Haemangiomas – the commonest tumour of infancy

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'Strawberries' and 'Port Wine'

Vascular lesions of the skin are common in infancy and childhood. Despite this, until a decade ago, "Modern Medicine" left both physicians and patients in the "Dark Ages" regarding the diagnosis, prognosis, and management of these common skin lesions. Lack of a uniformly accepted classification, a proper understanding of the natural course of these lesions, and above all the widely accepted misconception at the time that the majority of these vascular lesions would resolve spontaneously led to the state of confusion and apathy. This often resulted in misdiagnosis, a state of benign neglect and often a lifetime of stigmata and profound psychological stress to the patients and their parents.

Renaissance began in the mid 1980's with Mulliken and Glowacki taking a giant step forward with their biological classification of congenital vascular lesions[1]. Their classification was based on clinical and biological features and divided the congenital vascular lesions into two distinct entities; haemangiomas and vascular malformations. According to their classification, haemangiomas a) are usually not present at birth, b) show an initial proliferative phase during the first year of life, c) involute during childhood and, d) the vascular endothelial cells show a high rate of turnover during the proliferative phase. The vascular malformations a) are usually present at birth, b) do not proliferate, c) never involute, and d) the vascular endothelial cell turnover is normal.

International Society for the Study of Vascular Anomalies (ISSVA) was inaugurated in Budapest in 1992. After 4 years of retrospective and prospective studies on vascular lesions, the meeting in Rome in 1996 adopted the ISSVA Classification. According to this classification the suffix "oma" is used to describe vascular lesions arising from cellular hyperplasia, thus showing a high endothelial cell mitotic activity resulting in proliferative lesions. Other lesions are described as vascular anomalies and they result from (errors of morphogenesis) developmental "malformations" with no increase in endothelial cell turnover and therefore no disproportionate growth. However, vascular malformations show a slow and proportionate relentless increase in size throughout life which is due to expansion of the lesion and they would never involute. Though there have been recent reports of lesions showing minor variations from this classification, this forms the basis in diagnosis, prognostication and management of infantile and childhood vascular lesions in clinical practice.

Haemangiomas

Haemangioma is the commonest tumour in infancy. The vast majority are found within or just beneath the skin, with a few occasionally showing involvement of internal organs. The incidence, at the end of 1st year of life of the full-term newborns, varies between 10% - 12% of all white children and 0.8% - 1.4% amongst Asian and Black children[2]. Haeman-giomas occur 4 times more frequently in females than in males[3] and 1 in 4 of every newborn weighing less than 1kg[4]. Though the occurrence is sporadic, a familial transmission in autosomal dominant fashion has been documented[5]. A recent study of twins failed to implicate hereditary factors in the aetiology[6]. Chorionic villus sampling is a documented predisposing factor[7].

Nomenclature

Vascular lesions formerly referred to as "strawberry" or "capillary" haemangiomas are the ones that arise in the papillary dermis. In the proliferative phase they stretch the overlying skin and become bright red tumorous masses. Such lesions are now called "superficial haemangiomas". When the lesions are in the reticular dermis or the sub cutis, the subcutaneous tissues between the lesion and the epidermis give a bluish colouration or may appear skin coloured. Instead of being referred to as "cavernous haemangiomas" they are now termed "deep haemangiomas". When both the superficial and the deep component are present together, instead of the old term "capillary cavernous" these are now called "compound haemangiomas". Superficial haemangiomas are the commonest, making 50% to 60% of all the haemangiomas, with compound haemangiomas making 25% to 30% and deep haemangiomas less than 25%.

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Pathogenesis

Though the exact cause remains unknown a number of aetiological factors have been described in the pathogenesis of haemangiomas. An imbalance between the positive and negative angiogenic factors expressed by the haemangioma and normal adjacent tissues[8] with increased apoptosis during the second year of life leading to regression[9] have been postulated. Immunohistochemical studies have demonstrated an over-expression of basic fibroblast growth factor (BFGF), vascular endothelial growth factor (VEGF), proliferating cell nuclear antigen, and type IV collagenase during the proliferative phase. There is an increase in urinary BFGF during the proliferative phase and decrease during the involutional phase[10]. Unique tissue specific markers such as erythrocyte-type glucose transporter protein (GLUT1) and LewisY antigen (LeY) are co-expressed by haemangiomas and placental micro vessels suggesting a placental trophoblastic origin[11,12]. An increase of 30-40 fold of the number of mast cells have been seen within proliferating haemangiomas. Their role is thought to be complex and heterogenous.

