, Skalet et al., 2018).***

In the developed world, retinoblastoma has one of the best cure rates of all childhood cancers (95-98%), with more than nine out of every ten sufferers surviving into adulthood. In the UK, around 40 to 50 new cases are diagnosed each year. Good prognosis depends upon early presentation of the child in health facility. Late presentation of the child in hospital is associated with poor prognosis ***(Linabery and Ross, 2008, Friedman et al., 2016, Singh et al., 2000).***

AIM OF THE WORK

To classify retinoblastoma patients presented to oncology unit of Ain Shams department of ophthalmology to international groups and study presentation, modalities of treatment and treatment outcome of group A and B patients. To see to what extent in Ain Shams department of ophthalmology we succeed achieving eye salvage in early retinoblastoma patients group A and B.

Chapter 1
PATHOPHYSIOLOGY AND CLINICAL PRESENTATION

Retinoblastoma is a life threatening malignant neoplasm that manifests in the eye with features of painless leukocoria or strabismus. It is is the most common type of eye cancer in children. It arises from the immature neural retinal cells of the retina. It is usually found in children under the age of 2 years ***(Linabery and Ross, 2008, Huang et al., 2013).***

Pathophysiology

When the eyes are developing, they have progenitor (immature) multipotential precursor cell called retinoblasts. These cells divide into new cells and fill the part of the eye that will become the retina. Retinoblastoma is caused by changes (mutations) in the retinoblastoma 1 (RB1) gene (the long arm of chromosome 13 band 13q14) in the retinoblasts. Those mutations cause retinoblasts to grow out of control and form a tumour called retinoblastoma. There are 2 copies of the RB1 gene in every cell. There must be a change in both copies of the RB1 gene in a retinoblast cell for a retinoblastoma tumour to develop ***(McEvoy et al., 2014, Ewens et al., 2017).***

Depending on when and where the change in the RB1 gene occurs, 2 different types of retinoblastoma can result:

1. Congenital (hereditary) retinoblastoma

In about 1 out of 3 children with retinoblastoma, the abnormality in the RB1 gene is congenital (present at birth) and is in all the cells of the body, including all of the cells of both retinas. This is known as a germline mutation. In most of these children, there is no family history of this cancer. Only about 25% of the children born with this gene change inherit it from a parent. In about 75% of children the gene change first occurs during early development in the womb. The reasons for this are not clear. Children born with a mutation in the RB1 gene usually develop retinoblastoma in both eyes (known as bilateral retinoblastoma), and there are often several tumors within the eye (known as multifocal retinoblastoma). Because all of the cells in the body have the changed RB1 gene, these children also have a higher risk of developing cancers in other areas as well. A small number of children with this form of retinoblastoma will develop another tumor in the brain, usually in the pineal gland at the base of the brain (a pineoblastoma). This is also known as trilateral retinoblastoma. For survivors of hereditary retinoblastoma, the risk of developing other cancers later in life is also higher than average ***(Castera et al., 2010, de Oliveira Reis et al., 2012, Zhang et al., 2012, McEvoy et al., 2014, Ewens et al., 2017).***

2. Sporadic (non-hereditary) retinoblastoma

In about 2 out of 3 children with retinoblastoma, the abnormality in the RB1 gene develops on its own in only one cell in one eye. It is not known what causes this change. A child who has sporadic (non-hereditary) retinoblastoma develops only one tumor in one eye. This type of retinoblastoma is often found at a later age than the hereditary form. Children with this type of retinoblastoma do not have the same increased risk of other cancers as children with congenital retinoblastoma ***(Castera et al., 2010, de Oliveira Reis et al., 2012, Zajaczek et al., 1998, Zhang et al., 2012, Rushlow et al., 2013, McEvoy et al., 2014, Ewens et al., 2017).***

Intraocularly, it exhibits a variety of growth patterns, which have been described as outlined below:

1. Endophytic growth

Endophytic growth occurs when the tumor breaks through the internal limiting membrane and has an ophthalmic appearance of a white-to-cream mass showing either no surface vessels or small irregular tumor vessels. This growth pattern is typically associated with vitreous seeding, wherein small fragments of tissue become separated from the main tumor. In some instances, vitreous seeding may be extensive and allow tumor cells to be visible as spheroid masses floating in the vitreous and anterior chamber, simulating endophthalmitis or

iridocyclitis, and obscuring the primary mass. Secondary deposits or seeding of tumor cells into other areas of the retina may be confused with multicentric tumors ***(Apushkin et al., 2005a, Honavar and Singh, 2005, Palazzi et al., 1990).***

