Neurocutaneous Syndromes

4

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4.1 Neurofibromatosis 1 (NF 1)

NF 1 is the most common single-gene genetic disorder to affect the human nervous system and the estimated prevalence of 2 to 3 cases per 10,000 population (North 2000). It is inherited as a complex autosomal dominant manner due to mutations in germline NF1 tumour suppressor gene (Gutmann et al. 2017).

The clinical manifestation varies and almost all develops pigmentary lesions, such as café-au-lait macules, skinfold freckling and Lish nodules. Other systemic involvements are skeletal abnormalities (*scoliosis, tibial pseudarthrosis and orbital dysplasia*), brain tumours (*optic pathway gliomas and glioblastoma*), peripheral nerve tumours (*spinal neurofibromas, plexiform neurofibromas and malignant peripheral nerve sheath tumours*), learning disabilities, attention deficits and social and behavioural problems. These will negatively impact quality of life (Ferner et al. 2007).

The clinical manifestations according to three major studies are as follows (North 2000).

Dermatological Manifestations of NF1 (Friedman 1993) (Table 4.1)

4.1.1 Café-au-lait Spots

This is the first clinical manifestation. These macules are varied in sizes, but the typical spot is between 10 and 30 mm in size, ovoid in shape and uniform in colour, although the variations are not uncommon to this.

They normally do not appear in the scalp, eyebrow, palms and soles. Its melanocytes are histologically characterised with the presence of giant melanosomes; however, this finding is not unique to NF1 (Figs. 4.1, 4.2 and 4.3).

4.1.2 Axillary and Other Intertriginous Freckling

These are similar to café-au-lait spots in colour but smaller in size and occur in clusters. These can present even at birth but appear later in child-

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R. R. Ranawaka et al. (eds.), *Atlas of Dermatoses in Pigmented Skin*,
https://doi.org/10.1007/978-981-15-5483-4_4

Table 4.1 Incidence of Clinical Features of NF1

	%
Major disease features	
>6 café–au–lait spots	>95
Axillary freckling	65–84
Cutaneous neurofibromas	
0–9 years	14
10–19 years	44
20–29 years	85
>30 years	95
Lisch nodules	
0–4 years	22
5–9 years	41
10–19 years	82
>20 years	96
Minor disease features	
Short stature (height < 3rd centile)	≅30
Macrocephaly (head circumference > 97th centile)	≅45
Complications	
Plexiform neurofibromas	
All lesions	25
Large lesions of the head and neck	1–4
Cognitive deficits	
Mental retardation	4–8
Academic learning disability	30–60
Scoliosis	12–20
Optic pathway gliomas	
All lesions	15–20
Symptomatic	5–7
Neurological manifestations	
Headache	10–20
Epilepsy	3–5
Aqueduct stenosis	2.5
Pseudarthrosis of the long bones	3
Sphenoid wing dysplasia	<1
Malignant peripheral nerve sheath tumors	1–4
Renal artery stenosis	1–2
Noonan syndrome–like facies	7
MR1 T2 hyperintensities	60–70

Frequency of each disease manifestation derived from three major studies (Huson et al. 1988; Riccordi 1992; North 1993)—apart from figures for optic pathway gliomas (Listernick et al. 1995) and MRITZ–hyperintensities (Van Es et al. 1996). *NF1* neurofibromatosis type 1, *MRI* magnetic resonance imaging