Natural course

A common haemangioma is first observed characteristically during the first few weeks of neonatal life as a blanched macule. This often goes unnoticed until the development of telangiectasia with a blanched halo. The contrast with the uninvolved skin becomes obvious when the baby cries. This paradoxical blanching of a proliferative vascular lesion has been elucidated[2]. At the onset of increased endothelial cell activity, the cells become "plump", temporarily blocking the lumina leaving little room for the red blood cells giving rise to the pallor. Continued proliferation leads not only to increased vessel diameter but also increase in vessel number leading to telangiectasia and subsequently to the development of a red tumerous lesion.

Recent studies have shown that there are definite sites of predilection which correspond with lines of embryological fusion[2]. Majority of the haemangiomas tend to arise above the neck. The rate and timing of proliferation is variable but generally show two periods of intense growth. The first and the most marked is in the neonatal period and early infancy and the other between 4th and 6th month. The final dimensions of the lesion depends on the degree and duration of proliferation. There are no prognostic factors to predict the final outcome of an uncomplicated common haemangioma.

Involution begins as a gradual transition after the cessation of growth. This coincides with reduced levels of urinary BFGF, influx of mast cells, and induction of tissue inhibitors of metalloproteinases together with increased apoptosis. Period of involution may continue for 5 to 6 years. Once involuted most lesions still show a few superficial telangiectatic vessels on a background of loose and redundant skin.

"All haemangiomas are not 'strawberries"

Occasionally, prenatally formed haemangiomas present fully developed at birth. These do not follow the expected proliferative course of a common haemangioma. There are two such distinct types reported recently. The Congenital Non-progressive Haemangioma, as the name implies, does not proliferate postnatally. They are fully formed at birth as tumourous lesions and are histologically and immunophenotypically distinct from the classic common haemangioma with a complete lack of immunoreactivity to GLUT1 and LeY antigens, and are not pathogenically related to them[13]. Some have been detected by prenatal ultrasonography as early as 12th week of gestation. It may display different clinical patterns such as a telangiectatic hemispherical tumor with a pale rim, sometimes with central ulceration, a raised lobulated exophytic violaceous firm mass (Figure 1), or even a diffuse dermal-hypodermal infiltration of the skin. They involute rapidly in infancy and this distinction from the common type is important in counselling and management. Congenital proteinC deficiency, antiphospholipid syndrome and cryoglobulinaemia are reported associations in the mother of the infant with these congenital haemangiomas. This has led to the speculation that abnormalities in coagulation during gestation may be playing a role in the pathogenesis of this distinct form of congenital haemangiomas.

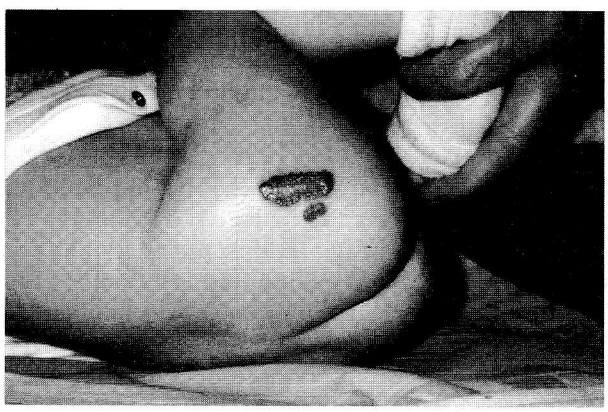

Figure 1. *Congenital Non-progressive haemangioma, present fully formed at birth, and showing signs of involution 3 months post-natally.*

The other, much more rare form, is the recently documented Noninvoluting Congenital Haemangioma[14]. These are slightly commoner in the male, occur as solitary lesions and are present at birth. They often show coarse telangiectasia, a pale rim at the periphery with intermingled areas of pallor as seen in involuting common haemangiomas. These haemangiomas are warm to touch. The course is that of slow progression proportionate to the growth of the child with no regression at all. Doppler ultrasonography reveals a fast flow, like in an arterio-venous (AV) malformation. Histologically there are AV fistulae (dermal AV microfistulae). These are best treated with surgical excision[15].

