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Review Article

Advances in paediatric dermatology
兒童皮膚病學新進展

CK Yeung 楊志強

Significant progress has been made in understanding of the pathobiology of many dermatological syndromes in children, allowing more precise and prompt diagnosis. The identification of *SPINK5* gene in Netherton syndrome and connexin defects in keratoderma illustrates the impact of the molecular biology in understanding the process of cornification. Recognition of at risk groups with congenital melanocytic naevi and vascular anomalies helps to intervene at early stage of the complications. Use of systemic corticosteroid, retinoids, azathioprine and methotrexate are now proved to be safe and effective for many dermatological conditions provided that proper ways of monitoring side effects are available.

現時對於多種兒童皮膚綜合症之病理生物學的理解有了切實的進展，從而令診斷更準確和迅速。在魚鱗樣紅皮病—竹髮—遺傳過敏綜合症 (Netherton syndrome)中發現*SPINK5*基因以及在角皮病中發現聯接蛋白的缺陷顯示了分子生物學影響了我們對角化過程的理解。對患先天黑素細胞痣及血管畸型高危人群的確認有助於在併發症出現的早期介入。對於系統性地應用皮質類固醇、維甲酸、硫唑嘌呤和氨甲喋呤，若能適當地監察其副作用，其安全性及有效性均已獲得證實。

Keywords: Congenital melanocytic naevus, glomangioma, haemangioma, Netherton syndrome

關鍵詞：先天黑素細胞痣，血管球瘤，血管瘤，魚鱗樣紅皮病—竹髮—遺傳過敏綜合症

Neonatal erythroderma

Netherton syndrome (NS) is an autosomal recessive condition characterised by a triad of generalised exfoliative dermatitis, hair shaft abnormality and atopic manifestations (Figure 1).[1]

Department of Medicine, Queen Mary Hospital, Hong Kong

CK Yeung, MBBS(Hons)(HKU), MRCP(UK), FHKAM(Medicine)

Correspondence to: Dr. CK Yeung

Department of Medicine, 4/F, Professorial Block, Queen Mary Hospital, 102 Pokfulam Road, Pokfulam, Hong Kong

There is classic ichthyosis linearis circumflexa with polycyclic double-edged scales.[2] The total IgE levels are markedly elevated. The diagnosis of NS is often delayed because of difficulty in recognising the condition and in obtaining diagnostic hair samples demonstrating trichorrhexis invaginata 'bamboo hair'.

The genetic defect of NS has recently been mapped to chromosome 5q32 by linkage analysis. More than 30 mutations have been described in *SPINK5* in NS, including nonsense and spice site mutations.[3] The mutations of *SPINK5* gene result in absence or abnormal expression

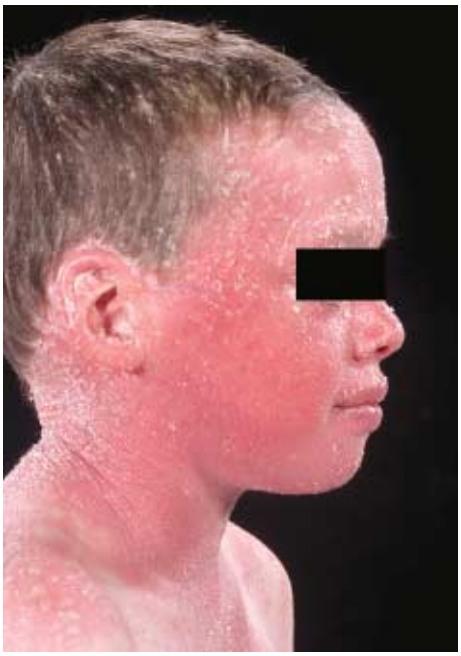

Figure 1. Netherton syndrome.

