Essay

Submitted for partial fulfillment of Master degree in

General surgery

By

(M.B., B.CH 2010)

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Acknowledgment

- *First, thanks are all due to **Allah** for Blessing this work until it has reached its end, as a part of his generous help throughout our life.*
- *I find no words by which I can express my extreme thankfulness, deep appreciation and profound gratitude to my eminent **Prof. Dr. Ahmed Medhat Zaki,** Professor of pediatric surgery , Faculty of Medicine, Ain Shams University, for giving me the privilege of working under his meticulous supervision and for his generous help, guidance, kind encouragement and great fruitful advice during supervision of this work.*
- *I am deeply indebted to, **Dr. Mohamed Moussa Dahab**, Lecturer of pediatric surger,y, Faculty of Medicine, Ain Shams University for his great support and careful supervision, which helped me to overcome many difficulties.*
- *Finally, I would like to express my sincere thanks to all those who helped me directly or indirectly during the preparation of this work.*

Tarek Gamal Mohamed Eid

Introduction

Hemangiomas are congenital abnormality that had an estimated incidence of 1% to 3% in white neonates and 10% to 12% in children by 1 year of age. In premature infants with a birth weight less than 1kg, the incidence raises to 23 % ***(Fischer, 2007)***.

Hemangiomas are categorized based on anatomical depth as superficial (50% to 60%), deep (15%), or combined (25% to 35%) ***(Mulliken, 2004)***.

Presentation depends on the location of hemangiomas. If they are on the surface of the skin, they are reminiscent of a ripe strawberry. However, if they are just under the skin they present as a bluish swelling. Sometimes they grow in internal organs such as the liver, larynx, or small and large intestine ***(Berenguer et al., 2003)*.**

Intial diagnosis of hemangioma of infancy is based on clinical presentation, history, and physical examination. Additional investigations may be helpful in determining the extent of involvement such as US with color flow Doppler, Computed tomography (CT), MRI and magnetic resonance angiography (MRA) ***(Holt, 2001).***

Most hemangiomas disappear without treatment, leaving minimal or no visible marks. This may take many years. Diagnostic and treatment decision-making should encompass considerations such as the differential diagnosis, the size and location of the tumor, the presence of complications, the age of the patient, and the rate of tumor growth ***(Fischer, 2007).***

Although most hemangiomas resolve without the need for intervention, there are indeed exceptions. Rapidly growing lesions can cause a wide variety of complications, including ulceration, infection, hemorrhage, necrosis, airway obstruction, loss of vision, and cardiac failure. ***(North, 2001)***.

Oral systemic corticosteroids are the mainstay of current medical therapy for life-threatening or function-threatening hemangiomas. In 30% of lesions, the response to oral systemic corticosteroids is dramatic; the hemangioma stops growing, begins to shrink, and loses its color intensity within 2 to 3 weeks. However, the potential transient side effects include irritability, adrenal suppression, immunosuppression, hypertension, hyperglycemia, and myositis ***(Fischer, 2007)***.

From 2008 the blood pressure medication propranolol is being used in treatment of infantile hemangiomas. Effectiveness of propranolol is highest within the first 6 months of the onset of hemangiomas ***(Hogeling et al., 2011).***

Other lines of medical treatment of hemangiomas like recombinant interferon could be useful in hemangioma resistant to steroid therapy, Vincristine, a mitotic spindle tubule inhibitor is also useful in treating steroid resistant life-threatening or function-threatening hemangiomas. ***(Enjolras, 2004).***

The Topically applied beta blocker solution/gel Timolol is also being trialed for small facial hemangiomas that do not justify systemic treatment ***(Pope, 2010)***.

Surgical removal is sometimes indicated, particularly if there has been delay in commencing treatment and structural changes have become irreversible. Surgery may also be necessary to correct distortion of facial features, again in the case of inadequate or failed early medical intervention. A pulsed dye laser can be useful for very early, flat, superficial lesions ***(Rogers, 2002).***

Aim

The aim of this study is to illustrate the different techniques in management of Hemangiomas as regard success rate, safety and complications.