Neonatal neoplasms such as fibrosarcoma, and rhabdomyosarcoma are more rare but may appear like congenital haemangiomas. The rate of growth is more rapid and has to be differentiated by biopsy.

The two newly described vascular tumours in this age group, the Kaposiform Haemangio-endothelioma (KHE) and the Tufted Angioma (TA) need to be considered in the differential diagnosis as well. 50% of KHE are present at birth and the others arise during the 1st year of life. It is an aggressive vascular tumour that grows rapidly from a common haemangioma-like lesion to a deep red to violaceous, indurated mass with an expanding rim of ecchymoses around it. It may grow up to over 5cms in diameter. Histological features are similar to that of Kaposi's sarcoma but the magnetic resonance imaging gives a distinctive picture. Mortality rate is as high as 30% to 40% from the Kassabach Merritt Phenomenon (KMP). Uncomplicated lesions show spontaneous regression over 5 to 6 years. KMP never occur in a true infantile haemangioma. The TA may be present at birth or appear during the 1st year as a deep red telangiectatic plaque with ill-defined margins mainly on upper back, shoulders and neck. There is tenderness and hyperhidrosis and shows a growth proportionate to that of the child. The period of growth varies from 6 months to 10 years. The "canon ball" appearance of the dermal capillary loops is a characteristic histological feature.

"Alarm bells"

Haemangiomas at certain anatomical sites merit prompt action after early and careful assessment.

a) Lumbo-sacral haemangiomas have been reported to be associated with spinal dysraphism and a constellation of congenital abnormalities[16]. The haemangioma may involve various portions of genitalia, buttocks, lumbo-sacral area and thighs. They are generally more flat and telangiectatic to begin with (Figure 2) and may later evolve into a classic superficial haemangioma. The ones that span the midline and remain flat have been known to be complicated with tethered cords and intraspinal lipomas[17]. Other complications reported in association with such haemangiomas include imperforate anus with fistulae, renal abnormalities, bony abnormalities of sacrum, abnormal genitalia and lipomeningomyelocoele. Deviation of the supra gluteal cleft (Figure 2) is a particularly concerning clinical sign.

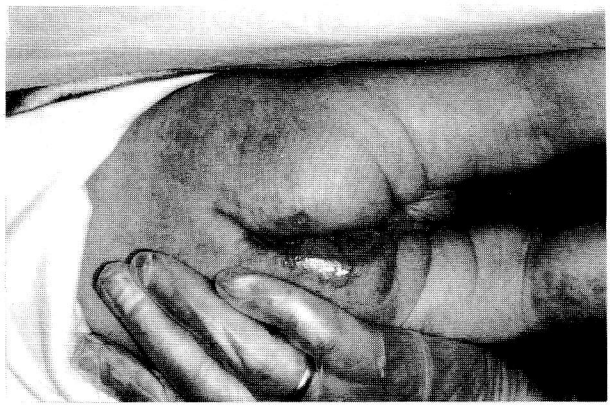

Figure 2. *Lumbo-sacral haemangioma with deviation of the supra-gluteal cleft.*

b) Haemangiomas on the upper eyelid can obstruct visual axis leading to deprivation amblyopia and failure to develop binocular vision[18]. Stimulus deprivation amblyopia is one of the leading causes of preventable blindness. An obstruction lasting 1 to 2 weeks is considered to be enough to result in permanent damage to the visual system. Pressure on the eye from a haemangioma on the eyelid or supra-orbital area may lead to refractive errors of astigmatism and myopia. Strabismus is another associated complication. Prompt consultation with an eye-surgeon is mandatory to prevent these complications.

