

Review Article

Approach to pigmented skin disorders in children

兒童色素性皮膚病的診斷方法

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Pigmented problems in children covers a wide area, and a simple approach may be to divide them into hypopigmentation and hyperpigmentation. Understanding the biology of the melanocyte pigment and the mechanisms allow one to diagnose the hypopigmented ones, The hyperpigmented problems are more complex and causal factors are many, some follows pigment patterns, e.g. lentigines, café au lait macules, some functions like the xerodermas and many are gene mutations like incontinentia pigmenti. Also included are acquired factors and environmental factors. Most of these childhood lesions are of cosmetic concern and may not need treatment. However, other organ systems may be involved in syndromes. Therefore other associated features in the clinical presentation play an important role in the diagnosis.

兒童色素沉著問題涉及範圍廣泛，簡單的處理方法可先將其分為色素減退或色素沉著過度兩大類。對黑色素細胞色素的生物學和機制的了解，可幫助我們去診斷色素減退疾病。而色素沉著問題則較複雜，因果因素繁多：有些遵循色素模式（例如黑痣、咖啡牛奶斑）、一些為功能問題仿如乾皮病，另許多是像色素失調症那樣的基因突變。除此，還包括獲得性因素和環境因素。這些兒童期病變大部分都只限於美容問題，一般不需要治療。然而，要留意某些綜合徵可能會涉及其他器官系統。因此，臨床表現中的其他相關特徵在診斷中起著重要作用。

Keywords: Biology of melanocytes, Genetics, Hyperpigmentation, Hypopigmentation, Pigmentary disorders

關鍵詞：黑素細胞生物學、遺傳學、色素沉著過度、色素減退、色素異常

Introduction

Skin disorders can present in childhood with hyperpigmentation or hypopigmentation and the pathogenesis is varied. So far, there is no

comprehensive integrated algorithm for diagnosing both common and rare disorders when confronted with pigmented-related disorders in children. Based on my experience with a wide spectrum of skin disorders, some simple suggestions are made in this review. Most pigmentary disorders in infancy and childhood are of cosmetic concern, but it is useful to understand the underlying pathogenesis as they may be associated with multisystem disease. These diseases are differentiated clinically by increased or decreased pigment distributed in a localised

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or diffuse pattern. Five groups are suggested in an algorithm in the approach to these pigmented disorders (Figure 1).

1. Genetic disorders arising from the biogenesis of the melanocyte or melanocyte transfer from the neurocrest to the skin¹⁻⁴

The biogenesis of the melanocyte and its pathway plays a role in understanding of the genetic congenital disorders. Rare, congenital hypopigmented disorders develop at three different phases of development.

- a. Development and differentiation: e.g. Piebaldism, Waardenburg disease.
- b. Migration/Maturation/Replication: e.g. Oculocutaneous Albinism.
- c. Production/Packaging/Distribution: e.g. Hermansky Pudlak disease, Chediak-Higashi syndrome.

Most of the others, mainly hyperpigmented disorders are more easily recognised and can be classified at the level where the pigment is present, and also in terms of the mechanism or mutation.

2. The Pigmented Lentiginos and their syndromes, including café au lait macules (CALM) syndromes

- a. Café-au-lait macule (CALM)-associated syndromes:
 - Neurofibromatosis: Small CALM can appear on the skin, axillae, 4-5 years before the neurofibromas. The eye should be examined for Lisch nodules, which are confirmatory of neurofibromatosis.
 - Tuberous sclerosis: A complex with hypopigmented ash leaf macules, Shagreen patches, adenoma sebaceum, and skin fibromas. Systemic features include central nervous system, kidney, heart and lung lesions.
 - McCune Albright: characterised by isolated large CALM, precocious puberty in girls, polyostotic fibrous dysplasia.
- b. Lentigo-associated syndromes(mutations):
 - Leopard syndrome
 - Multiple lentiginos
 - Peutz Jegher syndrome (These will be discussed later in the paper)