of the protein named LEKTI (lympho-epithelial Kazal type related inhibitor).[4] Besides, several genetic polymorphisms in *SPINK5* are associated with atopic dermatitis.[5] LEKTI is a serine protease inhibitor that is found to be totally absent in skin of patients suffering from NS. The function of LEKTI may be related to the regulation of extracellular matrix remodelling that affects the skin barrier formation and immunity. The exact effects of absence of LEKTI have not yet been fully elucidated. It has been suggested that LEKTI may function by inhibiting epidermal protease responsible for dissolution of cell-cell junction.[6] Cell-cell junctions may be important in both epidermal barrier and hair shaft formation. Reduced LEKTI activity may lead to excessive desquamation and abnormal hair development. The altered expression of antimicrobial peptide β-defensin 2 and transglutaminases in the epidermis has been noted in NS, which may account for the impaired epidermal barrier. Elevated hydrolytic activity in stratum corneum in NS patients suggests an important role for LEKTI in normal desquamation by controlled breakdown of desmosomal proteins. The increase in proteolysis may also contribute to the protease-mediated inflammation of the skin in NS.

It is now possible to diagnose Netherton syndrome earlier by using immunohistochemical method against LEKTI in the skin biopsy specimen.[4] Patients with NS showed absent or very reduced staining of LEKTI that is normally localised to the stratum granulosum. With the known genetic defects in *SPINK5*, this molecular advance now provides an opportunity for molecular diagnosis in patients with neonatal erythroderma with indistinct features as well as for prenatal testing.

Several types of autosomal recessive congenital ichthyosis, including non-bullous ichthyosiform erythroderma (NBIE) and lamellar ichthyosis (LI) (Figure 2), can present with neonatal erythroderma. Classically, both can present with collodion babies. The distinguishing features are the nature of the scales and intensity of erythroderma. In classic LI, the scales usually appears large, dark and plate-like with minimal

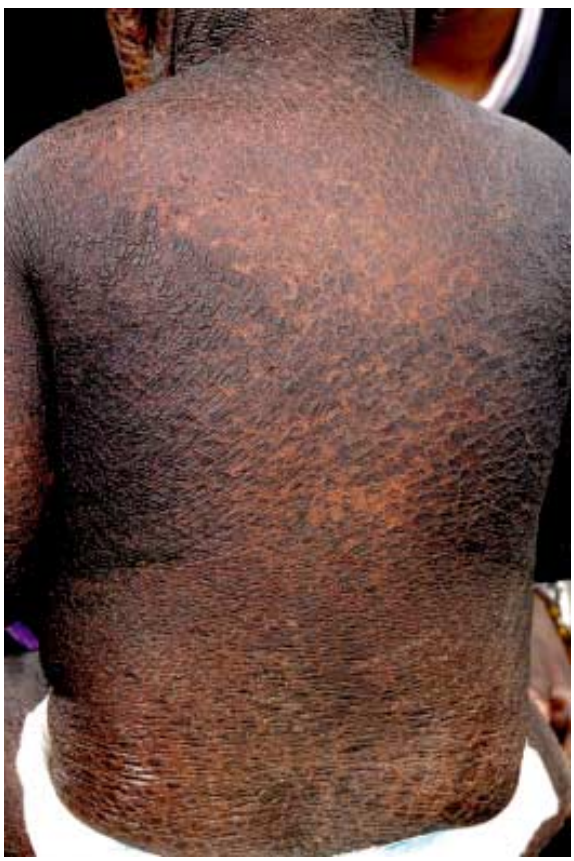

Figure 2. Lamellar ichthyosis.

underlying erythema while the degree of inflammation of skin is usually more marked in NBIE with finer and whiter scales. However, clinical and genetic distinction between congenital ichthyosiform erythroderma and lamellar ichthyosis is not always possible based on clinical, histological and ultrastructural changes. Genetic defect in the transglutaminase-1 (*TGM1*) in 14q11.2 is now evident in some patients suffering from LI with abnormality of the cornified cell envelope and stratum corneum formation.[7] Transglutaminase (TGase) 1 is a membrane-associated TGase of about 92 kDa expressed in the epidermis. Patients harbouring *TGM1* mutations can now be easily detected by demonstrating markedly reduced in situ TGase activity in the epidermis. Mutations in lipoxygenase 3 gene (*ALOXE3*) and 12(R)-lipoxygenase gene (*ALOX12B*) in 17p13.1 can also lead to both keratinisation disorders. However, only a limited correlation between *TGM1* genotype and phenotype has been shown in LI and NBIE patients so far.