c) Haemangiomas in the "beard" area of the face (pre-auricular, chin, anterior neck, and lower lip) are known to be associated with upper respiratory tract and sub-glottic involvement[19] which can be life-threatening. It develops insidiously between 6 and 12 weeks with a progressively worsening inspiratory and/or expiratory stridor which becomes particularly evident during crying and feeding. There is often hoarseness, cough and cyanosis and the majority of the children require tracheotomy.

d) The term PHACES has been coined as an acronym for association of large cervico-facial haemangiomas, particularly the segmental type, with a number of congenital abnormalities[20]. They are a) Posterior fossa malformations, b) Haemangioma, c) Arterial abnormalities, d) Coarctation of aorta, e) Eye abnormalities, and f) Sternal nonunion and Supra-umbilical raphe. The cardinal feature is the plaque like and segmental haemangioma involving one or more facial dermatomes commonly occurring in a female infant. Rarely intracranial haemangiomas are known to occur on the same side. Over 50% of those affected with PHACES syndrome show structural brain malformations, the commonest being the Dandy-Walker type with hypoplastic or absent cerebellar vermis and a markedly dilated 4th ventricle. Cervico-cranial arterial anomalies have been reported in over one third of these infants. They include persistent embryonic intra- and extracranial arteries, absence of ipsilateral carotid/vertebral vessels, and coarctation of the right sided aortic arch. Hemiparesis and/or seizures have been described resulting from cerebral infarction[21]. The commonest cardiac defect described is coarctation of the aorta followed by tricuspid and aortic atresia, patent ductus arteriosus, and ventricular septal defects. About 25% of these infants show abnormal eye changes which include increased retinal vascularity, microphthalmia, optic nerve hypoplasia, exophthalmos, choroidal haemangiomas, strabismus, congenital cataracts and glaucoma. These infants need thorough investigation and management under the combined care of paediatric, neurological, ophthalmological, and dermatological expertise.

e) Multiple haemangiomas have been reported to occur in as many as 25% of patients with infantile haemangioma[22]. Often the multiple haemangiomas are limited to the skin only and then it is termed Benign Neonatal Haemangiomatosis (BNH). Rarely the haemangiomas may involve at least 3 separate organ systems when it is called Disseminated Neonatal Haemangiomatosis (DNH). Haemangiomas in BNH show rapid involution within the first two years of life. In contrast, the infants with DNH have a high morbidity and mortality rates usually from high output cardiac failure, visceral haemorrhages and seizures. Liver is the commonest organ to be involved followed by lung, brain and intestines. Infants with multiple cutaneous haemangiomas should alert the clincian to the possibility of visceral involvement and be carefully monitored and investigated with the help of radiology, cardiology, neurology, and paediatric colleagues. Abdominal ultrasonography, computed tomographic imaging, and magnetic resonance imaging are useful and essential screening procedures.

Diagnosis

The history and clinical features alone are often adequate to make a correct clinical diagnosis of a haemangioma. The most important distinction is to decide whether it is a vascular malformation or a haemangioma. This distinction is necessary for proper counselling and from the point of view of therapy. The three important questions to ask is 1) was the lesion present at birth, 2) has it grown, and 3) has it shrunk? The ambiguous and atypical lesions warrant observation of changes over 2-4 weeks and/or radiological investigations to confirm the diagnosis. The slightest suspicion of malignancy calls for biopsy and histological evaluation. Magnetic resonance imaging (MRI) is the single most valuable investigation for atypical or deep lesions. The typical MRI appearance of a common haemangioma show a fast flow lesion with flow voids and tissue preponderance and help to differentiate the atypical haemangioma from vascular malformations, dermoid cysts, meningocoeles, and other benign and malignant infantile tumours. In addition, MRI provides the vital information about the exact localisation, extent and involvement, and with midline lesions the presence of spinal or cranial dysraphism.

