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Dermatologic Manifestations of Neurologic Disease

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Abstract

Background: Many diseases present with both neurologic and dermatologic manifestations. Eight such clinical cases are presented, along with clinical photographs of the skin lesions, in the format of a self-evaluation. Each case is followed by a discussion and a brief review of the characteristic cutaneous and neurologic findings. The intent is to demonstrate classic dermatologic manifestations of diseases seen by neurologists.

Introduction

Many disorders have a combination of neurologic and dermatologic findings in patients. This manuscript provides an overview of neurocutaneous disorders and organizes them into clinically relevant groups of use to the practicing physician. Many neurological conditions are accompanied by skin changes, which frequently appear before the onset of the neurological symptoms. In some cases a rash may herald the start of an infectious process. In others, skin changes may mirror pathological processes that are also occurring in the brain or peripheral nerves. Careful examination of the skin can therefore provide important clues when making a neurological diagnosis, allowing early treatment and avoiding unnecessary tests. Instead of presenting an exhaustive list of cutaneous manifestation of every neurological condition, we aim to provide practical knowledge for the non-dermatologist to aid neurological differential diagnosis. We highlight the more common skin changes that occur in association with stroke, peripheral neuropathy, meningitis, encephalitis, malignancy and HIV.

In addition, we cover the most frequently encountered neurocutaneous conditions and finally, we will remind the reader of skin changes associated with adverse reactions to drugs commonly used by neurologists. This article aims to cover the most important and meaningful dermatological disorders that you may encounter within neurology. An exhaustive list of all potential cutaneous findings would not necessarily be useful in diagnosis and management; rather, we aim to provide a practical selection of management altering dermatological signs within the context of common neurological presentations. We also review some commonly encountered neurocutaneous disorders, skins lesions at different

stages of HIV/AIDS and remind the reader of important drug reactions [**1,2**].

A-Neurocutaneous Disorders Associated With Stroke

In young patients, the skin can provide important clues as to the cause of stroke [**1,2**]. There are some skin manifestations in patients with stroke as belows;

1.Livedo reticularis (Cutis marmorata): It is characterised by mottled red–blue discolouration, net-like appearance, especially over the legs, and exacerbated by cold. Livedo reticularis is not uncommon in young women and can be completely benign. However, it may indicate an underlying hyperviscosity syndrome or vasculitis. It appears in 25% of those with systemic lupus erythematosus and antiphospholipid syndrome and is a common association of vasculitis involving medium sized vessels like polyarteritis nodosa and small sized vessels like cryoglobulinemia. *Sneddon*'s syndrome is characterised by widespread livedo reticularis in association with multiple strokes. Here, patients tend to have high titres of antiphospholipid antibodies and typically livedo reticularis develops several years before stroke. Patients with polycythaemia may appear plethoric and, in addition to livedo, often complain of itchy skin, especially when exposed to warm water [**3**].

2. Purpura: Purpura is non-blanching red or purple macular lesions. A petechia is a small, less than 1-2 mm diameter, red or purple spot on the body, caused by a minor hemorrhage. Purpura and petechia from bleeding beneath the skin are common in the older patient but may be significant in young patients with stroke. Frequently, this indicates small vessel vasculitis and platelet disorders, including thrombotic thrombocytopenic purpura [**2**].

3. Telangiectasia: Telangiectasia is small vascular lesions, prone to haemorrhage. Hereditary haemorrhagic telangiectasia is characterised by telangiectasia of the skin and mucosal linings of the nose and gastrointestinal tract, with brain involvement in 10% of cases. Most patients complain of nosebleeds. Telangiectasias are best seen on the lips, tongue, nose and fingers [**1**].

4. Angiokeratomata: It is characterised by small red or black vascular malformations. Fabry's disease is a rare X linked recessive disorder caused by a deficit in the enzyme α-galactosidase, resulting in deposition of glycolipids in blood vessels and various organs. There is multisystem involvement. Typically patients are male, presenting in childhood or early adolescence with painful neuropathy and in adulthood with ischaemic strokes. Discrete angiokeratomata appear in a 'bathing suit' distribution early in disease and usually before any neurological symptoms [**1**].

5. Lax stretchy skin/hypermobility: Pseudoxanthoma elasticum is associated with premature atherosclerosis and aneurysm formation. It manifests cutaneously as patches of lax redundant skin like plucked chicken appearance, typically around the neck and inguinal folds. Arterial dissection and aneurysm formation also occur in Ehlers–Danlos syndrome type IV as a result of defective collagen, which causes thin translucent skin, easy bruising and joint hypermobility [**2**].

6. Xanthomata and xanthelasmata: It is characterised by yellow papules and plaques with cholesterol deposits [**2**].

7. Varicella zoster infections: On rare occasions following trigeminal shingles, varicella zoster virus may infect arteries in close proximity to the trigeminal ganglion and cause ischaemic stroke [**2**].

8. Diabetic skin manifestations: Dermatological examination can also provide clues to the more common risk factors for stroke. Dyslipidemia commonly manifests in the skin, especially familial forms. Neurologist should look specifically for tendon xanthomata, xanthelasmata, eruptive xanthomata and palmar striae. And they do not forget to look for nicotine stained fingers and hair. Diabetes mellitus has many cutaneous manifestations, including necrobiosis lipoidica diabeticorum (a well demarcated waxy yellow/brown plaque, usually on the shins, with surface telangiectasia and ulceration), non-specific dermopathy (red/brown discolouration often over the knees), blisters or acanthosis

nigricans (velvety pigmented skin in body folds) [**2**].