Embryology

The histological structure of blood vessels consists of three layers: an inner layer, the tunica interna (intima), a single layer of flattened endothelial cells (ECs) supported in most blood vessels by a basement membrane and subendothelial connective tissue; an intermediate muscular layer, the tunica media (media), smooth muscle cells (SMCs) and fibrocytes intermingled with networks of elastin and collagen; and an outer layer of connective tissue, the tunica externa (adventitia), containing *vasa vasorum* (blood vessels and lymphatics), immune cells, and nerves. The media is reduced with the size of the vessels and finally absent in the capillaries, which can be associated with pericytes in the blood vascular ***(Witte et al., 2006).***

The cardiovascular system is the first organ system to form and function in vertebrate embryos. In human beings, the first contractions of the heart can be detected by ultrasound around the 21st day of embryonic development (days post conception), which is only 7 days after the first missed menstrual period ***(Bazigou, 2013).***

At this early stage of development, the human embryo is only 2–3 mm long, and the length of his heart is about

0.5 mm. The beginning of cardiac pumping action coincides with the establishment of the first closed vascular circuit, which connects the embryo proper with the developing placenta ***(Männer et al., 2010).***

The components of this vascular circuit are a valveless tubular heart, which contracts in a peristaltic fashion and pumps the blood from its venous in flow into a common arterial root termed the aortic sac ;a bilaterally symmetric pair of pharyngeal arch arteries , which connects the aortic sac with bilaterally symmetric pair of dorsal aortae ;a bilaterally symmetric pair of umbilical arteries , which connects the paired dorsal aortae with the placental vasculature; and a bilaterally symmetric pair of umbilical veins, which connects the placental vasculature to the venous in flow of the embryonic heart tube ***(Männer et al., 2010).***

General Schedule for the Development of Embryonic Blood Vessels

Formation of "Primary Vascular Plexuses" and "Primary Plexiform Vascular Channels"

The wall of early embryonic blood vessels consists only of endothelial cells so that the initial structure of embryonic arteries and veins resembles the structure of capillaries in the mature organism ***(Wilting, 2002).***

Thus, endothelial cells and their precursors - the so-called angioblasts - are the fundamental cellular building blocks from which early embryonic blood vessels are assembled, and the commitment of angioblasts may be regarded as the initial step in the formation of embryonic blood vessels. Blood vessel angioblasts (BV-angioblasts) derive from undifferentiated mesenchymal cells and their assemblage to primitive endothelial blood vessels occurs in spaces filled with mesenchyme ***(Schmidt et al., 2007).***

The process of de novo formation of endothelial blood vessels via the assemblage of BV-angioblasts within the primary avascular mesenchyme is named "vasculogenesis" ***(Risau, 1997).***

In the implanted human egg, mesenchyme first appears in the extraembryonic compartments such as the placenta (chorion mesenchyme) and the yolk sac (yolk sac mesenchyme) by the end of the 2nd week of development (4th post-menstrual week). The first intraembryonic mesenchyme appears during the 3rd week of development (5th post-menstrual week). It stems from primitive streak-derived mesoderm. Corresponding to the extraembryonic to intraembryonic sequence of mesenchyme formation, extraembryonic vasculogenesis precedes intraembryonic vasculogenesis ***(Schmidt et al., 2007).***

The precondition for vasculogenesis is the presence of scattered BV-angioblasts within the local mesenchyme. In a given subcompartment of the extra- or intraembryonic mesenchyme, BV-angioblasts may derive from local mesenchymal cells that are competent to develop into BV-angioblasts or from an extrinsic source, which provides migratory BV-angioblasts that colonize distant mesenchymal compartments ***(Schmidt et al., 2007).***

In the yolk sac mesenchyme and in the mesenchymal layer covering of the primitive gut endoderm (the so-called splanchnopleura), BV-angioblasts derive from local mesenchymal cells, while the local mesenchyme of the developing body wall (the so-called somatopleura) becomes colonized by BV-angioblasts derived from the somites ***(Yvernogeau et al., 2012).***

