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Reported by HL Lo 盧曉麗, CTY Ng 吳子霙, CK Yeung 楊志強

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Beta-blockers for infantile haemangiomas: Successes and failures

Speaker: C Léauté-Labrèze
Pellegrin Children's Hospital, Bordeaux, France

Since the first case report of efficacy of oral propranolol for severe infantile haemangiomas (IH) in 2008, a lot of research work and clinical studies have been published to confirm its efficacy & safety in infants leading to the approved use of oral propranolol solution for this condition in 2014. Meta-analysis of over 1000 publications indicated use of propranolol leads to meaningful improvement of IH in more than 80% of the cases.

A phase II/III randomised double-blind international study for IH at age of treatment initiation at 1 to 5 months during proliferative phase of IH was published in 2015. The study outcome was complete or nearly complete resolution of IH at week 24 (6 months of treatment at 3 mg/kg per day) with minimal residual telangiectasia, erythema, skin thickening, soft tissue swelling or distortion of anatomical landmarks. 456 infants participated the study with 60% achieved the primary outcome compared with 4% in placebo group ($P>0.001$).

Further study on the efficacy of Propranolol was carried out in infants with high-risk IH between 6 and 12 months of age, with extension of propranolol treatment beyond 6 months up to a maximum of 12 months of age. The study reported a meaningful increase in the success rate with satisfactory safety profile. The success rate after 6 months of treatment was 47%, increasing to 76% at the end of treatment period. Success was maintained in most patients (68%) up to 3 months after stopping treatment.

A systematic review of the safety of oral propranolol for the treatment of IH revealed the largest amount of safety data among all the medications for IH treatment. Oral propranolol was well tolerated if appropriate pretreatment assessments and monitoring were performed to exclude patients with contraindications and to minimise serious side effects during treatment. No unexpected side effect was noted and acrocyanosis and sleep disorders, though not uncommon were mostly benign. There was no significant effect on blood pressure and bradycardia was rare and mainly seen in infants with prematurity or low birth weight. Hypoglycaemia was a rare but severe adverse effect and parental education to ensure infant feeding was crucial to minimise this side effect. Long term safety is observed in preclinical toxicology study and clinical studies, in which infants with IH who were treated with propranolol were followed up till 6-7 years of age.

Studies on other beta-blockers, including acebutolol, atenolol and nadolol, indicated no superiority in terms of efficacy compared with propranolol in IH. Hypoglycaemia is more

frequent with nadolol because of its long half-life. Sleep disorders are more frequent with nadalol than propranolol. Hence, propranolol is the only US FDA approved agent for management of problematic IH and should be considered the first line therapy for those who require systemic therapy. Oral propranolol may be considered before imaging results are obtained in patients with life-threatening or function-threatening IH such as obstruction of the visual axis or airway involvement in PHACE.

The optimal duration of beta-blocker treatment remains to be determined as relapses with rebound growth are observed after 6 months of treatment in 10-25%. One half of the rebound cases need a second course of propranolol, especially those with segmental IH and/or with deep component. If incomplete regression of IH is observed at the end of 6 months of propranolol treatment at 3 mg/kg/day, therapy should be maintained. Segmental IH often needs longer treatment until one year of age, even up to 2 years in case of lower face (beard area) involvement. After 6 months of treatment, if no further improvement is observed during follow-up, treatment can be stopped, while therapy can be maintained if ongoing improvement is observed.

The exact mechanism of action of beta-blockers remains to be elucidated as pathophysiology of IH is not fully known, in relation to theory of hypoxia, role of VEGF, bFGF, beta-receptors and RAS/Catecholamine systems. Recently, a type of dendritic cells named telocytes, located at peripheral stromal layer was found to be communicating with vascular cells in IH. Telocytes respond to propranolol via aquaporin-1 receptor.

Topical timolol has been shown to be of limited efficacy in the resolution of IH, although it is well tolerated. A randomised placebo-controlled trial indicated topical timolol failed to prevent further growth of IH when used in the first 2 months of age during the proliferative phase of IH. The limited benefits are mainly observed in small thin, superficial haemangiomas related to the improvement of colour but not the size of lesions. There might be a risk of systemic side effects with the use of topical beta-blocker treatment for small superficial haemangioma. Moreover, the use of topical may lead to a delay in the implementation of oral treatment in early stage as some small IH can grow rapidly within 2-3 weeks. Thus oral treatment should be considered timely in high-risk IH even in cases of small localised IH in at-risk location such as periorbital area.