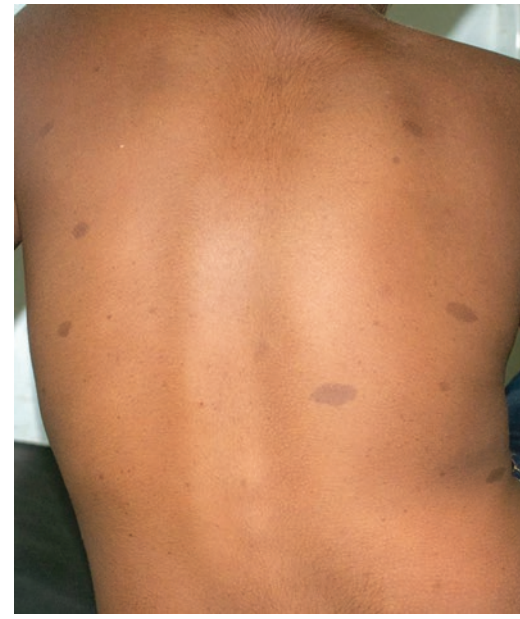

Fig. 4.1 Cafe-au-lait spots

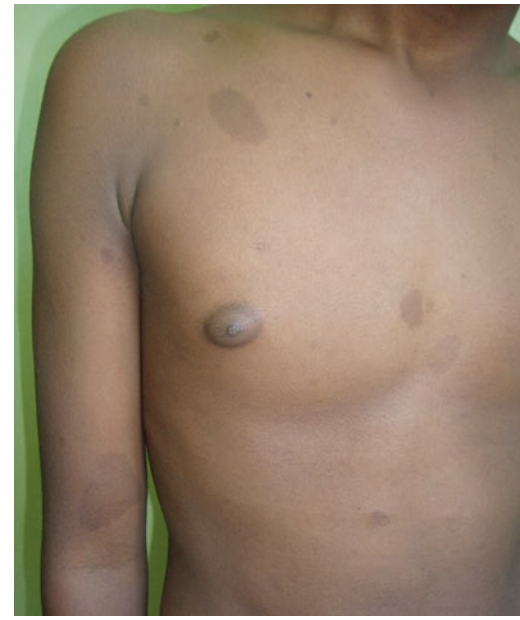

Fig. 4.2 Multiple cafe-au-lait spots (photographed by Dr. Ranthilaka R. Ranawaka)

hood. They appear also on other flexural sites such as upper eye lids, inguinal regions and around the neck. Sometimes, they can be seen in the face, trunk and proximal extremities (Fig. 4.4).

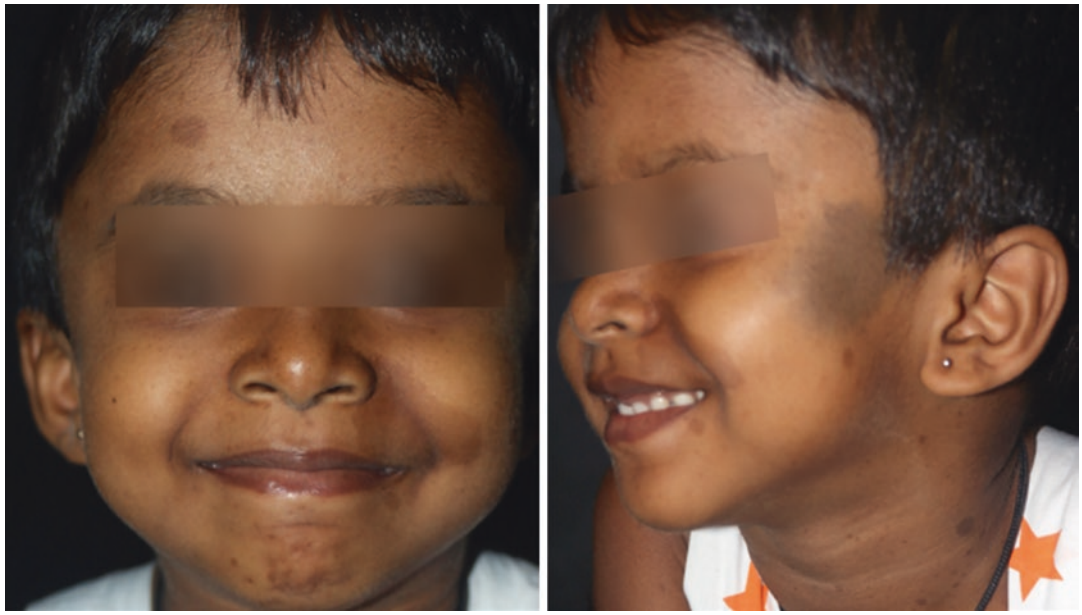

Fig. 4.3 Multiple cafe-au-lait spots

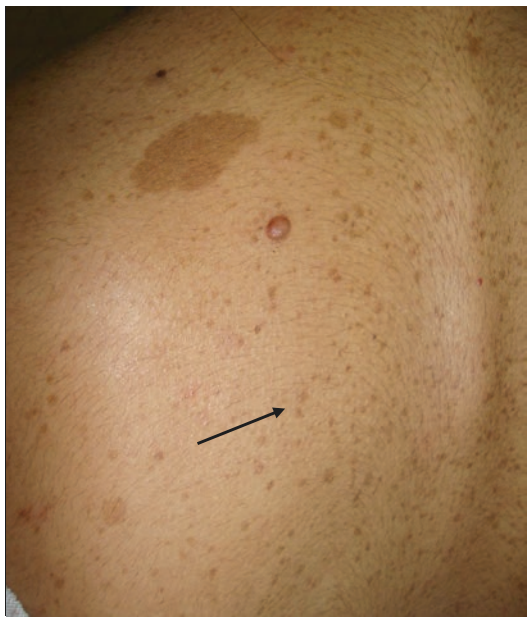

Fig. 4.4 Freckling on the trunk in NF1 (photographed by Dr. Ranthilaka R. Ranawaka)

