Update on the Management of Infantile Haemangiomas

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This article has been selected by the Editorial Board of the Hong Kong Medical Diary for participants in the CME programme of the Medical Council of Hong Kong (MCHK) to complete the following self-assessment questions in order to be awarded one CME credit under the programme upon returning the completed answer sheet to the Federation Secretariat on or before 31 March 2007.

Classification and Clinical Behaviour of Infantile Haemangiomas

Haemangiomas are the most common tumours in the infancy period and affect approximately 10% of infants. However, due to the confusing terminology previously used for various vascular anomalies, inappropriate advice on treatments had often been given to the wrong type of haemangiomas. Mulliken and Glowacki's originally proposed a classification of vascular anomalies that divided them into either haemangiomas or vascular malformations. A revised classification was subsequently suggested by the International Society for the Study of Vascular Anomalies (ISSVA) in 1996 by using the same backbone but subdivided these 2 groups of lesions into more refined categories. Among the vascular tumours, it includes infantile haemangiomas, pyogenic granulomas, tufted angiomas, kaposiform haemangioendotheliomas, and spindle-cell haemangioendotheliomas. For vascular malformations, it is classified based on the type of blood vessels involved. For clinical management purpose, it can further be subdivided into low-flow lesions (including port-wine stains, venous malformations, lymphatic malformations, and some combined lesions) and high-flow lesions (including arteriovenous malformations). In order to have a better correlation between the type of haemangiomas and their outcome, the Haemangiomas and Congenital Vascular Malformations Nijmegen working group developed an additional set of diagnostic guidelines. It is based on six distinguishing historical characteristics including: 1) the presence of the anomaly at birth; 2) proliferative rate; 3) evidence of involution; 4) change in volume; 5) pain; and 6) outflow. It also considers 5 physical examination characteristics including: 1) the possibility of emptying or pushing aside the anomaly; 2) changes in volume during engorgement; 3) murmur/thrill/pulsation; 4) phleboliths; and 5) hyper-or hypotrophy. These characteristics can assist us in determining the nature of the vascular lesions so we can apply appropriate treatment strategy.

Haemangiomas are caused by inappropriate increase in the proliferation of the vascular cells while vascular malformations are due to inborn errors in vascular morphogenesis. They have distinct clinical behaviour and require different therapeutic approaches. Among vascular tumours, the commonest form in childhood is infantile haemangiomas (also known as capillary haemangiomas, strawberry haemangiomas in the past).

Its natural history is well known. It typically emerges after birth and gradually increases in size throughout the subsequent 18 months before starting to regress. The involution process may take several years to complete and often leaves behind a hypopigmented scar. Another problem is that it may induce asymmetry between the involved and normal parts, usually in the form of hypertrophy of the affected region. In the past, active non-intervention remains the mainstay of therapy for most uncomplicated infantile haemangiomas. However, with an improved understanding of the natural course of haemangiomas, more active intervention was adopted in recent years for selected infantile haemangiomas including those found around the “beard areas”, periorbital and facial regions.

Infantile haemangiomas located in the head and neck region with a “beard” distribution (including the preauricular areas, chin, anterior neck, and lower lip) are associated with symptomatic obstructive haemangiomas in the upper airway or subglottic areas and some eventually may require tracheotomy. Around 80% of infantile haemangiomas are found in the head and neck region and 8.5% of head and neck infantile haemangiomas have a beard distribution. Those with multiple haemangiomas (i.e. >3 or 4) around the beard areas are particularly at risk. Associated haemangiomas in the upper airway should be monitored closely.

Periorbital infantile haemangiomas including those involving the eyelids may cause amblyopia secondary to occlusion of the pupil. This may eventually lead to anisometropia or strabismus. Those with a size greater than 1 cm in largest diameter are commonly associated with amblyopia and almost 50% of these patients eventually require intervention. Diffuse haemangiomatosis and haemangiomas in patients with PHACES syndrome (Posterior fossa malformations, Haemangiomas, Arterial anomalies, Cardiac defects and coarctation of the Aorta, Eye abnormalities, and Sternal abnormalities or ventral developmental defects) are also highly associated with visual impairment.

Diffuse haemangiomatosis presenting in neonatal life or early infancy can progress rapidly with a fatal outcome. The affected infants usually have multiple cutaneous haemangiomas as well as deep-seated lesions in different visceral organs such as the liver or sometimes in the central nervous system. Development of hepatomegaly,
high-output cardiac failure, unexplained anaemia or thrombocytopenia in these infants reflects disseminated and aggressive nature of the disease. Early recognition with implementation of effective treatment is essential to improve the chances of survival. Another commonly associated feature of infantile haemangiomas is acquired hypothyroidism. This is secondary to an increase in the type 3 iodothyronine deiodinase secreted by the haemangiomas and is particularly common among infantile hepatic haemangiomas.