Connexins are protein components of the intercellular channels termed gap junctions. Six monomers of connexin bind each other to form a hexamer (connexon), located in the plasma membrane and bound with another connexon to form intercellular channel. The epidermal connexin gene defect dominantly interferes with the formation or function of gap junction within the intercellular channels implicated in cell to cell signalling between keratinocytes.[8] The connexin defects also interfere inner ear function. Connexin defects are now known to be responsible for some disorders of cornification, such as erythro-keratoderma variabilis. Keratitis-ichthyosis-deafness (KID) syndrome comprises of keratoconjunctivitis, atypical ichthyosis with prominent follicular keratoses on head and extremities and congenital sensorineural deafness.[9] There is a palmoplantar keratoderma with a pebbly quality. The skin changes are more consistent with erythrokeratoderma. Scarring alopecia and squamous cell carcinoma can occur.[10] A *de novo* mutation in the *GJB2* gene encoding connexin-26 was found in patients with KID syndrome.[8]

Vascular birthmarks

Congenital vascular malformation always enters an important differential diagnosis of haemangioma of infancy (HOI). Vascular malformations (VM) typically present with slowly enlarging mass with blue hue in the affected regions at birth (Figure 3). Inherited glomangioma is now recognised to be a distinct entity from malformation and both conditions can now be differentiated using a set of clinical criteria.[11] Glomangioma arises from harmatomatous growth of the glomus cell responsible for temperature-sensitive arteriovenous shunt bypasses the capillary bed of the dermis. Multiple glomus lesions of hereditary type are more often seen in children. Glomangioma is transmitted in an autosomal dominant fashion. A known genetic defect is located at glomulin (*GLMN*) gene in chromosome 1p21-22 in familial cases (63.8%) while most children with vascular malformation

Figure 3. Venous malformation on right upper limb.

occur as sporadic cases (98.8%).[11] The abnormal phenotype of vascular smooth-muscle cells in glomangioma suggests that glomulin plays an important role in differentiation of these cells and in vascular morphogenesis. Inherited glomangioma is caused by several loss-of-function mutations in glomulin gene.

Glomangioma typically gives a purple tinge. It is firm in consistency and pain is induced by compression. In contrast, VM are soft, blue and localised. Glomangioma tends to develop along the Blaschko's line in segmental type or appear nodular but scattered in distribution. Glomangioma can present with cobblestone-like appearance with minor hyperkeratosis on extremities. They usually involve dermis and subcutis only whereas VM can involve deep tissue such as muscle and joints. Elastic garments improve VM while compressive garments aggravate pain in glomangioma. For histology of glomangioma, vascular channels are surrounded by poorly differentiated cuboidal cells with pale or eosinophilic cytoplasm, stained positively for vimentin and smooth muscle α-actin.

Thrombocytopenia and coagulation defects are occasionally encountered in vascular tumours or anomalies in infancy. Chronic localised vascular coagulopathy is not uncommon in patients with diffuse limb VM that can result in severe bleeding. Blood stagnation with activation of coagulation, consumption of coagulation factors and generation of thrombin and fibrin can occur within the distorted, enlarged slow-flow venous channels of VM. Low fibrinogen and elevated D-dimer levels are the main findings.[12] The clotting profiles are markedly deranged. Coagulation abnormalities associated with slow flowing VM have been misdiagnosed as Kasabach-Merritt syndrome (KMS).

Thrombocytopenia may be apparent in VM but not as profound as seen in KMS. KMS presents with marked thrombocytopenia related to platelet trapping within a vascular tumour of infancy. Haemangioma of infancy is no longer considered to cause this syndrome. The vascular tumours responsible for KMS are Kaposiform haemangio-endothelioma and tufted angioma.[13] The clinical clues of KMS are the rapidly enlarging ecchymotic tumours with board-like consistency. In VM, low molecular weight heparin is the only mean proved to control the clotting abnormalities and pain.[12] In contrast, aggressive treatment is often necessary for KMS, including systemic corticosteroid in the range of 3-5 mg/kg/day, interferon-α2b and vincristine.[13] Failure to distinguish localised intravascular coagulopathy in VM and thrombo-cytopenia in KMS can lead to complications related to inappropriate treatment.