Treatment

The majority of infantile haemangiomas remain uncomplicated with a predictable course and prognosis. All that is required to manage such lesions is "active non-intervention". Adequate parental counselling, with understanding and patience on the part of the physician, is of paramount importance when the parents are faced with a rapidly enlarging, tumorous, vascular lesion in a new born infant often causing a degree of disfigurement. The fact that parents are remorseful, anxious, fearful and experience shame and guilt should never be underestimated[22]. Regular reviews should be arranged at frequent intervals with proper photo-documentation at each visit which helps to appreciate the course of the haemangioma both by the clinician and the parents. Haemangiomas at special sites like the eyelids, periorbital, beard region of the face, large facial lesions, lumbo-sacral, and multiple haemangiomas call for co-ordinated consultation and management amongst the appropriate specialities from the initial visit.

The commonest complication and the cause for intervention of an infantile haemangioma is ulceration. The single most common site for ulceration is the perineum. The rapid proliferation leading to over-

stretching of the overlying epidermis and outstripping its own blood supply together with maceration and friction are all contributory factors that lead to ulceration (Figure 3). Though ulceration occurs usually during the proliferative phase of the haemangioma, a few have been reported to occur after the rapid proliferative phase. Ulceration is always painful and often leads to some degree of bleeding. Local wound care with wet saline compresses, Vaseline impregnated gauze, occlusive hydrocolloid dressings, mupirocin ointment, metronidazole gel are all helpful in this situation. Metronidazole gel is particularly helpful in the perineum to prevent and treat superinfection of an ulcerated haemangioma with bowel flora.

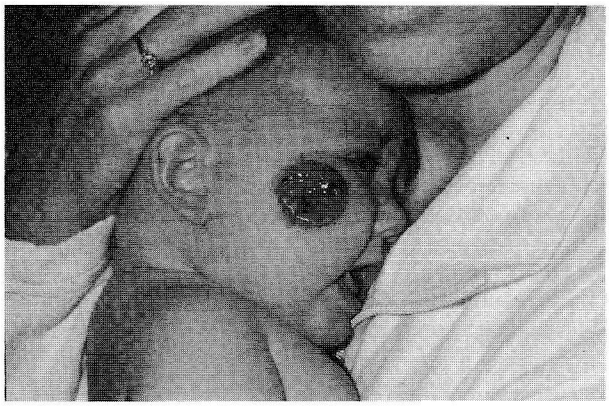

Figure 3. *Ulcerated compound facial haemangioma*

Bleeding is rarely profuse but gives rise to a great degree of anxiety and concern to the parents and the family physician. Application of hand pressure and/or a cold pack easily arrests the bleeding in the vast majority of cases. Rarely there may be a profuse bleed when the treatment of choice is pulsed dye laser therapy.

Adequate pain control is vital since the pain associated with an ulcerated haemangioma is severe. The affected infant will suffer from sleep disturbances, irritability and go off feeds as well.

Infantile haemangiomas that interfere with normal vital functions, threaten permanent disfigurement, and rare life threatening situations have to be treated with systemic therapy in conjunction with the equally important modalities of therapy already outlined. Systemic corticosteroids and interferon alpha 2-a and 2-b have been used successfully to arrest proliferation, induce involution and prevent permanent undesirable sequelae[23]. The desired result is due to their antiangiogenic effect on the vascular endothelium. A comprehensive evidence based study carried out recently has revalidated the use of these agents for treating infantile haemangiomas[24].

Oral prednisolone in a dose of 2-3 mg/kg per day is effective in shrinking and/or stabilising most proliferating haemangiomas. This dosage has to be maintained until cessation of growth or shrinkage is accomplished. Only then the dose is tapered gradually depending on the indication, age of the patient, toxicity, etc. Short course and rapid tapering is known to give rise to rebound growth. The average period of treatment required with the starting dose is around 6-8 weeks. A single morning dose is preferred to avoid alteration in hypothalamic-pituitary-adrenal functions, which could otherwise be seen within a few days with twice a day dosage regime[25]. Corticosteroids are of use only during the proliferative phase and not during the involuting phase. Appropriate dose of a histamine H2 receptor antagonist is used concurrently to prevent steroid associated gastritis. If no response is observed within one week of starting therapy, prednisolone should be discontinued. Intralesional steroids have been used to treat small and well defined haemangiomas[26]. Three to 6 injections of triamcinolone at a concentration of 5-10mg/ml with a total maximum of 3 mg/kg per procedure is administered intralesionally every 6-8 weeks. Skin atrophy after resolution has been recorded with this procedure. Peri-ocular haemangiomas treated with intralesional steroids have been complicated with serious adverse effects such as eye lid necrosis, central retinal artery occlusion, and adrenal suppression.