Pyogenic granuloma is also known as lobular capillary hemangioma. It is a benign acquired vascular tumour of the skin and mucous membrane and is characterised by an erythematous, dome-shaped papule that bleeds easily. It can be found in the nostrils, oral cavity and the umbilical stump. Majority of the pyogenic granulomas run an uncomplicated course and can be easily treated with localised treatment such as excision or electric cautery. Most will not recur and have good cosmetic results. Other forms of infantile vascular tumours include tufted angiomas and kaposiform haemangioendotheliomas. These vascular tumours are associated with low grade disseminated intravascular coagulopathy clinically manifested as thrombocytopenia with low fibrinogen level (Kasabach-Merritt phenomenon). These proliferative vascular tumours are usually associated with hypertrophy of the affected parts of the body or limb. They are now considered as a different disease entity as compared to infantile haemangiomas and have a distinct pattern in their pathogenesis, histology, natural history and response to treatment. They typically respond poorly to systemic corticosteroids and interferon.

Also found in the infancy period is Sturge-Weber syndrome. It is a neurocutaneous syndrome with facial port wine stain (mostly unilateral but can be bilateral). Port wine stain is a form of vascular malformations rather than haemangiomas but patients may also have leptomeningeal angiomatosis and congenital glaucoma. The leptomeningeal angiomatosis is associated with epilepsy in 75-90% of the cases and 60% of them are unfortunately refractory to anticonvulsant treatment. In selected cases, lobectomy with complete excision of the angioma or even hemispherectomy may have to be considered.

**Treatment Options of Infantile Haemangiomas**

Uncomplicated infantile haemangiomas can be observed for spontaneous involution, especially for those which are small and proliferating slowly in the trunk. However, for those life- or function-threatening, or with the potential of being associated with structural anomalies should be treated as soon as possible.

Corticosteroids can be applied topically, intralesionally or systemically. Topical corticosteroid is effective only for small and superficial lesions. Oral corticosteroid in the form of prednisolone 2 to 3 mg/kg/day remains the commonest form of treatment for infantile haemangiomas. The dose of corticosteroid can be titrated downward clinically according to the response and patients may require a prolonged maintenance phase with a personalised lower dosage over a total duration of 12 to 18 months. We usually attempt to taper the corticosteroids to alternate day low dose and keep it till 12-month of age. Due to the low potency of this approach and high incidence of corticosteroid induced side effects such as stunning growth and obesity in young children, some centres advocated pulse methylprednisolone intravenously 2 mg/kg twice daily for 2 days as an alternative. It has to be followed by a maintenance phase of lower dose oral steroid treatment (2 mg/kg/day) of oral prednisolone. Gradual tapering is recommed. Intralesional corticosteroid injection or laser treatment may be the treatment of choice. A variety of different lasers and light sources have been used in the treatment of vascular lesions based on the principle of selective photothermolysis. There are vascular lesions that can easily be treated but some are difficult, the main considerations are the extent and size, anatomical site involved, and the depth of the lesions (i.e. superficial versus subcutaneous). Voluminous haemangiomas (thickness of over 10 mm) can be treated with intralesional therapy using the potassium, titanyl, phosphate (KTP) laser, and superficial haemangiomas can be treated with a pulsed dye laser. Fibrosis associated with intralesional therapy can be decreased by injecting small amounts of dilute steroid solution during treatment of the deep haemangiomas. Ulcerated haemangiomas or post-involution sequelae like telangiectasia can also be treated with specific laser. However, the mainstay of therapy for ulcerated haemangiomas remains to be good local wound care, analgesics and treatment of secondary infection.

Interferon alpha (IFN-α) or other agents such as vincristine, thalidomide are therapeutic options for complicated haemangiomas which do not respond to corticosteroids. INF-α is a cytokine with anti-viral, anti-tumour, and anti-angiogenic properties. IFN-α inhibits the secretion of angiogenic factors such as basic fibroblast growth factor and is an effective treatment modality for high-risk haemangiomas in children, especially those with steroid-resistance. The most commonly used dosage is 3x10⁶ units/m² IFN-α2b subcutaneously daily for a period of 3 months. According to the response, IFN-α can be tapered to every alternate day or less frequent administration subsequently. However, the most serious complication of this form of treatment is early neurological toxicity in the form of seizure and spastic diplegia, especially among infants.

New drugs such as topical 5% imiquimod cream 3 to 5 times weekly may be helpful in controlling superficial
infantile haemangiomas but has minimal effect on either mixed or deep subcutaneous infantile haemangiomas. Imiquimod induces production of interferon, tumour necrosis factor-α, and antiangiogenesis factors and when applied topically, there is no systemic adverse reaction noted and local irritation with or without crusting are the most common adverse effects. 2