4.1.3 Neurofibromas

It is a benign tumour arises from any peripheral nerves. Schwann cells and fibroblasts are the predominant cells seen in it. There are four clinical types, namely, discrete cutaneous neurofibroma, discrete subcutaneous neurofibromas, nodular plexiform neurofibroma and diffuse plexiform neurofibroma and deep nodular neurofibroma.

Discrete cutaneous neurofibroma—sessile but become pedunculated later.

Discrete subcutaneous neurofibroma—commonly seen in middle to late childhood, soft to touch and rarely painful, very slowly grow in size and number.

Nodular plexiform neurofibroma—can involve minor or major nerves and part of it or the whole length beneath the dermis. Sometimes, the whole sacral, brachial plexus or spinal nerves at multiple levels can be affected. They arise in adulthood.

Diffuse plexiform neurofibromas—can be seen very early in the life and may be congenital. As the name implies, diffuse involvement of surrounding normal tissues apart from peripheral nerves. Appear superficially or deeply in the face, neck, trunk or limbs (Figs. 4.5, 4.6 and 4.7).

4.1.4 Lisch Nodules

These are hamartomas in the iris and do not affect visual function. These are most commonly seen in childhood when they are older than 10 years. It is very characterised to NF1. On slit-lamp examination, these appear as three-dimensional translucent masses punctuated by melanin-containing cells. It has to be differentiated from iris naevus, which is very common among normal individuals.

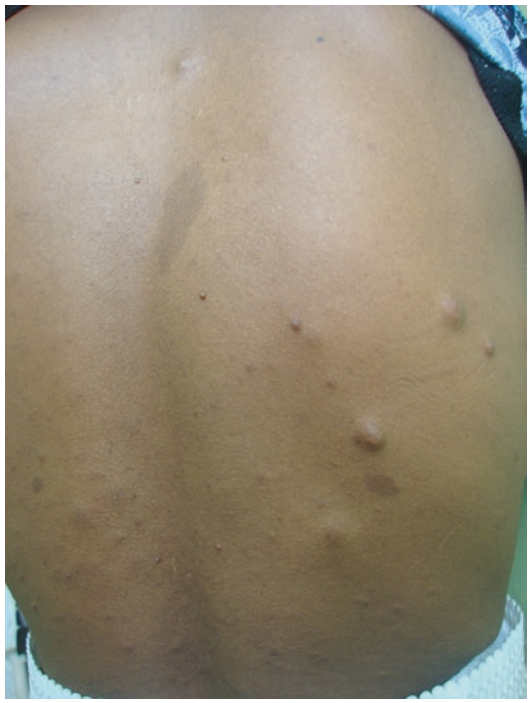

Fig. 4.5 Discrete cutaneous and subcutaneous neurofibromas in a patient with NF1 (photographed by Dr. Ranthilaka R. Ranawaka)

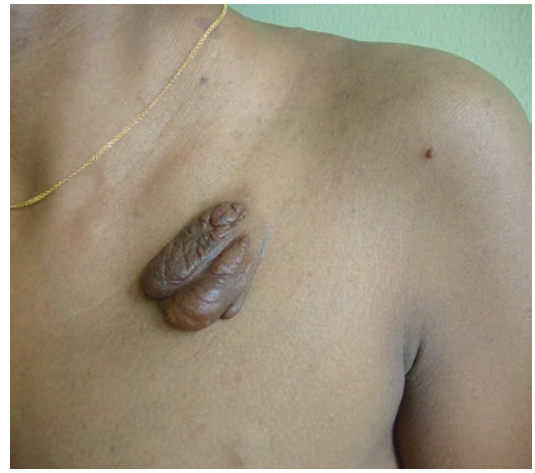

Fig. 4.6 Plexiform neurofibroma in NF1 (photographed by Dr. Ranthilaka R. Ranawaka)