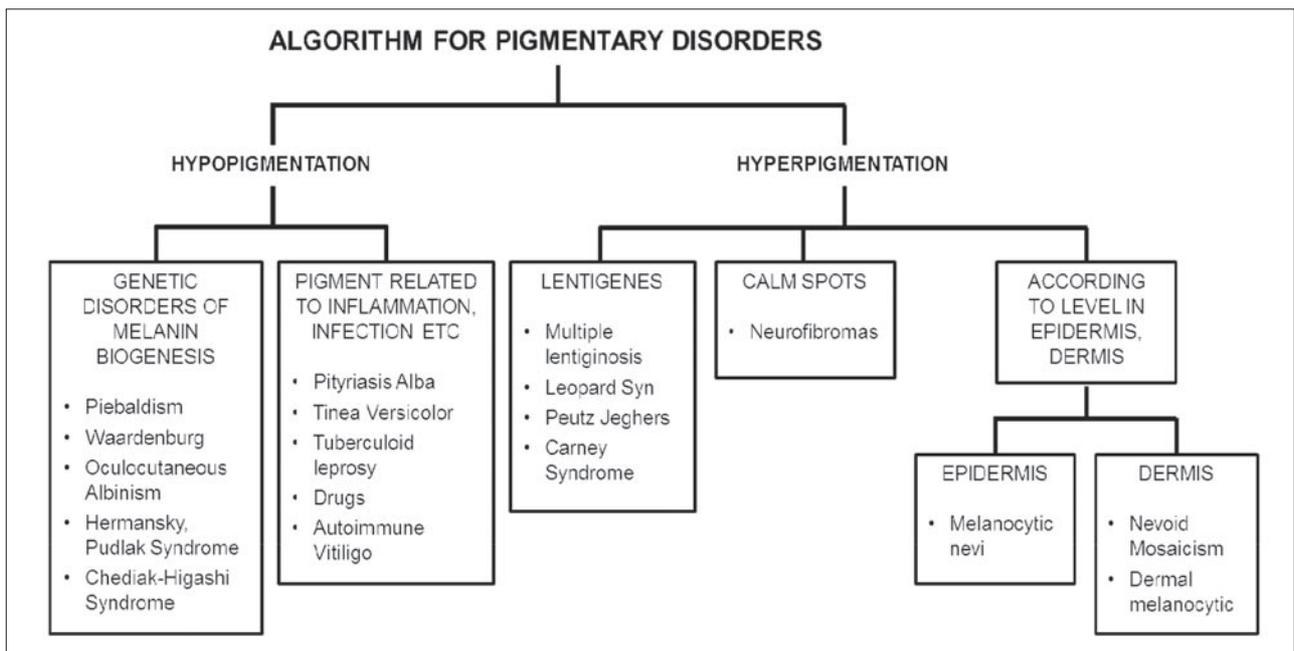


Figure 1. Algorithm of Pigmentary diseases ref GiamYCR.

3. Some associated pigmentary syndromes, where the pathogenesis is related to functions other than the biogenesis of the melanocyte e.g. xeroderma pigmentosa

- Xeroderma pigmentosa
- Incontinentia pigmenti

Gene mutation studies are required in some of these conditions.

4. Disorders found in the epidermis and dermis

- Congenital : Congenital naevus
 - Acquired : Halo nevus, Spitz naevus
 - Naevi that can be present at birth/or later
- a. Blue naevus, Naevus spilus: These are present from birth and have a brown background with darker naevus macules.
 - b. Becker's naevus: mottled hyperpigmentation, onset at puberty. Hairs may be seen. This may be associated with underlying smooth muscles.

5. Dermal melanocytic disorders

- Congenital: Mongolian spots, Naevus of Ota
- Acquired: Pigmentary mosaicism, Idiopathic eruptive macular pigmentation, Dermal melanocytosis.

6. Some skin diseases associated with inflammation or infections

These are associated with inflammatory, infectious, autoimmune, malignancy.

These are common and result in a patchy depigmented dermatitis. A compatible history and familiarity with the clinical features are required to differentiate among the disorders.

- Common diseases: Pityriasis alba, phytophotodermatitis, tuberculoid leprosy, lymphomatois papulosis, mycosis fungoides.