New insight has been made in identifying the specific marker for HOI. GLUT1 is a glucose transporter protein that is uniquely expressed in the endothelial cells of haemangioma, but not in other vascular lesions.[14] GLUT1 is normally expressed in the microvascular endothelia of the placenta and other blood-tissue barrier. Some authors postulated that the tissue origin of haemangioma cell may come from invading angioblasts that differentiate toward a placental phenotype. HOI also show immuno-reactivity for the placenta-associated vascular antigens FcγRII, merosin and LeY. These findings have led some authors postulating that haemangioma may originate from embolised placental cells. This theory is falling out of favour as HOI lack villous architecture of placenta and do not express known placenta trophoblastic markers.[15]

Worrisome features are now identified to recognise those haemangioma associated with structural anomalies or complications. An HOI on the jaw area and anterior neck raises suspicion of upper airway compromise by growing upper airway haemangioma. Features of upper airway obstruction such as stridor necessitate further investigation by direct laryngoscopy while magnetic resonance imaging (MRI) has no place in defining the risk of upper airway compromise.[14] HOI in large segmental distribution on face are associated with structural anomalies. PHACES encompass posterior fossa malformation, haemangioma, arterial anomalies, congenital heart defects, eye abnormalities and sternal cleft.

MRI of the brain and the great vessels is the investigation of choice for PHACES.[15]

Meta-analysis has been done to confirm the efficacy of systemic corticosteroids in the treatment of HOI potentially causing functional impairment or severe disfigurement.[16] The overall response to treatment defined by cessation of growth or shrinkage was 84% with onset on action within 2 weeks and rebound was noted in 36%. Haemangioma tends to respond to higher doses of 3 mg/kg/day of corticosteroid for 4 weeks followed by dose tapering. No major side effects were reported with this dosage of systemic corticosteroid in children for this indication.

More experience has been accumulated to use vincristine in haemangioma with life-threatening consequence when the tumours do not respond to systemic corticosteroids. Vincristine is a vinca alkaloid that exerts strong inhibition of angiogenesis.[13] Serious side effects were not observed in reported series on use of vincristine in refractory haemangioma. The most common side effect is peripheral neuropathy manifesting as depression of ankle tendon reflex resulting from vincristine-induced neuropathy at the dose of 1.5 mg/m^2/week. Adverse reactions to vincristine are dose-related and reversible. Regular neurological examination and full blood count are to be performed regularly during treatment for early detection of side effects.

Congenital melanocytic naevus

Melanocytes originate from ectodermal cells of the neural crest cells. Neurocutaneous melanosis is defined by an increased number of melanocytes found in the central nervous system (CNS) associated with congenital melanocytic naevi (CMN), particularly those with numerous satellite lesions. Neurocutaneous melanosis can result in neurological symptoms including intractable seizures and developmental delay. CMN, notably of larger size on scalp can be associated with a variety of CNS anomalies, including Dandy-Walker malformation and meningioma, with onset of neurological symptoms in 13-14% before 18 months of age.[17] Magnetic resonance imaging (MRI) of brain and spine with gadolinium enhancement is the investigation of choice if the CMN of considerable size (>2 cm) is located on the head and neck region or overlying the spine in posterior midline. In a series of 43 children with CMN on head or spine, 9 had neurological deficits within the first 18 months of life. Seven had abnormal MRI findings and 6 had both clinical and radiological abnormalities.[17] Only 3 showed MRI features of intracranial melanosis. Close follow up by paediatrician and dermatologist is necessary for cases suffered from neurocutaneous melanosis and other structural brain abnormalities in order to pick up features of raised intracranial pressure, mass lesions and spinal cord compression. Some of the associated CNS disorders, such as astrocytoma, are benefited from early surgical intervention.

The relative risk of developing malignant melanoma in giant CMN (>20 cm in diameter) is now better defined, ranging from 5% to 40%.[18] The cumulative 5-year life-table risk of melanoma is 4.5% in giant CMN and is greatest in the first decade. However, the early aggressive surgical removal of CMN does not entirely eliminate the risk of melanoma because of the deep infiltration of naevus cells to the underlying tissue in some cases. Close regular surveillance by dermatologists and biopsy of suspicious lesions still the most important measure to detect early melanoma. Nevertheless, for CMN less than 1.5 cm in diameter, the risk of melanoma arising from naevi is minimal in childhood. The relative risk of melanoma developed from CMN of intermediate size (1.5-20 cm) remains to be determined.