Learning points:

Propranolol has revolutionised the management of complicated IH and it is now an approved treatment for severe IH. Indications and monitoring during treatment are well defined. The optimal duration of treatment and management of rebounds remain to be determined. Topical beta blockers are of limited benefits with less predictable response and yet it is well tolerated.

Update of neonatal skin: Pustular disorders in neonates

Speaker: P Hoger
Catholic Children's Hospital Wilhelmstift, Hamburg, Germany

Pustules can be found in 26.8% of all neonates. Common conditions include erythema toxicum, neonatal cephalic pustulosis, transient neonatal pustular melanosis and miliaria rubra. Other less common pustular conditions such as staphylococcal disease, candidiasis, scabies and neonatal herpes simplex infection can be potentially dangerous, requiring early recognition and treatment. Types of pustules in neonates can be generally divided into generalised versus localised and infectious versus non-infectious causes. Hence uncommon but important or serious causes of pustules in neonatal period should be recognised.

Primary cutaneous aspergillosis

About 130 cases have been reported in the literature, 12% of cases were diagnosed in neonates, especially in preterm infants. Potential sources of Aspergillus are from occlusive dressing, bandages, tape at catheter sites and gloves contaminated by the fungus. Mortality is high in the range of 10-20%. Treatment includes intravenous liposomal amphotericin B, voriconazole or posaconazole.

Tinea

Dermatophytosis often presents with centrifugal annular plaque with confluent pustules on face, body and limbs. The differential diagnoses are annular erythema of infancy and neonatal lupus erythematosus. Less than 20 cases of neonatal tinea (faciei) have been reported ranging at day 2 to 30 of age. The potential source is inconspicuous maternal skin infections. The prognosis is good. Limited disease shows good response to topical clotrimazole while widespread lesions or tinea capitis requires use of oral or intravenous fluconazole or itraconazole.

Congenital self-limiting Langerhans cell histiocytosis

This benign form of cutaneous histiocytosis can present with congenital varicelliform rash with good general condition. The cutaneous presentation is variable ranging from papules, pustules, crusted and ulcerative lesions in solitary or disseminated forms. Screening of internal organ involvement is essential. Skin Biopsy revealed Langerhans cell positive for S100. The prevalence is 4-8 per million with spontaneous resolution in 80-90% of the cases but there is a possible association of late-onset diabetes insipidus.

Congenital erosive and vesicular dermatosis

The condition presents with varicelliform eruption with vesicles, erosions and pustules at birth covering over 70% of the body surface area in otherwise stable infants. It spontaneously clears in weeks with post-inflammatory hyperpigmentation and supple reticulated scars. 36 cases have been reported so far and 80% were preterm infants and the condition may recur within the first few months of life. Aetiology is unknown and differential diagnoses are congenital herpes simplex, varicella-zoster infection, transient bullous dermolysis and Langerhans cell histiocytosis.

Eosinophilic pustular folliculitis of infancy

This condition can present in neonatal period with recurrent itchy eruptions of follicular papules and pustules initially on scalp. It has truncal involvement in 20%. It can last for weeks to months with intense pruritus and remits by age of 3 years. The differential diagnosis is scabies. The folliculitis responds well to topical corticosteroid but oral dapsone may be used in severe cases. Neonatal onset is noted in 20% of infantile eosinophilic pustular folliculitis (EPF) with male predilection (M:F 4:1). Less than 100 cases have been described. The aetiology is unknown but it might be related to upregulation of IL-36 cytokines in follicles.

Hyper IgE syndrome

Hyper IgE syndrome is a primary immunodeficiency disease with a wide array of clinical features caused by dominant negative mutations in STAT3. The syndrome can present in infancy with localised or confluent pustules and febrile infective episodes. It often presents with eczema and recurrent skin abscess. Differential diagnosis in the setting of neonatal pustular lesions and immunodeficiency include chronic granulomatous disease (CGD), deficiency of IL-1 receptor antagonist (DIRA) and deficiency of IL-36 receptor antagonist (DITRA). Skin biopsy reveals eosinophilic folliculitis.

Learning points:

Although there are many causes of pustular lesions in neonates and most are benign conditions, its clinical importance should not be underestimated and self-limiting benign disease should not be assumed and alternative diagnosis should be considered. Multidisciplinary approach from both dermatological and pediatric assessment are often required if alerting features are present, such as failure to thrive, hepatosplenomegaly, lymphadenopathy and history of uncommon infections.