The importance of some of the above disorders are now briefly discussed.

1. Conditions arising from disorders in melanocyte development and transfer¹⁻⁴

The following pathway of the biogenesis of the melanocyte highlights the pathogenesis of the rare hypopigmented disorders: Piebaldism, Waardenburg syndrome, Oculocutaneous albinism, Hermansky-Pudlak syndrome and Chediak-Higashi syndrome and Griscelli syndrome.

a. Melanoblast migration from neural crest to peripheral sites/skin .¹

Failure of migration leads to Piebaldism and the Waardenburg syndromes (types 1-4). These are characterised by localised hypopigmented patches.

- Piebaldism: Patients are born with symmetrical localised white macules, often misdiagnosed as vitiligo (Figure 2). However, there is the characteristic "white forelock," patch of white hair on the prefrontal scalp. The mutation is in the c-Kit proto-oncogene.
- Waardenburg syndrome: Types 1-4. Type 1: this shows the white forelock of hair, heterochromia irides (irises of different colour), broad nasal root, dystopia canthorum, and deafness. The affected genes are PAX3, MITF genes. Type 3 does not exhibit any hearing loss.

b. Melanin synthesis

Failure of melanin production leads to oculocutaneous albinism types 1-4.⁵ Newer types are now being recognised. Visual dysfunction includes photophobia, nystagmus, poor vision, red eyes. Gene mutations include OA1/GPR143, and TRYP1, MAP/SCLASA2, SCL24AS.

c. Melanosome formation and reduced tyrosinase activity and defects in Lysosomal Trafficking LRO

The following enzymes are needed for melanosome trafficking from the endoplasmic reticulum (ER) via Golgi apparatus to the developing melanosome: TYR (tyrosinase) TYRP1 (Tyrosinase-related protein 1).

Mutations in the genes that regulate this function, BLOC-1, BLOC-2, BLOC-3, AP-3 lead to structural abnormalities of the melanosomes leading to Hermansky Pudlak syndrome and Chediak-Higashi syndrome (CHS).⁶

The affected gene in Chediak-Higashi syndrome is the *LYST* gene. In CHS, there is white light skin, brown to blond hair, decreased iris pigment manifesting as brown eyes. There may be life-threatening bleeding disorders although the platelet defect is not a great problem in children. Giant inclusions are found in white blood cells. The immunodeficiency manifests as infections by *Staphylococcus aureus*, *Streptococcus pyogenes* and pneumococci.



Figure 2. Piebaldism, white macules on knees, lesions look like vitiligo.

d. Transfer of pigment granules to keratinocytes

Failure of transfer of pigment granules to keratinocytes causes the Griscelli syndrome (types 1-3).

2. Conditions characterised by epidermal, dermal and gene mutations

Lentigo-associated syndromes:

- Multiple Lentiginosis syndrome without systemic involvement (Figure 3).
- Peutz Jegher syndrome.⁷

a. LEOPARD syndrome:⁸

LEOPARD syndrome (LS) was described by Gorlin in 1969. It is of autosomal dominant inheritance.



Figure 3. Male with multiple lentiginosis without no systemic involvement.

Mutation is in the **PTPN11** gene on chromosome 12q24.1 (present in 80% of cases). PTPN11 encodes for protein tyrosinase phosphate, SHP2, a positive regulator of RAS-MAPK signalling. Clinically, there is progressive macular hyperpigmentation with sparing of the mucosa.

This syndrome includes the following:

- Lentiginos
- ECG conduction defects
- Ocular hypertelorism
- Pulmonary stenosis
- Abnormal genitalia
- Retardation of growth
- Deafness-sensorineural (rare)

b. **Lentiginosis syndrome**⁹

In lentiginosis syndrome (LS), there are multiple lentiginos but no systemic involvement. Management includes exclusion of organ involvement in LS.

c. **Café au lait-associated syndromes**¹⁰

i. Neurofibromatosis NF1

Ninety-five percent of patients present with more than six (Crowe) café au lait macules by five years of age.¹¹ Other signs include axillary freckling, Lisch nodules in the eyes, and sphenoid fossa calcification. The neurofibromas arise later from age of 2-5 years. Tumours may arise later. Localised segmental cutaneous types have also described and may be accompanied by plexiform neurofibromas.

ii. McCune Albright syndrome

McCune Albright syndrome is a rare condition characterised by CALM patch on the abdomen. It is a triad of café-au-lait spots (50%), on the forehead, neck, sacral, buttock areas. and precocious puberty in girls, polyostotic fibrosis and associated mutations in the GNAS1 gene.