Therapeutic advances

The indications of systemic retinoids in children include acne vulgaris, psoriasis and inherited disorders of cornification. Apart from teratogenicity in treating fertile women, the skeletal side effects

especially for bone growth have long been a concern for oral retinoids to be used in children. Diffuse idiopathic skeletal hyperostosis (DISH) and calcification of tendons and ligaments have been reported with long term therapy.[19] Premature epiphyseal closure compromising the potential bone growth has only been recorded in several children on higher doses of retinoids (over 3 mg/kg/day).[20] It is proposed that the closure of the growth plates resulted from fractures across the growth plates owing to minor trauma in the background of retinoid-induced osteopenia.

Many of the reported skeletal abnormalities in children are on relatively high dosage, often well exceeding 1 mg/kg/day. No evidence of skeletal toxicity in 42 children treated with etretinate over 11-year period with a dosage not exceeding 1 mg/kg/day.[20] Growth in all the studied children on long term etretinate has been normal. The risk of skeletal abnormalities in children treated with acitretin is low. In another appraisal of acitretin, 43 out of 46 children receiving acitretin with the optimal dosage of around 0.5 mg/kg per day had considerable overall improvement without irreversible side effects.[21]

Mild to moderate mucocutaneous dryness was frequent with minor abnormalities of liver function tests and triglyceride level.[22] It represents a safe and effective treatment in children provided that the minimal effective dose is maintained and that side effects are carefully monitored.[21] The data available so far indicates that it is safe to use systemic retinoid in children with minimal skeletal side effects provided that the dose of acitretin is kept below 1 mg/kg/day. Every effort is to be made to use minimal dose (preferably ≤0.5 mg/kg/day) that is effective to control the underlying skin diseases. Transient decrease in bone densities was observed in patients taking isotretinoin for nodulocystic acne in some studies but findings could not be repeated by others.[19] The optimal bone study to perform remains to be determined. Baseline bone study is advocated for those requiring prolonged retinoid treatment with subsequent studies guided by musculoskeletal symptoms.

Azathioprine can be used with caution at a dose of 2-3.5 mg/kg/day for various disorders including systemic lupus erythematosus, dermatomysositis, pemphigus vulgaris and severe atopic dermatitis refractory to topical treatment.[23] Azathioprine is an anti-metabolite with *in vivo* conversion to 6-thioguanine nucleotides which is responsible for immunosuppression and myelotoxicity in patients (Figure 4). Polymorphism in the thiopurine methyltransferase (TPMT) gene predicts haematological adverse effects occurring in 5-10% patients taking azathioprine. Homozygotes for low enzyme activity ($TPMT^L$) with prevalence of 1 in 300 predispose someone taking azathioprine to profound myelosuppression. Azathioprine should not be used in patients with very low or absent TPMT activity (below 3 nm/h/ml RBC). Conversely, homozygotes for high enzyme activity ($TPMT^H$) may show inadequate response to conventional doses of azathioprine. Pretreatment TPMT levels is advocated to stratify patients at different risk of myelosuppression and to determine the optimal doses more accurately.[23]

In a retrospective study on treatment of severe atopic dermatitis with azathioprine in 48 children, 28 had an excellent response, 13 had a good response and 7 had a poor response.[24] No patient developed neutropenia after screening with TPMT. Reversible abnormalities in liver function tests were seen in five children without other serious toxicity. The results of previous studies suggest that azathioprine may be effective in some patients with atopic dermatitis and the improvement is modest.[23] This drug has been used for many years as a treatment for severe atopic eczema but only recently has a double-blind placebo-controlled study been undertaken. In this double blind 12-week study using a TPMT-based dose regime produced a mean decrease in disease activity by 39% with azathioprine and a 24% decrease with placebo. Those responders often showed prolonged improvement 3-6 months after treatment.[25]

Methotrexate is originally licensed to treat juvenile rheumatoid arthritis. The use of this