Reactive infectious mucocutaneous eruptions

Speaker: A Yan
Children's Hospital of Philadelphia, Pennsylvania, USA

Apart from toxic epidermal necrolysis, Stevens-Johnson syndrome and erythema multiforme (EM) being regarded as severe mucocutaneous reactions in children related to infections and drug hypersensitivity, **r**eactive **i**nfectious **m**ucocutnaneous **e**ruptions (RIME) has been increasingly reported. The key clinical features often include significant mucositis involving conjunctiva, oral cavity or genital mucosa, and relatively mild rashes ranging from atypical target lesions to vesicobullous eruptions. Intense mucous membrane involvement of at least two mucosal areas are common (94%). In contrast, it is uncommon to have extensive rashes (19%). Skin lesions are often sparse (43%) or sequalae. Vesicobullous and targetoid lesions are common cutaneous features.

RIME was mainly reported to be triggered by *Mycoplasma pneumoniae* infection. It is likely related to abnormal host response. PCR is the method of choice to detect mycoplasma infection because of its high sensitivity combined with IgM in children. RIME has also been described in chest infection with fever and respiratory symptoms due to *Chlamydia pneumoniae*, which is more common in males with morbilliform rash and mild mucositis. Supportive management is often adopted beside individual reports of efficacy using systemic corticosteroid and intravenous immunoglobulin (IVIg). RIME can be triggered by influenza B virus with widespread truncal atypical target lesions and the treatment includes IVIg and oseltamivir. RIME can be associated with clinically mild COVID-19 with mucositis of multiple mucosal areas and sparse atypical target lesions on the trunk. RIME is temporally closer to the active infection than recurrent EM after herpes simplex infection.

Diagnostic workup for RIME includes screening of culprit infections, such as PCR and serology of mycoplasma, chlamydia, SARS-CoV-2 and influenza B in the respiratory viral panel. Therapeutic approaches to RIME comprise active nonintervention, antibiotics for mycoplasma/chlamydia, systemic corticosteroid, IVIg and cyclosporine. There is evidence of efficacy of systemic corticosteroid, resulting in shorter hospital stay than combining with IVIg or IVIg alone. Cyclosporine 3-5 mg/kg/day for 7 to 10 days has been reported to induce rapid significant improvement in RIME associated with mycoplasma.

Learning points:

RIME is an umbrella term denoting a mucocutaneous syndrome associated with infectious triggers with limited skin involvement mostly in the form of blisters or atypical target lesions. Infectious triggers identified so far include mycoplasma, chlamydia, influenza B, SARS-CoV-2. Specific host response may predispose patients to more severe reactions and recurrences. Treatment of RIME with oral steroids and cyclosporine may reduce hospital length of stay.

Adverse drug reaction in paediatric dermatology

Speaker: MJA Koh
Dermatology Service, KK Women's and Children's Hospital, Singapore

Paediatric patients should not be regarded as a miniature form of adults. Disease cause, clinical presentation, treatment and prognosis could be quite different from adult patients. Our speaker had a comprehensive review on causes, presentation, prognosis and treatment of Stevens-Johnson syndrome- toxic epidermal necrolysis (SJS-TEN) and Drug reaction with eosinophilia and systemic symptoms (DRESS) in paediatric patients.

SJS-TEN is well known to be the most severe form of drug allergy. The spectrum ranges from <10% epidermal detachment in SJS to >30% epidermal detachment in TEN with at least 2 mucosal involvement. The causes are categorised into drugs e.g. antiepileptic, antibiotic, sulphonamide, non-steroid anti-inflammatory drug (NSAID), allopurinol; infections e.g. mycoplasma pneumonia, herpes simplex virus; and vaccinations e.g. MMR, DTaP, varicella, pneumococcal, influenza.

Children usually present with prodromes e.g. fever, malaise, URI symptom for days to one week. The rash is initially erythematous dusky macules or papules which will later become painful, purpuric patches and plaques, targetoid lesions, flaccid blisters with positive Nikolsky's sign.