Patients presenting with Kasabach-Merritt phenomenon have a high morbidity and mortality rate. The majority of them do not respond to corticosteroids and interferon and recently, the use of low dose vincristine (0.5mg/m²) intravenously at weekly interval was shown to be an effective and safe modality. Increase in platelet count and fibrinogen level can usually be achieved within a few weeks. Most patients also showed significant decrease in the size of the vascular lesions but this occurred at a later stage as compared to the recovery of the platelet count and fibrinogen level. The average duration of treatment was around 20 to 30 weeks. Complications included constipation; jaw, bone and abdominal pain; loss of deep tendon reflexes or even foot drop. Regular monitoring of the emergence of peripheral neuropathy by nerve conduction study is mandatory. Most of the neuropathies are transient in character and will resolve spontaneously upon stopping of the vincristine. Another potential risk of this form of treatment is the skin burn induced by extravasations of the vincristine. Therefore this form of treatment should be given in specialty centres and sometimes the use of central venous catheter is recommended due to the difficult venous access. We had treated 3 patients with Kasabach-Merritt phenomenon who were refractory to corticosteroids and interferon treatment and 2/3 patients responded with no significant complications. The only one who failed to respond had kaposiform lymphoendothelioma by biopsy. Whether the difference in histology may account for the suboptimal response remains to be proven. 15

Conclusion

Vascular tumours are commonly found in infants and young children and they have marked heterogeneity in terms of their clinical behaviour and response to treatment. If not managed optimally and early, disfiguring or dysfunctioning long term complications may occur in some patients. In severe cases such as haemangiomas of the upper airway or disseminated haemangiomatosis, it may even lead to fatal outcome. When we encounter an infant with haemangiomas, active non-intervention should be applied with caution and corticosteroids may not be the best initial option always. For complicated cases, early referral to specialty units can help to minimise unnecessary delay or treatment complications.

References

MCHK CME Programme Self-assessment Questions

Please read the article entitled "Update on the Management of Infantile Haemangiomas" by Dr. Godfrey CF Chan, and complete the following self-assessment questions. Participants in the MCHK CME Programme will be awarded 1 CME credit under the Programme for returning completed answer sheets via fax (2865 0345) or by mail to the Federation Secretariat on or before 31 March 2007. Answers to questions will be provided in the next issue of The Hong Kong Medical Diary.

Questions 1-10: Please choose the best answer.

1. The revised classification by the International Society for the Study of Vascular Anomalies (ISSVA) includes the following as vascular tumours, except:
   a. pyogenic granulomas
   b. tufted angiomas
   c. angiofibroma
   d. infantile haemangiomas
   e. kaposiform haemangioendotheliomas

2. The revised classification by the International Society for the Study of Vascular Anomalies (ISSVA) includes the following as vascular malformations, except:
   a. aortic aneurysm
   b. port-wine stains
   c. venous malformations
   d. lymphatic malformations
   e. arteriovenous malformations

3. The additional set of diagnostic guidelines by the Haemangiomas and Congenital Vascular Malformations Nijmegen working group includes the followings, except:
   a. the presence of the anomaly at birth
   b. proliferative rate
   c. evidence of inflammation
   d. change in volume
   e. pain

4. Infantile haemangiomas (capillary haemangiomas) can undergo involution spontaneously but in which of the following location, early treatment or intervention is currently recommended:
   a. haemangioma around the periorbital area
   b. haemangioma around the periumbilical area
   c. haemangioma around the perineal area
   d. haemangioma around the waist area
   e. haemangioma around the neck area

5. Since infantile haemangiomas (capillary haemangiomas) may have the following potential adverse outcome(s), intervention is advisable if it is located in the facial region: (choose the best answer)
   a. may take a long time to involute
   b. often leaves behind a hypopigmented scar
   c. may induce asymmetry
   d. untoward psychological effect on the child
   e. all of the above

6. Infantile haemangiomas located in the "beard" areas are associated with symptomatic obstructive haemangiomas in the upper airway and some eventually may require tracheotomy. The "beard" areas include the followings, except:
   a. preauricular areas
   b. chin
   c. anterior neck
   d. upper lip
   e. lower lip

7. Which of the following statements about infantile haemangiomas is correct:
   a. 50% of infantile haemangiomas are found in the head and neck region
   b. 85% of head and neck infantile haemangiomas have a beard distribution
   c. haemangiomas affect approximately 20% of infants
   d. periorbital haemangiomas >1 cm diameter are commonly associated with amblyopia
   e. multiple haemangiomas (i.e. >3 or 4) around the periorbital areas are at risk of having concomitant haemangiomas in the upper airway.
8. Corticosteroids remain to be the commonest form of treatment for infantile haemangiomas. Which of the following statements about steroid treatment is correct:
a. standard dose of oral corticosteroid (2mg/Kg/day) should be applied for at least 6 to 12 months
b. the maximum duration of oral steroid therapy is 12 months
c. pulse methylprednisolone regimen can replace the maintenance oral steroid
d. topical corticosteroid is as effective as oral steroid
e. haemangiomas with a deep or subcutaneous component often do not respond to oral steroid

9. The most threatening complication of interferon alpha (IFN-α) treatment in infancy period is:
a. neurological toxicity
b. hypothyroidism
c. neutropenia
d. anaphylaxis
e. none of the above

10. The current recommended treatment for Kasabach-Merritt phenomenon is:
a. low dose vincristine
b. pulse methylprednisolone
c. interferon alpha
d. thalidomide
e. no effective treatment

Please return the completed answer sheet to the Federation Secretariat on or before 31 March 2007 for documentation. 1 CME point will be awarded for answering the MCHK CME programme (for non-specialists) self-assessment questions.

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