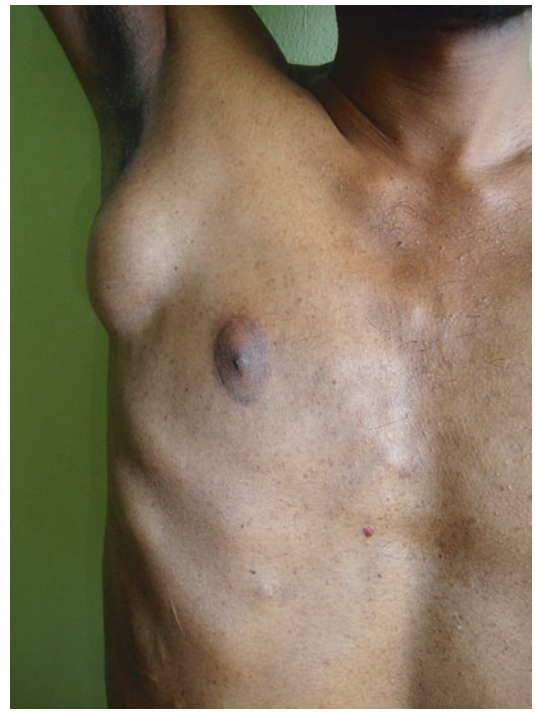

Fig. 4.7 Nodular plexiform neurofibroma in NF1 (photographed by Dr. Ranthilaka R. Ranawaka)

4.2 Sturge-Weber Syndrome (SWS)

SWS is a sporadic congenital neurocutaneous syndrome caused by a somatic activating mutation in *GNAQ*. It affects 1 in every 20,000 to 50,000 newborns. The disorder is characterized by a facial port-wine stain, leptomeningeal angiomatosis and glaucoma (Sudarsanam and Ardern-Holmes 2014).

Seizures are the most common **neurological manifestation** and occur in the first month of life. Glaucoma can develop at birth or later in life (Higueros et al. 2017).

The characteristic **cutaneous manifestation** in port-wine stain (PWS) or naevus flammeus is due to capillary or venular malformation. This presents at birth on one side or both sides in variable sizes. The colour of the rash ranges from pale pink to purple. This can be confused with salmon patches (naevus simplex), which is poorly defined, rose-coloured macules and located in the midline. But the PWS is more lateralized and have more intense colour, and the border is well defined (Higueros et al. 2017).

Management: Standard treatment for Sturge-Weber syndrome includes laser treatment for the port-wine stain, anticonvulsants, and medical or surgical treatment for the glaucoma. Prognosis depends on the extent of leptomeningeal involvement and the severity of the glaucoma (Fig. 4.8).

4.3 Tuberous Sclerosis Complex (TSC)

Tuberous sclerosis complex (TSC) is inherited by autosomal dominant with almost complete penetrance but variable expressivity. This disorder is characterized by the potential for hamartoma formation in almost every organ: central nervous system, kidney, heart, eyes, blood vessels, lungs, bone and gastrointestinal tract. An erroneous cell migration, proliferation and differentiation during embryological development can be identified pathologically. The hallmark of the disease is cortical tubers, and it is pathognomonic for cerebral tuberous sclerosis (Curatolo et al. 2002). Epilepsy is the most common **neurological manifestation** (96%) and occurs in the first months of life. This is often severe and intractable. The identification of hamartomas in more than two organ systems guides to the diagnosis. Treatment is symptomatic and organ-specific. A multidisci-