Reactive infectious mucocutaneous eruption (RIME) is a new terminology which includes all postinfectious mucocutaneous eruptions e.g. Chlamydia pneumonia, adenovirus, SARS-CoV2. The widely reported Mycoplasma pneumoniae-induced rash and mucositis (MIRM) is also included in this category. Cutaneous manifestation varies and can mimic erythema multiforme and SJS-TENS. Mucosal involvement is detected in majority of cases, with oral mucosa being most frequently affected, followed by ocular and urogenital involvement. However, near 50% may not present with cutaneous eruption. Majority of patients recover fully. Reported complications include conjunctival shrinkage, corneal ulceration, synechiae, labial fusion, urethral stricture etc. Recurrence can be up to 20%.

Regarding prognosis assessment, paediatric modified tools were not found to be superior to SCORTEN in predicting the outcomes of paediatric epidermal necrolysis. Multiple new investigations are used in research for early diagnosis of SJS-TEN and can assist in culprit drug determination. Cytokine profiling early diagnosis such as granulysin and granzyme B levels, can aid early diagnosis, while lymphocyte transformation test and T-cell activation assay are gaining recognition in assisting identification of culprit drug.

Regarding the treatment of paediatric SJS-TEN, the most important part is also immediate cessation of culprit medication. Apart from treating associated infection, supportive treatment is still the mainstay. Other options are similar to adult group e.g. systemic corticosteroid, intravenous immunoglobulins (IVIG), ciclosporin, and biologics. Our speaker shared his own experience in using cyclosporine 3-3.5 mg/kg/day BD for 1 week and reduced in next 2 weeks in 4 paediatric patients (3 with RIME, 1 with drug induced SJS) with good result of an average time to cessation of disease progression in 4 days.

In diagnosing DRESS/Drug hypersensitivity Syndrome, RegiSCAR is also used in paediatrics. Common drug culprits are anti-epileptics, antibiotics, allopurinol etc. Viral activation especially HHV-6 was found in up to 60-80% in patient with DRESS in some studies. There is no consensus in the use of antiviral medications but viral reaction might be linked to flares and possibly a marker of severe disease. Hence, some might consider monitoring HHV-6, HHV-7, CMV and EBV viral loads and antibody titers in 1-2 weeks intervals for severe cases.

Most important treatment is again cessation of offending medication and supportive treatment. Systemic corticosteroid with initial dose of 1-3 mg/kg/day with slow tapering for up to 3 months can be considered especially for patients with internal organ involvement. Cases series also suggested use of IVIG with a total dose of 1-2 g/kg in cases resistant to systemic corticosteroid. Other options e.g. ciclopsorin, mycophenolate, rituximab lack evidence in paediatric patients. Prognosis of DRESS is better in children compared to adults. Mortality rates are around 3-5%. However, we still have to be cautious about possible long term sequalae such as liver failure, DM, hypothyroidism.

Learning points:

SJS-TEN and DRESS are rare but important severe cutaneous adverse reactions in paediatric patients. Most important management are the identification and cessation of culprit drug and supportive care. Infection related MIRM/ RIME have better prognosis but it is still essential to monitor closely for long term complications.

The role of the microbiome in atopic dermatitis

Speaker: S Christen-Zach
Lausanne University Hospital, Switzerland

Atopic dermatitis (AD) is a chronic inflammatory skin disease that manifests in childhood, driven by an imbalance of TH2. A westernised lifestyle is thought to be related to the increase in prevalence through a change in the microbiome in the body. Via a new method known as metagenomics, microorganisms and their relative abundance can be analysed in detail.

The skin microbiome is found to be significantly different between normal individuals and patients with atopic dermatitis even during non-flare periods. Patients with atopic dermatitis have a lower skin microbiome diversity and many are colonised with *Staphylococcus Aureus (S. Aureus)*. During flare up of eczema the diversity further decreases with increasing abundance of staphylococcus. Increase in *S. Aureus* species specifically is associated with worse flares and increased SCORAD. Certain strains of *S. Aureus* were found to be associated with more severe disease. Lack of inhibitory flora, namely coagulase negative staphylococcus, on the skin of AD patients allow for *S. Aureus* overgrowth in these patients. Novel treatment of autologous microbiome transplant works differently from antibiotics. Instead of killing *S. Aureus,* it also provides potential long term protection by changing the microbiome in AD patients. Certain strains of probiotics, via affecting the gut microbiome, have been shown to prevent AD or reduce its severity when taken in pregnancy, infancy and patients with AD.

Learning points:

Aside from novel biologic treatment against specific cytokines that increase in AD, promising new treatments that target on the microbiome in AD patients are on the way. Probiotics are safe and possibly beneficial for AD patients.