Interferon, unlike corticosteroids, affects not only the endothelial cell migration and proliferation but also inhibits effects of BFGF and VEGF. Its use is therefore not limited to the proliferative phase only. The rate of regression seen with interferon is slower and has more serious potential side effects. Febrile reactions, transient neutropaenia, anaemia, elevation in liver enzymes are common undesired effects. Irreversible spastic diplegia has been reported with interferon therapy for haemangioma. In view of these side effects interferon is best used only in life or sight threatening complications of haemangiomas. The recommended dose is 3×10^6 units/m^2 body surface area given as a daily subcutaneous injection. This dose regimen is continued as long as there is a response, and until the indication for its use no longer exists.

Laser therapy with the pulsed dye laser (PDL) has come to be the treatment of choice of vascular lesions of the skin and is used successfully in treating ulcerating and bleeding infantile haemangiomas[27]. Excellent results with rapid relief of pain, rapid arrest of bleeding and re-epithelialisation has been achieved

even 2 weeks after one treatment. The response is better with thinner lesions and with the superficial component than deeper component. The side effects of PDL treatment is minimal and include immediate, but transient, post-treatment purpura, and minimal blistering. A number of studies are in progress presently to evaluate the efficacy of PDL treatment of haemangiomas during the pre-proliferative and early proliferative phases.

Surgery is confined to haemangiomas that threaten vital functions and/or cause significant disfigurement not responding to systemic therapy. Thermoscalpels, by heating the cutting edge of the scalpel blade with electrical energy, are also used with the added advantage of better haemostasis. The surgical scar may sometimes be worse than the results of spontaneous resolution of an uncomplicated haemangioma.

Active non-intervention, which by no means is a form of benign neglect, with frequent follow up to evaluate progress seen with help of photo-documentation, to discuss prognosis and to give emotional support to the parents at each visit remains the mainstay of management of an infantile haemangioma. All other therapeutic options must be considered on an individual basis after a thorough consideration of the risk benefit ratios of each treatment modality. Managing haemangiomas at special anatomical sites call for a good understanding and co-operation between the different specialities involved, to avoid a lifetime of disfiguring, lasting, and sometimes crippling sequelae.