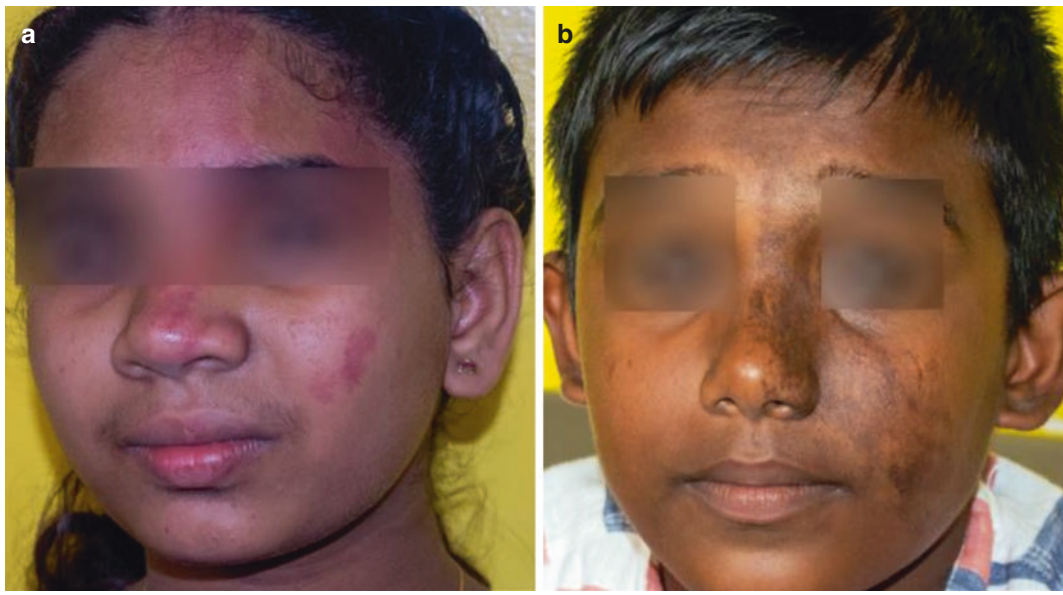

Fig. 4.8 (**a**, **b**) Port-wine stain

plinary team approach is necessary in every case (Randle 2017; Curatolo et al. 2002).

The **dermatological manifestations** are hypomelanotic macules, facial angiofibroma, shagreen patch, periungual and ungual fibroma, molluscum fibrosum pendulum and café-au-lait spots. Other uncommon skin manifestations are confetti lesions (stippled hypopigmentation), poliosis (a white patch or forelock) and thumbprint macules.

The hypomelanotic macules or "ash leaf spots" (European mountain ash tree) are the most common dermatological manifestations. They are typically rounded at one end and tapered at the other. Sometimes, an ultraviolet light (Wood's lamp) is needed to visualize the macules in fair skinned individuals. Ninety percent of TS patients will have this, and it presents at birth and almost apparent by 2 years.

The differential diagnosis of hypopigmented macules is numerous, but these should be considered (Hemady and Noble 2007).

Selected Differential Diagnosis of Hypopigmented Macule

Condition	Characteristics
Hansen's disease (leprosy)	Mycobacterial disease; macule with diminished sensation
Nevus anemicus	Solitary asymptomatic macule; pressure causes macule to transiently blend in with surrounding normal skin
Tinea versicolor	Fungal etiology; multiple asymptomatic macules with fine scales; more common in adolescents
Tuberous sclerosis	Solitary or multiple, asymptomatic, "ash-leaf spots" without scaling. Wood's lamp makes lesions prominent

The facial fibroangioma (adenoma sebaceum) is the second most common skin manifestations. It can be seen in 75% of TS patients. They appear in preschool years and grow very slowly in size and number with age. These lesions are distributed in malar region as small pink to red dome-shaped papules in a "butterfly distribution". A variation of angiofibroma is forehead plaque which occurs in 20% of TS patients. It begins to appear in early childhood and it very slowly enlarges with time. Later, it becomes as a firm and elevated plague (Figs. 4.9, 4.10, 4.11 and 4.12).

The shagreen or "leather" patch is seen in 20–30% of TS patients. The lesion is characteristically irregularly shaped, greyish-green or light brown and unevenly thickened plaque with a cobblestone or orange-peel appearance. They are typically seen in the lumbosacral area. It begins to appear during young adolescent.

The periungual or ungual fibromas (Koenen tumours) are seen adjacent to or underneath of nails, more commonly in toes than fingers. It is smooth, firm, nodular or fleshy, and occasionally, it develops following trauma. 20% of adolescent or young adult TS patients can have these lesions (Fig. 37.82).

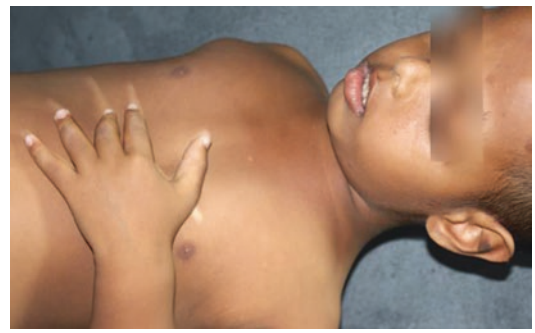

Fig. 4.9 Tuberous sclerosis complex. Hypopigmented macules and adenoma sebaceum on the face