3. Other syndromes where functions are affected

a. **Incontinenti pigmenti**

Mutation in the IKBKG or NEMO gene which encodes the inhibitor of nuclear factor kappa NF-KB, leads to incontinenti pigmenti (IP). Clinically, there are four stages, starting from birth, there are blistering linear lesions which may become infected showing pustules. These become verrucous, then macular lesions in a whorled fashion (Figure 4). The fourth stage is hypopigmentation within the previous lesions. A differential diagnosis is the whorled bizarre hyperpigmented naevus (pigmentary mosaicism) although it does not go through these four stages. Dental, ocular, central nervous systems may also be affected in IP.

b. **Xeroderma pigmentosa (with malignancy)**

Xeroderma pigmentosa is a rare autosomal recessive condition with 2.3/million people affected in Western countries. Patient present with skin dryness, abnormal pigmentation, severe sunburn, accelerated photodamaged skin. Skin cancer risk is increased by more than 1000 fold. The mechanism is related to defective post-UV DNA repair due to defect of nucleotide excision repair (NER). Clinically, cases can be divided into seven complementation groups A-G.

4. Disorders of melanocytes at the epidermal and dermal levels of skin, including naevi

a. **Congenital: Congenital naevus**

b. **Acquired: Halo naevus , Spitz naevus, naevus depigmentosus:**

- i. The above naevi are uncomplicated. Acquired melanocytic naevi can arise in early childhood, They can evolve from junctional naevi to intradermal naevi and are increased during puberty.

- ii. Halo naevus: cytotoxic T lymphocytic cells reduce the pigment causing a white halo around the naevus.
- iii. Spitz naevus: have a red appearance and are associated with rapid growth. Its histology show large cells.
- iv. Naevus depigmentosus¹⁷ its formation is hypothesised to be due to an abnormality of melanosome function, thus preventing pigment transfer to the keratinocytes or a defect of the function of keratinocyte , preventing melanin uptake. Clinically, there can be a systematised form with whorled lesions on one side.

c. Naevi that are present at birth/or later:

- i. Blue naevus
- ii. Naevus spilus

d. Dermal melanocytic disorders

- Congenital:
 - i. Mongolian spots: melanin is in the deeper dermis but fade by puberty.
 - ii. Naevus of Ota: common in Asians. Corneal involvement is often seen.
- Acquired: Pigmentary mosaicism
 - i. Naevus spilus
 - ii. Idiopathic eruptive macular pigmentation
 - iii. Dermal melanocytosis

The above group are mainly naevi, and some need to be biopsied to differentiate from malignancy.

- e. Pigmentary mosaicism:** previously called as Hypomelanosis of Ito (Figure 5).^{12,13} Its pathogenesis now thought to be due to two lines of cells, leading to hypopigmented patterns. These are gene mosaicism of affected areas along Blaschko lines of embryonic development. Commonly may appear as localised hypopigmented naevoid lesions.

The differential diagnosis includes tuberose sclerosis complex, which can be characterised by seizures, lung cysts, renal angioliomas and calcified non-cranial tubers.

f. Idiopathic eruptive macular pigmentation

These appear from age of one year, and males and females are equally affected. The lesions consist of oval, circumscribed, homogeneous pigmented macules (Figure 6). Clinically, there is an eruption of brownish, non-confluent, asymptomatic macules involving the trunk, neck, and proximal extremities in children and adolescents. Histologically, there is basal cell layer hyperpigmentation of the epidermis and prominent dermal melanophages. No specific treatment has been proposed. The lesions tend to resolve spontaneously. The differential diagnosis includes drug eruption, postinflammatory pigmentation, mastocytosis, erythema dyschromicum perstans (ashy dermatosis).