References

1. Mulliken JB, Glowacki J. Haemangiomas and vascular malformations in infants and children: A classification based on endothelial characteristics. *Plast Reconstr Surg* 1982; **69**: 412.
2. Haemangiomas and vascular malformations of the head and neck. Ed. Waner M, Suen JY, 1999. Wiley-Liss
3. Enjorlas O, Mulliken JB. Vascular tumors and vascular malformations (new issues). *Adv Dermatol* 1997; **13**: 375-422.
4. Holmdhal K. Cutaneous vascular lesions in premature and mature infants. *Acta Paediatr.* 1995; **44**: 370-379.
5. Blei F, Walter J, Orlow S, et al. Familial segregation of haemangiomas and vascular malformations in an autosomal dominant trait. *Arch Dermatol* 1998; **134**: 718-722.
6. Cheung DSM, Warman ML, Mulliken JB. Haemangiomas in twins. *Ann Plast Surg* 1997; **38**: 269-274.
7. Burton BK, Schultz CJ, Angle B, Burd L. An increased incidence of haemangiomas in infants following chorionic villus sampling. *Prenat.Diag.* 1995; **15**: 209-214.
8. Beilenberg DR, Bucana CD, Sanchez R, Mulliken JB, et al. Progressive growth of infantile cutaneous haemangioma is directly correlated with hyperplasia and angiogenesis of adjacent epidermis and inversely correlated with the expression of the endogenous angiogenesis inhibitor, IFN-beta. *Int J Oncol.* 199; **14**: 401- 408.
9. Razon MJ, Kraling BM, Mulliken JB, Bischoff J. Increased apoptosis coincides with onset of involution of infantile haemangioma. *Microcirculation* 1998; **5**: 189-195.
10. Takahash K, Mulliken JB, Kozakewich HPW. Cellular markers that distinguish the phases of haemangioma during infancy and childhood. *J Clinical Invest* 1994; **93**: 2357-2364.
11. North PE, Waner M, Mizeraeki A, et al. A unique microvascular phenotype shared by juvenile haemangiomas and placenta. *Arch Dermatol* 2001; **137**: 559-570.
12. Brea AF, Siegfried E, Nahass G, et al. Infantile haemangiomas. Speculation on placental trophoblastic origin. *Arch Dermatol* 2001; **137**: 573-577.
13. North PE, Waner M, James CA, et al. Congenital Non-progressive Hemangioma: A distinct clinicopathologic entity unlike infantile haemangioma. *Arch Dermatol* 2001; **137**: 1607-620.
14. Enjorlas O, Mulliken JB, Boon LM, et al. Non-involuting congenital haemangioma: A rare cutaneous vascular anomaly. *Plast. Reconstr Surg* 2001; **107**: 1647-1654.
15. Goldberg NS, Herbert AA, Esterly NB. Sacral haemangiomas and multiple congenital anomalies. *Arch Dermatol* 1986; **122**: 684-687.
16. Albright AL, Gertner JC, Weiner GS. Lumbar cutaneous haemangiomas as indicators of tethered spinal cords. *Paediatrics* 1989; **83**: 977-80.
17. Deans R, Harris G, Kivlin J. Surgical dissection of capillary haemangiomas. *Arch Ophthalmol* 1992; **110**: 1743-1747.
18. Orlow S J, Isakoff MS, Blei F. Increased risk of symptomatic haemangiomas of the airway in association with cutaneous haemangiomas in a "beard" distribution. *J Paediatr* 1997; **131**: 643-646.
19. Frieden IJ, rease V, Cohen D. PHACE syndrome: the association of posterior fossa malformations, haemangiomas, arterial anomalies, coarctation of the aorta and cardiac defects, and eye abnormalities. *Arch Dermatol* 1996; **88**: 1257-1267.
20. Burrows PE, Robertson RL, Mulliken JB, et al. Cerebral vasculopathy and neurologic sequelae in infants with haemangiomas: report of 8 patients. *Radiology* 1998; **207**: 601-607.
21. Achaeuer BM, Chang C, Vander VM. Management of haemangiomas of infancy; Review of 245 patients. *Plast Reconstr Surg* 1997; **99**: 1301-1308.

22. Tanner JL, Decher MP, Frieden IJ. Growing up with a facial haemangioma: Parent and child coping and adaptation. *Pediatrics* 1998; **101**: 446-452.

23. Drolet BA, Esterly NB, Frieden IJ. Haemangiomas in children. *N Eng J Med* 1999; **341**: 173-174.

24. Bennett ML, Fleischer AB, Chamlin SL, Frieden IJ. Oral corticosteroid use is effective for cutaneous haemangioms. An evidence-based evaluation. *Arch Dermatol* 2001; **137**: 1208-1213.

25. Harter JG, Reddy WJ, Thorn GW. Studies on an intermittent corticosteroid dosage regimen. *N Eng J Med* 1963; **269**: 591.

26. Mctry DW, Herbert AA. Benign cutaneous vascular tumours of infancy. When to worry, what to do. *Arch Dermatol* 2000; **136**: 905-914.

27. Scheepers JH, Quaba AA. Does the pulsed tunable dye laser have a role in the management of infantile haemangiomas? Observations based on 3 years experience. *Plast Reconstr Surg* 1995; **95**: 305 -312.