2. *Exophytic growth*

Exophytic growth occurs in the subretinal space. This growth pattern is often associated with subretinal fluid accumulation and retinal detachment. The tumor cells may infiltrate through the Bruch membrane into the choroid and then invade either blood vessels or ciliary nerves or vessels. Retinal vessels are noted to increase in caliber and tortuosity as they overlie the mass ***(Apushkin et al., 2005a, Honavar and Singh, 2005, Palazzi et al., 1990).***

3. *Diffuse infiltrating growth*

This is a rare subtype comprising 1.5% of all retinoblastomas. It is characterized by a relatively flat infiltration of the retina by tumor cells but without a discrete tumor mass. The obvious white mass seen in typical retinoblastoma rarely occurs. It grows slowly compared with typical retinoblastoma ***(Shields et al., 2008).***

Epidemiology

Frequency

International

Worldwide, the incidence of retinoblastoma is recorded to be about 11 cases per million children younger than 5 years. A more commonly used estimate is 1 case of retinoblastoma per 18,000-30,000 live births, depending on the country.

Incidence rates of retinoblastoma vary from a low of 3.4 per million in Bulgaria to a high of 42.5 per million in Mali. Incidence rates have been noted to vary greatly within Asia (6.3 to 19.6) and Africa (10.6 to 42.5), while incidences in Europe (six to 12) and Australia (10.3) generally show less variability. Incidences in Central and South America range from 7 per million in Uruguay to 17.1 in Colombia ***(Broaddus et al., 2009, Seregard et al., 2004, Tamboli et al., 2015).***

Mortality/Morbidity

Survival rates for patients with retinoblastoma range from a reported 86-92% in the united states, Great Britain and European countries. It is decreased in developing regions versus developed regions. However, these figures must be kept in the context of the retinoblastoma cancers. In actuality, the survival rate drops with each decade of life for patients with the genomic mutation ***(Linabery and Ross, 2008, Tamboli et al., 2015, Eng et al., 1993, MacCarthy et al., 2009, Marees et al., 2009).***

The genomic mutation is a gene mutation within every cell of the individual's body. These patients typically present with either bilateral disease or unilateral-multifocal (one eye with multiple distinctly separate tumor foci) disease. These individuals have a predisposition for developing second cancers later in life. Mortality in these individuals is consequently much higher than rates for those with somatic mutations (i.e., affecting one retinal cell only and unilateral-unifocal disease). The greatest predictor of death is extraocular extension, either directly through the sclera or via extension along the optic nerve ***(Linabery and Ross, 2008, Eng et al., 1993, Leal-Leal et al., 2006, Friedman et al., 2016, Tamboli et al., 2015).***

Race

No racial predilection appears to exist for retinoblastoma.

No difference in incidence exists among blacks and whites ***(Linabery and Ross, 2008, Broaddus et al., 2009, Seregard et al., 2004, Tamboli et al., 2015, Truong et al., 2015).***

Sex

Studies show no significant difference in the incidence of retinoblastoma by sex for children aged 0-14 years.

The estimated boy-to-girl ratio is reportedly 1.12:1 ***(Linabery and Ross, 2008, Broaddus et al., 2009, Seregard et al., 2004, Tamboli et al., 2015, Truong et al., 2015).***

Age

Retinoblastoma is diagnosed in patients at an average of 18 months, two-thirds of patients diagnosed younger than 2 years and 90% of cases diagnosed in patients younger than 5 years ***(Linabery and Ross, 2008, Zajaczek et al., 1998, Broaddus et al., 2009, Seregard et al., 2004, Tamboli et al., 2015).***

Children who are affected bilaterally are diagnosed at an average age of 13 months, while patients with unilateral retinoblastoma are diagnosed at an average age of 24 months ***(Linabery and Ross, 2008, Zajaczek et al., 1998, Broaddus et al., 2009, Seregard et al., 2004, Tamboli et al., 2015).***

When a known family history of retinoblastoma exists, patients with bilateral retinoblastoma are diagnosed at an average age of 11 months ***(Rothschild et al., 2011, Richter et al., 2003, Abramson et al., 1998b).***

A few cases of retinoblastoma in adults (aged 20 y and older) have been reported in the literature. Some theorize that these lesions arise from a previously existing retinocytoma that underwent malignant transformation ***(Linabery and Ross, 2008, Zajaczek et al., 1998, Broaddus et al., 2009, Seregard et al., 2004, Tamboli et al., 2015).***