INTRODUCTION

Infantile haemangiomas are the most common benign tumours of infancy. They affect approximately one in ten infants ***(Zimmermann et al., 2010)***. They are more common in Caucasian populations and in female infants. A higher incidence is observed in premature babies and those who were subject to chorionic villous sampling in-utero ***(Schwartz et al., 2010)***. The majority of haemangiomas are located in the head and neck region with lesions on the trunk and extremities being less common ***(Zimmerman et al., 2010)***.

The cutaneous lesions present soon after birth and are characterized by rapid proliferation during the first year of life, followed by a gradual involution over the next five to ten years. Whilst most haemangioma are non-problematic, requiring no treatment, approximately 10% cause significant morbidity predominantly through airway obstruction, ocular compression, functional impairment or ulceration ***(Starkey et al., 2011)***.

They are extremely heterogenous and cause a range of complications depending on their morphology, size and location **(*Adams et al., 2018)***

Most of IH resolve spontaneously; however, treatment is recommended in patients who develop complication. Propranolol is recommended as first line therapy by authors, while the treatment of choice in patients who are unresponsive

to first line therapy depends on the clinical experiences of each center ***Dunzel et al., (2019)***.

Tanner et al. (1998) interviewed parents of 25 children with IH. Parents related feelings of disbelief, guilt, sadness, panic, or fear related to their child's hemangioma .Social interactions were described as stressful by a majority of parents, and accusations of child abuse were reported by 36% of those interviewed. Using a validated generic quality-of-life instruments designed for children as well as hemangioma-specific questions were administered to Dutch children aged 1–15 years with a history of IH, parents reported that public reactions made them and their children more aware of the hemangioma ***(Hoornweg et al., 2009)***.

AIM OF THE STUDY

Primary:

To measure the quality of life in IH, both in infants and children by a disease specific questionnaire filled by their parents.

Secondary:

1- To relate the severity of IH to quality of life

2- To show the outcome of treatment modalities adopted in relation to the quality of life.

Chapter (1)
INFANTILE HEMANGIOMA

Classification of vascular anomalies:

Different classifications have been described for vascular anomalies. Any classification is successful only if it's diagnostic applicability helps in planning therapy and studying of pathogenesis ***(Finn, 1983)***.

Vascular tumors comprise a vast spectrum of diseases and are therefore difficult to diagnose and classify. Benign vascular tumors can be mistaken for vascular malformations, but even more frequently vascular malformations are misdiagnosed as vascular tumors, such as infantile hemangiomas. Inappropriate misnomers and delayed diagnoses as well as false classification are responsible for wrong treatment approaches, which may delay appropriate therapy, or lead to significant morbidity and mortality ***(Moriz et al., 2019).***

1- Virchow, 1863 and Wegener, 1877 classifications:

Virchow, the father of cellular (and surgical) pathology, deserves credit as the first to categorize vascular anomalies by microscopic features. He called them angiomas simplex, angioma cavernosum and angioma racemosum ***(Virchow, 1863)***.

2- Mulliken and Glowacki biologic classification, 1982:

The current classification system for vascular anomalies can be attributed to ***Mulliken and Glowacki (1982)***.

They divided them into: **vascular tumors** and **vascular malformations,** Infantile hemangiomas comprise the majority of vascular anomalies ***(Haggstrom et al., 2007)***.

In this classification, hemangiomas are defined as benign tumors of endothelium, characterized by increased cell turnover (hypercellularity and endothelial multiplication), while vascular malformations on the other hand are structural abnormalities; the end result is of faulty morphogenesis of embryonic vascular plexus, and they exhibit a normal rate of endothelial turn over (no endothelial proliferation) ***(Murthy, 2010)***.

3- Mulliken modification of the biologic classification 1992 (table 1):

A modification to the **biologic classification** was done by ***Mulliken** in **1992***. In this classification, hemangiomas were divided into proliferating and involuting phases. While vascular malformations were subcategorized as slow-flow anomalies, fast flow anomalies.

Slow and fast flow is based on the speed of flow and the rate of shunting between the arterial and venous components, which is detected by angiography ***(Buckmiller et al., 2010)***.

Table (1): Mulliken modification of the biologic classification ***(Marshalleck and Johnson, 2006)***

Hemangiomas	**Vascular malformations**
Proliferating	**1- High-flow (Fast):** • Arteriovenous malformation (AVM) • Arteriovenous fistulae (AVF)
Involuting	**2- Low-flow (Low):** • Capillary malformations (CM)**)** • Venous malformations (VM) • Lymphatic malformations (LM) • Mixed malformations

4- Updated ISSVA (Mulliken updated) classification, 1997 (table 2):

Table (2): Updated ISSVA classification of Mulliken modification ***(Enjolras et al., 2007)***