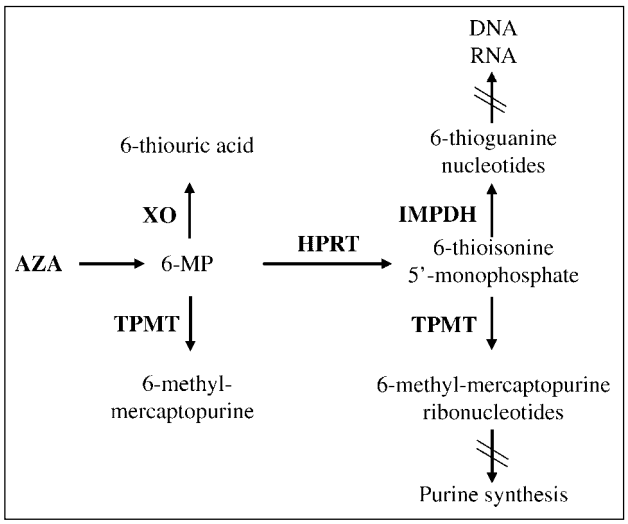

Figure 4. Azathioprine metabolism: azathioprine (AZA) is initially converted to 6-mercaptopurine (6-MP). 6-MP is then transformed by one of three competing enzymatic pathways (XO, xanthine oxidase; TPMT, thiopurine methyltransferase; HPRT, hypoxanthine phosphoribosyltransferase). Both 6-MP and 6-thioisonine 5'-monophosphate (TIMP) are inactivated by methylation to me-MP and me-TIMP, respectively. This reaction is catalysed by TPMT. Methylation competes with the activation pathway and regulates the amount of TGNs present in the target cell. Once formed, TIMP can either be converted into 6-thioguanine nucleotides by the rate-limiting inosine monophosphate dehydrogenase (IMPDH), or be methylated into 6-methyl-mercaptopurine ribonucleotides.

drug in paediatric dermatology is mainly for severe, refractory pustular or erythrodermic psoriasis, pityriasis rubra pilaris, morphoea, linear IgA disease, vasculitis and dermatomyositis.[26] Methotrexate is a competitive inhibitor of dihydrofolate reductase. There have been reports advocating the use of methotrexate therapy together with systemic corticosteroid in the treatment of widespread or disfiguring active morphoea.[26] Nausea, anorexia, stomatitis and vomiting are the most common side effects of methotrexate. The potential drug interaction especially with sulphonamide must be born in mind. Hepatotoxicity resulting from long-term methotrexate therapy is the adverse effect of greatest concern. Liver function test including the transaminase levels may be normal even in the setting of significant hepatic fibrosis or cirrhosis and so this test is not a sensitive screening method. Standards of care are not well established in paediatric patients while adult psoriatic patients undergo liver biopsy after a total dose of >1.5 g of methotrexate.

Use of blood amino-terminal propeptide of type III procollagen (PIIINP) levels in predicting the risk of hepatic fibrosis and cirrhosis is now increasingly applied in patients taking methotrexate.[27] The correlation between PIIINP and age-sex difference was found in children, reflecting the high bone and soft tissue turnover during childhood growth.[28] Many patients are dissuaded from considering methotrexate because of the threat of repeated liver biopsy. If PIIINP monitoring could be widely adopted after normal paediatric range is defined, methotrexate would become a more acceptable option for children. The safety data from children taking methotrexate for juvenile rheumatoid arthritis showed that methotrexate may be better tolerated in children than adults.[29] No severe pulmonary or liver toxicity related to methotrexate is observed in a multicentered study in patients with JRA. Transient elevation of hepatic transaminase levels and leukopenia is the most common laboratory abnormality, associated with obesity and viral infections.

Summary

Vascular lesions and melanocytic naevi are common in children. Appropriate and timely management can be offered if pitfalls in diagnosis and early identification of the complications can be unveiled. Further pursuit in molecular medicine will sharpen our tools to diagnosis and treat those skin diseases with genetic basis. Therapy that is well established in adults may not be entirely applicable to children because of growth and organ maturation. Advances in enhancing safety in potentially toxic drug helps to widen the therapeutic options of many refractory paediatric skin conditions.

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