Dermal melanocytosis: histologically, deep layers of melanocytes are seen in the dermis. This condition is harmless.

5. Pigmentary diseases associated with inflammation or infections¹⁴⁻¹⁹

- a. Pityriasis alba:** Clinically, there are depigmented asymptomatic patches on the face and exposed parts of limbs. This is seen often in atopic patients after exposure to sun.
- b. Tuberculoid leprosy:** this is due to infection by *Mycobacterium leprae*. Patients present with hypopigmented anaesthetic lesions.
- c. Mycosis fungoides (Figure 7):** often these appear as hypopigmented macules, especially on the buttocks after Pityriasis lichenoides, and



Figure 4. Infant with linear streaky brown incontinentia pigmenti.



Figure 5. Girl with hypopigmented macules in pigmentary mosaicism (Hypomelanosis of Ito).

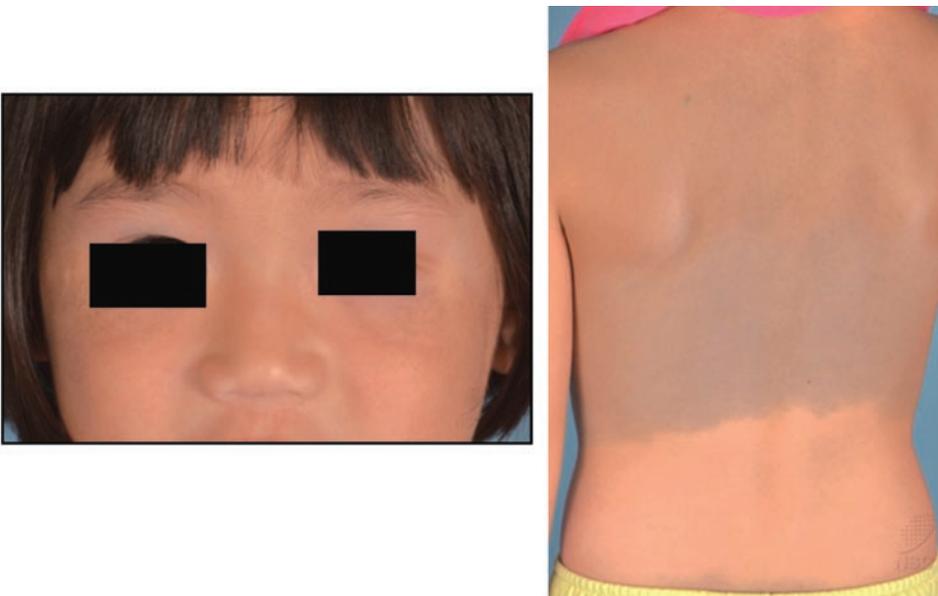


Figure 6. Girl with Idiopathic eruptive macular pigmentation.

atypical pityriasis rosea. The histology show large malignant lymphocytes infiltrating the epidermis. This is seldom progressive and best treated with UVB therapy.

d. Vitiligo:²⁰ some points of note. Childhood vitiligo is a distinct subset of vitiligo and separate from adult vitiligo. It has a prevalence of 1-4% and is higher in Indians. Average age of onset is 4-5 years. By age 8 years, 25% of vitiligo will have developed. 78% are vitiligo vulgaris, *higher incidence of segmental vitiligo*. HLA-A31 and 4 are seen in non-familial patients. 12-35%, thyroiditis is the most commonly associated autoimmune disease.



Figure 7. White poorly-demarcated outlines of macules in a child with mycosis fungoides.

Vitiligo pathogenesis: there are the following hypotheses: Melanocyte loss can result from cellular immunity, abnormal immune response autoantibodies, tetrahydrobiopterin pathways or MIFTM gene expression and immune process. If familial, it is a complex polygenic multifactorial inheritance.

e. Post-inflammatory pigmentation. Hyperpigmentation or hypopigmentation are commonly seen after inflammation as well as after drug reactions.