The origin of BV-angioblasts found within the chorion mesenchyme has not been clarified up to now. The first visible sign for the onset of vasculogenesis is the coalescence of primary scattered BV-angioblasts to solid cell aggregates or cell cords termed "angioblastic aggregates" or "angioblastic cords" **(Fig.1).** During subsequent development, a fluid-filled lumen is formed within these primary solid structures ***(Cleaver et al., 2011).***

The primitive vascular anlagen thereby assume the phenotype of endothelium-lined vesicles, which may be termed “blood vessel islands” (BV-islands).

During subsequent development, the originally isolated BV-islands fuse with neighboring BV-islands. Consequently, a primitive vascular plexus is formed, which is frequently named the “capillary vascular plexus” since the wall of its vascular meshes consists only of endothelial cells. We should note, however, that the vessel diameters found in primitive embryonic vascular plexuses are larger than the diameters of most of the mature capillaries. Therefore, if we compare such plexuses with vascular beds of the mature human body, we will find that they have more resemblance with the sinusoidal vessels of the adult spleen or bone marrow than with typical capillary beds. We, therefore, think that the term *capillary vascular plexus* is a misnomer that may provide a wrong picture of important components of the embryonic vasculature. We prefer usage of the term “primary vascular plexus ***(Hirschi, 2012).***

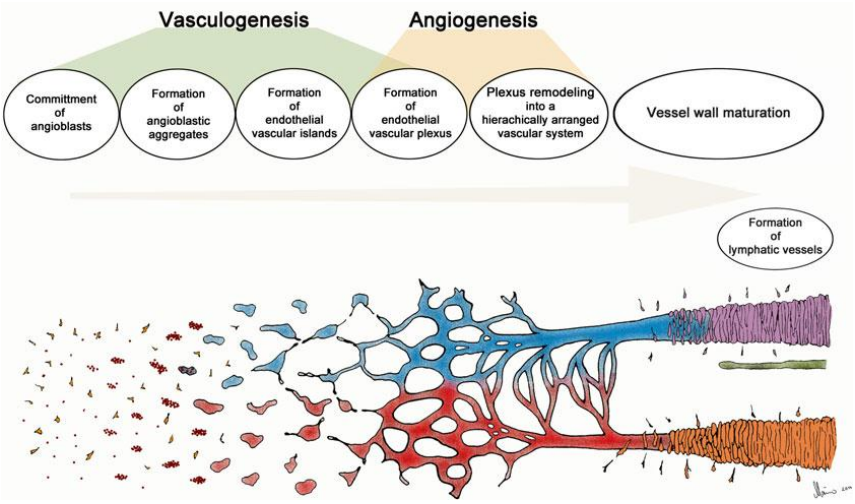

Fig. (1): Schematic illustration of the general principles of the stepwise development of a local vascular circuit within extensive mesenchymal spaces. The main steps are (1) formation of a primary vascular plexus, (2) plexus remodeling, and (3) maturation of the vessel wall ***(Hirschi, 2012).***

Remodeling of Primary Vascular Plexuses into Hierarchically Arranged Vascular Circuits

As already noted, primary vascular plexuses lack externally visible signs for a hierarchical arrangement of their vascular meshes. The situation changes, however, when a primary vascular plexus becomes connected to already perfused blood vessels. Subsequent to the establishment of permanent blood flow through a primary vascular plexus, the plexus undergoes a process of vascular remodeling, which leads to the establishment of a

hierarchically arranged vascular bed consisting of large vascular channels, representing arteries and veins, and of small vascular channels representing capillaries**.** ***(Eichmann, 2005).***

The wall of all these vessels still consists only of endothelial cell, but their arterial, venous, or capillary identities can be deduced from their topography and the direction of blood flow. During remodeling, the arterial and venous channels first appear as plexiform vascular channels before they assume the phenotype of tubular vessels **(Figs. 1)** ***(Culver et al., 2010).***