Vascular tumors	Vascular malformations
Infantile hemangiomas **Congenital hemangioma (RICH and NICH)** **Kaposiform hemangioendothelioma (with or without Kasabach- Merritt Phenomenon)** **Tufted angioma (with or without Kasabach-Merritt Phenomenon)** **Spindle- cell hemangioendothelioma** **Other rare hemangioendotheliomas (epitheloid, composite, retiform, polymorphous, Dabska tumor (DT), lymphangioendotheliomatos is.** **Dermatologic acquired vascular tumors (pyogenic granuloma (PGs), targetoid hemangioma, glomeruloid hemangioma, microvenular hemangioma)**	**Fast-flow vascular malformations:** Arterial malformation (AM) Arteriovenous malformation (AVM) Arteriovenous fistula (AVF) **Slow-flow vascular malformations:** **Capillary malformation (CM)** Port-wine stain Telangiectasia Angiokeratoma **Venous malformation (VM)** Common sporadic VM Blue rubber bleb nevus syndrome Familial cutaneous and mucosal VM (VMCM) Glomuvenous malformation(GVM, glomangioma) Maffucci syndrome **Lymphatic malformation (LM)** **Complex-combined vascular malformations**: **Slow-flow combined vascular malformations:** Capillary- lymphatic (CLM). Lymphaticovenous(LVM) Capillary lymphaticovenous (CLVM) **Fast-flow combined vascular malformations:** Capillary-lymphatic AVMCapillary-lymphatic AVF

Table (3): Distinguishing features of Hemangiomas and vascular malformations

Hemangiomas	**Vascular malformations**
Benign tumor	Congenital abnormality
30% visible at birth, seen as red macule; 70% become apparent during first few weeks of life	Present at birth, but may not be evident until months or even years later
Females more commonly affected (gender ratio of 3:1)	No gender predilection
Rapid postnatal growth followed by slow involution	Slow steady growth, with no involution; may expand secondary to sepsis, trauma, or hormonal changes
Endothelial cell hyperplasia	Normal endothelial cell turnover
Increased mast cells	Normal mast cell count
Multilaminated basement membrane	Normal thin basement membrane
Primary thrombophilia, No coagulation abnormalities	Primary stasis (venous);localized consumptive coagulopathy
Radiographic findings: well circumscribed, intense lobular-parenchymal staining with equatorial vessels	Radiographic findings: diffuse, no parenchyma low-flow: phleboliths, ectatic channels highflow: enlarged ,tortuous arteries with arteriovenous shunting
Infrequent "mass effect" on adjacent bone; hypertrophy rare	Low-flow: distortion, hypertrophy, or hypoplasia high-flow: bone destruction, distortion, or hypertrophy
80%-90% respond dramatically to corticosteroid treatment in 2 to 3 weeks	No response to corticosteroids or antiangiogenic agents
Immunopositive for biologic markers GLUT1 (glucose transporter protein 1), Fc_RII, merosin, and Lewis Y antigen.	Immunonegative for these biologic markers

(Adams and Lucky, 2006)

Epidemiology of infantile hemangioma:

The incidence in the general newborn population is between 1.1 and 2.6%, but increases to up to 12% by one year of age. About 30% of IH are noticed at birth and (70–90)% appear during the first four weeks of life ***(Cordisco, 2009).***

In a prospective cohort study ongoing in the United States, data in 1058 patients revealed that 68.9% of patients were Caucasian, 14.4% were Hispanic and 2.8% were African-American.

Female-to-male ratio was 2.4:1.0 . Distribution of IH according to the different types are: localized 72%, segmental 18%, indeterminate 9%, and multifocal 3% ***(Haggstrom et al., 2006).***

Etiology of infantile hemangioma:

There are currently many competing hypotheses (or lines of evidence) which are, however, not mutually exclusive:

a. Embolization:

This theory hypotheses that embolization of placental endothelial cells. IH share many immunohistochemical markers as glucose transporter protein-1 (GLUT-1), Lewis Y antigen, merosin, CCR6, CD15, indoleamine 2, 3-deoxygenase (IDO) with human placental microvessels ***(Limaye and Vikkula, 2015).***

Embolization of placental endothelial cells to the fetus has been hypothesized, but subsequent molecular genetic investigations revealed no evidence for that in children with solitary hemangiomas ***(Pittman et al., 2006)*.**

b. Increased angiogenic and vasculogenic activity:

Expression of vascular endothelial growth factor receptor 1 (VEGFR) is reduced in hemangioma endothelial cells. Low VEGFR1 expression results in VEGF-induced activation of VEGFR2 and downstream signaling pathways, leading to stimulation of angiogenesis ***(Jinnin et al., 2008)***.

In contrast to previously held views, vasculogenesis, in addition to stimulated angiogenesis, plays a role in the pathogenesis of IH as well. There is recent evidence that IH arise from bone marrow-derived endothelial progenitor stem cells (EPC) capable of inducing postnatal formation of vascular tissue ***(Boscolo and Bischoff, 2009)*.** EPC express hypoxia-inducible factor 1α (HIF-1α) which in turn promotes local production of VEGF ***(Drolet and Frieden, 2010)***.

c. Tissue hypoxia:

Tissue hypoxia seems to be the most powerful inducer of angiogenesis (and vasculogenesis). Two studies have shown an association between placental hypoxia and IH ***(Gutierrez et al., 2007 and Colonna et al., 2010)***.

d- Somatic mutation theory:

However, there are other aspects of IH which still remain unexplained. IH are distributed unevenly over the body surface: about 60– 65% are located on the face and neck area. Patterned segments could be identified which correspond to embryonic fusion lines and point to the involvement of neural crest-derived cells ***(Haggstrom et al., 2006)***.