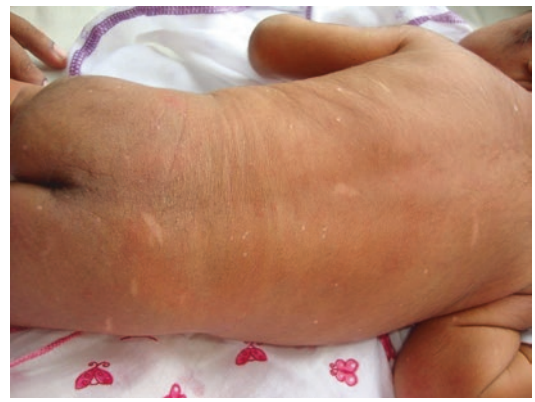

Fig. 4.10 Tuberous sclerosis complex in a newborn baby girl with white ovoid or ash leaf-shaped macules. She had multiple hypomelanotic macules (major criteria) and multiple cardiac rhabdomyomas (major criteria). The hypomelanotic macules or "ash leaf spots" are the most common dermatological manifestations in TSC and present at birth (photographed by Dr. Ranthilaka R. Ranawaka)

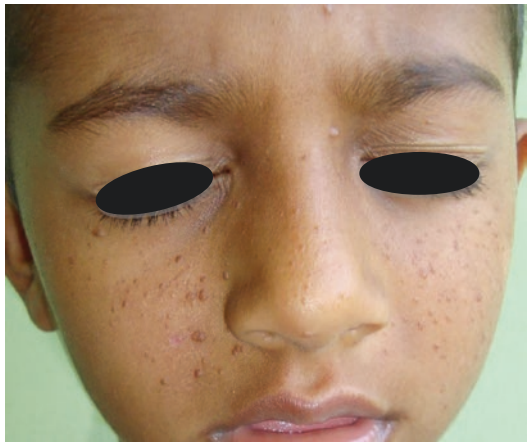

Fig. 4.11 Adenoma sebaceum (angiofibromas) in a 7-year-old boy with TSC. Angiofibromas may rarely be present at birth or develop in infancy but usually appear between the ages of 3 and 10 years and sometimes later. They often become more extensive at puberty and then remain unchanged (photographed by Dr. Ranthilaka R. Ranawaka)

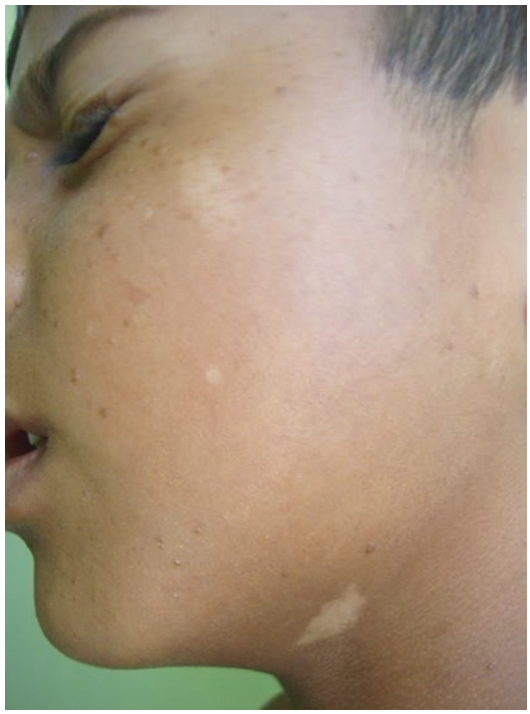

Fig. 4.12 Above child has two hypomelanotic macules (**ash leaf macules**) on the face and neck. They appear at birth or early infancy. They are valuable clinical signs which suggest TCS in infants with convulsions. Adenoma sebaceum and ash leaf macules are pathognomonic in TCS (photographed by Dr. Ranthilaka R. Ranawaka)

The molluscum fibrosum pendulum is soft, large, pedunculated, flesh-coloured papules and nodules. It is commonly seen in flexural areas: neck and axilla.

Café-au-lait patches less than six in numbers are observed in 30% of TS patients.

Management: The most common neurological manifestations of TSC are epilepsy, mental retardation and autistic behaviour. Epilepsy usually occurs during childhood, and they need anticonvulsant medications through their life. In adulthood, multiple hamartomas are distributed in the kidney and lung. Individuals with lesions more than 4 cm in diameter or with extensive renal involvement should be referred to a nephrologist or urologist (Randle 2017).

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