Remodeling of primary vascular plexuses is accomplished by a set of various morphogenetic mechanisms, which facilitate locally confined changes in size and number of the vascular meshes **(Fig. 2).** The number of originally existing vascular meshes is reduced either by fusion of two neighboring vessels or by the regression of vessels. Vasculogenesis may still contribute to an increase in the number of vascular meshes of the plexus. However, the majority of new blood vessels that become added to a plexus now are generated either by the formation of vascular sprouts that grow out from already existing vessels or from the splitting of already existing vessels. The formation of new blood vessels from

preexisting vessels is generally termed "angiogenesis" ***(Ribatti, 2006).***

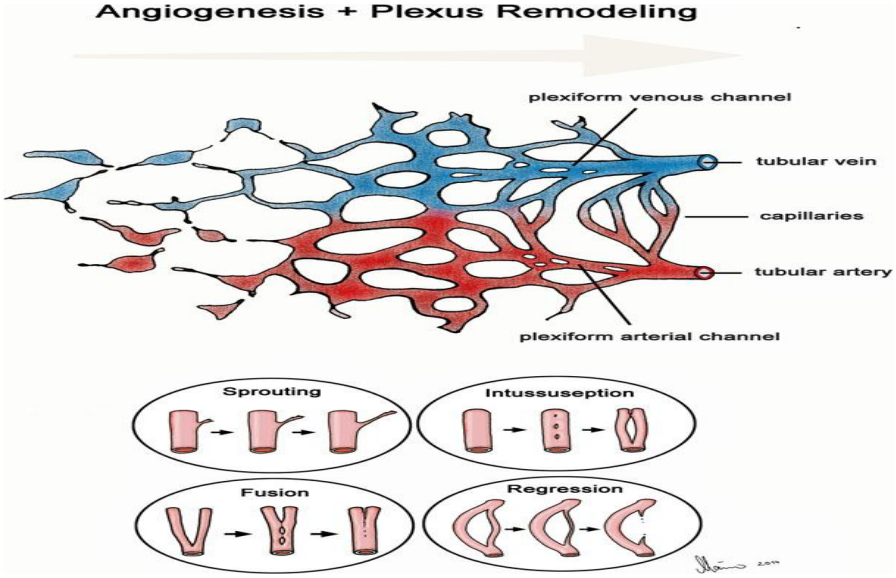

Fig. (2): Schematic illustration of the development of a hierarchical vascular tree. (1) Remodeling of the primary vascular plexus into a hierarchically arranged vascular circuit consisting of arteries, capillaries, and veins. (2) Four distinct morphogenetic mechanisms contributing to the remodeling process ***(Ribatti, 2006).***

Vessel Wall Maturation

The formation of primary vascular plexuses **(Fig. 1),** primary plexiform vascular channels, as well as plexus remodeling **(Fig. 2)** is induced and controlled by an interplay of genetic factors, such as the expression of regulatory genes and signaling molecules ***(Udan et al., 2013),*** and epigenetic factors, such as oxygen, metabolites and hemodynamic loads ***(Fraisl et al., 2009).***

During embryonic development, all these factors continuously change in a highly dynamic fashion. Corresponding to the continuously changing genetic and epigenetic landscape of the embryo, the developing cardiovascular system undergoes continuous growth and remodeling, which is facilitated by the primary endothelial structure of its vessel walls. At a certain size, however, purely endothelial vessel walls cannot withstand the continuously increasing hemodynamic loads (e.g., blood pressure) acting on the walls of main vascular channels. At this stage of blood vessel development, the walls of the main arterial and venous channels become reinforced by the recruitment of vascular smooth muscle cells (VSMCs) and fibroblasts as well as by the synthesis of extracellular matrix components such as collagen and elastin ***(Roman et al., 2012).***

This leads to the establishment of the well-known, multilayered wall structure of mature arteries and veins. The establishment of the mature arterial wall structure generally proceeds in a proximal-to- distal direction suggesting that hemodynamic factors play fundamental roles in the maturation of blood vessels ***(Culver et al., 2010).***