Pathology of infantile hemangioma:

Infantile hemangioma displays a unique life-cycle of proliferationfollowed by involution. The ‘‘proliferating phase’’ spans the first several months of infancy, with most of the growth occurring by 5 months of age. Histological analysis of IH tissue sections show that the tumors are highly cellular, with clusters of plump cells expressing endothelial markers and small vascular channels with barely discernable vessel lumens

Growth of IH slows dramatically in the ‘‘involuting phase’’, which typically begins soon after the child’s first birthday and lasts for 4–6 years. As involution proceeds, vascular channels become more prominent and are lined with flattened endothelial cells the clusters of plump immature cells are no longer evident ***(Barnes et al., 2005 and Barnes et al., 2007)*.**

A hallmark of IH is that eventually, the disorganized mass of vessels will regress when the child reaches 8–10 years

of age. This final, ‘‘involuted phase’’ is characterized by sparse, thin-walled vessels. However, the bulk of involuted hemangioma tissue is composed of adipocytes and connective tissue ***(Pittman et al., 2006)*.**

Factors predicting complications and treatment of infantile hemangioma:

The influence of hemangioma size and subtype on the need for treatment and development of complications was studied, using a random-effects logistic model. Controlling for hemangioma size, hemangioma subtype was a strong predictor for development of complications and need for treatment. Segmental hemangiomas were 8 times more likely to receive treatment compared with localized hemangiomas after controlling for hemangioma size. Similarly, segmental hemangiomas were 11 times more likely to develop complications (including ulceration, bleeding, visual compromise, auditory compromise, cardiac compromise, or airway obstruction) than localized hemangiomas after controlling for size. When comparing outcomes between subtypes, segmental hemangiomas consistently had higher rates of complications and treatment compared with indeterminate and localized hemangiomas ***(Haggstrom et al., 2011)***.

Complications of infantile hemangioma:

Even though infantile hemangiomas are innocuous birthmarks that regress, in a small subset of patients' hemangiomas can endanger vital structures or be associated with other abnormalities carrying significant morbidity and even mortality ***(Enjolras et al., 1990)***.

Physicians caring for children with hemangiomas can expect questions from parents regarding prognosis and, therefore, must understand which hemangiomashave the greatest risks of complication and need for treatment. Because hemangiomas proliferate rapidly in the first few weeks to months of life, there may be a window of opportunity to intervene in high risk hemangiomas in an attempt to prevent complications ***(Mulliken et al., 2002)***.

1-Ulceration:

Ulceration is a common complication in up to 8–13% of IH, and occurs most often but not exclusively during the proliferative phase, and most frequently in the plaque ***(Kim et al., 2001)***. It is one of the commonest reasons for referral to a specialist, and may cause pain, scarring and disfigurement. It occurs more commonly in hemangioma of mucosal sites (lip and anogenital) or intertriginous sites (neck, perineum**)** ***(Chamlin et al., 2007)***.

2-Bleeding:

Bleeding is also a surprisingly uncommon complication, with severe bleeding occurring in approximately 1% in a referral population. Ulceration of preorificial sites (perioral and anogenital areas) is most concerning because of obvious functional and esthetic consequences ***(Chamlin et al., 2007)*.**

3- Visual impairment:

Periocular hemangiomas usually involve the upper eyelid as, but can also involve the lower lid and retrobulbar space. Orbital hemangiomas are classified as superficial, deep, and compound, with superficial lesions located anterior to the orbital septum, deep hemangiomas posterior to the orbital septum and often causing mass effect, and compound

hemangiomas having both a superficial and deep component ***(Mulliken et al., 2000)***.

Periocular hemangiomas may cause ptosis (downward displacement of the upper eyelid), strabismus (deviation of the eye which the patient cannot overcome) and anisometropia (condition in which the two eyes have an unequal refractive power), each of which may in turn result in astigmatism (Unequal curvature of the refractive surface) of the eye ***(Goldberg and Rosanova, 1992)*.**

4- Airway obstruction:

Airway obstruction may result from hemangiomas occurring at any level from the nose to the trachea, though the most common site of airway involvement is the subglottic region. A hemangioma growing within the nasal tip may block the vestibular passages during the first three months of life, when the infant is obligatory nose breather. However, the obstruction of the nasal airway is usually unilateral, so the infant adapts to breath orally. Subglottic and/or tracheal infantile hemangioma is the most common neoplasm of the infant airway ***(Rahbar et al., 2004)***.

Although subglottic hemangioma is a benign condition, yet it can be associated with a fatal outcome. Without proper diagnosis and treatment 30% -70% mortality rate has been reported ***(Mulliken et al., 2000)*.**