In conclusion, most of these childhood lesions are of cosmetic concern and may not need treatment, although other organ systems may be involved as part of a syndrome. Therefore other associated features need to be considered in the clinical presentation.

References

1. Biology of the melanocyte. From Neural Tube to Melanocytes in Epidermis. Lin & Fisher 2007.
2. Boissay RF, Nordlung JJ. Molecular basis of congenital hypopigmentary disorders in humans: a review. *Pigment Cell Res* 1977;10:12-24.
3. Dessinioti C, Stratigos AJ, Rigopoulos D, Katsambas AD. A review of genetic disorders of hypopigmentation lesions learned from the biology of melanocytes. *Exp Dermatol* 2009;18:741-9.
4. Genodermatoses with pigmentary disorders, Chapter 104; Disorders of Pigmentation. 101.4-101.15 R M Ross Hearn. And chapter 138 Harper's Textbook of Pediatric Dermatology, 3rd ed. Irvine AD, Hoeger PH, Yan AC. Wiley Blackwell, 2011.
5. Gronskov K, Ek J, Brondum-Nielson K. Oculocutaneous albinism. *Orphanet J Rare Diseases* 2007;2:43.
6. Huizing M, Helip-Wooley A, Westbroek W, Gunay-Aygun M, Gahl WA. Disorders of lysosome-related organelle biogenesis: clinical and molecular genetics. *Ann Rev Genomics HumGenet* 2008;9:359-86.
7. Tovar JA, Eizaguire I, Albert A, Jimenez J. Peutz-Jeghers syndrome in children: report of two cases and review of the literature. *J Pediatr Surg* 1983;18:1-6.
8. Sarkozy A, Digilio MC, Dallapiccola B. Leopard syndrome. *Orphanet J Rare Dis* 2008;3:13.
9. Chong WS, Klanwarin W, Giam YC. Generalized lentiginosis in two children lacking systemic associations:

- Case report and review of the literature. *Pediatric Dermatology* 2004;21:139-45.
10. Shah KN. The diagnostic and clinical significance of café-au-lait macules. *Pediatric Clin North Am* 2010; 57:1131-53.
 11. Neurofibromatosis, chapter 128.7-128.2 Genodermatoses with pigmentary disorders, *Disorders of Pigmentation. Harper's Textbook of Pediatric Dermatology*, 3rd ed. Irvine AD, Hoeger PH, Yan AC. Wiley Blackwell, 2011.
 12. Disorders of Pigmentation, Chapter 6, 148-158 John Mavropoulos and Bernard Cohen. *Pediatric Dermatology*, 4th ed, Saunders 2013.
 13. Xu AE, Huang B, Li YW, Wang P, Shen H. Clinical, pathological and ultrastructural characteristics of nevus depigmentosus. *Clin Exp Dermatol* 2008;33:400-5.
 14. Kuster W, Kong A. Hypomelanosis of Ito: no entity, but a continuous sign of mosaicism. *Am J Med Gener* 1999; 85:346-50.
 15. Hypomelanosis of Ito. Chapter 131. Genodermatoses with pigmentary disorders, *Disorders of Pigmentation. Harper's Textbook of Pediatric Dermatology*, 3rd ed. Irvine AD, Hoeger PH, Yan AC. Wiley Blackwell, 2011.
 16. Hyperpigmentation, Chapter 67, Bolgna JC, Shaeffer JV, Cerron L, *Dermatology*, 4th ed. Elsevier 2016.
 17. Hypopigmentation Chapter 66 Bolgna JC, Shaeffer JV, Cerroni L, *Dermatology*, 4th ed. Elsevier 2016.
 18. Disorders of Pigmentation, Chapter 11, 245-316. *Clinical Pediatric Dermatology*, 5th ed. Paller A, Mancini A, Saunders 2015, Elsevier.
 19. Kincannon J, Boutzale C. The physiology of pigmentary nevi. *Pediatrics* 1999;104:1042-5.
 20. Phiske MM. Vitiligo in Children: A Birds Eye View. *Curr Pediatr Rev* 2016;12:55-66.