Antiphospholipid Syndrome

Antiphospholipid syndrome is a hypercoagulable state resulting from antibodies that neutralize anionic phospholipids on endothelial cells and platelets. It is a multisystemic disorder, and patients may present with a wide range of neurologic manifestations, fetal loss, mild thrombocytopenia, valvular heart disease, and livedo reticularis. Antiphospholipid syndrome is associated strongly with systemic lupus erythematosus (SLE) and patients with SLE are considered to have secondary antiphospholipid syndrome. The term primary antiphospholipid syndrome is reserved for cases of unknown etiology. The disorder is characterized by high titers of antiphospholipid antibodies (APLA), ie, lupus anticoagulant and anticardiolipin antibodies. Studies suggest that antibodies are not directed against phospholipids but are directed at phospholipid-binding proteins such as B2-glycoprotein I and prothrombin. The cutaneous manifestations most commonly seen include livedo reticularis and leg ulceration. Livedo reticularis is a mottled, bluish, netlike discoloration that changes from red-blue to deep blue on cold exposure. This nonspecific reaction pattern has been reported in other disorders, such as polyarteritis nodosa, cryoglobulinemia, disseminated intravascular coagulation, and endocarditis. Other cutaneous manifestations, including acrocyanosis (*Raynaud*-like phenomenon) and *Degos* malignant atrophic papulosis, are rare findings. Neurologic complications may be misdiagnosed as multiple sclerosis. Clinical findings include multiinfarct dementia, focal deficit, epilepsy, and recurrent stroke. Transitory weakness, vertigo, ataxia, and dysarthria may occur. Neurocognitive defects including dementia, atypical migraines, depression, and delusional states also have been reported [**4**].

Research to predict outcome in patients with antiphospholipid syndrome has shown that patients with elevated IgG have increased risk of recurrent thrombotic events. Tektonidou et al predicted that risk of a second event was highest in patients with B2-glycoprotein I antibodies in whom autoimmune hemolysis was the first event. Patients without antibodies, who had recurrent abortions as their first event, were at lowest risk. The study reported that recurrent events are of the same type as the presenting symptom. Therefore, initial clinical features can help predict the prognosis of the disorder. Specific clinical features tend to cluster during the course of the disease. A variety of therapies have been tried. Use of long-term anticoagulants to maintain the international normalized ratio at 3 or greater may help prevent recurring thromboembolism. Aspirin is of clinical benefit and may help decrease the incidence of fetal loss in some patients. Plasmapheresis and cyclophosphamide have been used. Ancrod (purified pit viper venom) has been used successfully in one patient. A review of clinical and laboratory characteristics of 50 patients by *Asherson* et al described a 70% survival rate in patients treated with anticoagulation, steroids, and treatments that decrease antiphospholipid antibodies, such as plasmapheresis and/or intravenous IgG. Statins have been used in antiphospholipid syndrome because of their antithrombotic, anti-inflammatory, and pleiotropic effects on vascular endothelium. Statins may block the antiphospholipid-induced endothelial cell activation, which is thought to be a mechanism of thrombus formation in antiphospholipid syndrome [**4**].

Sneddon Syndrome

Sneddon syndrome is characterized by livedo reticularis and multiple strokes resulting in dementia. Antiphospholipid antibodies and anti–B2-glycoprotein antibodies also have been detected in some patients with this disorder. The cutaneous manifestation of livedo reticularis may precede the cerebrovascular episodes, thus alerting the clinician[**5**].

B- Neurocutaneous Disorders Associated With Peripheral Neuropathy

Many neuropathies are associated with skin changes. Some reflect underlying vitamin deficiencies (B12, niacin) while others suggest microvascular damage (angiokeratoma, diabetes mellitus, lupus erythematosus, amyloid, small vessel vasculitis) or infection (*Lyme* disease, syphilis, leprosy).

1. Hyper/hypopigmentation, especially in sun-exposed areas. Pigmentary changes are seen in leprosy, syphilis and pellagra. Leprosy remains a common cause of neuropathy in South America, East Africa and the Indian subcontinent. Tuberculoid leprosy is characterised by anaesthetic hypopigmented lesions whereas lepromatous leprosy results in cutaneous nodules containing massive numbers of Mycobacterium leprae. Neurological complications associated with syphilis usually present in secondary or tertiary disease. Primary syphilis is typically characterised by a painless, firm ulcerated lesion (chancre) 3–90 days after infection and secondary syphilis, 4–10 weeks later, with a diffuse macular or papular rash which often involves the palms and soles.

2. Erythema nodosum: It is characterised by tender red nodules, appearing on the shins. Erythema nodosum may indicate early lupus erytematosus or sarcoidosis.

3. Photosensitivity, in sun exposed areas: Photosensitivity is a feature of lupus and occurs in pellagra.

4. Purpura and Raynaud's phenomenon: Purpura is characterised by non-blanching red or purple lesions (<3 mm=petechiae). *Raynaud* phenomenon manifests as recurrent vasospasm of the fingers and toes and usually occurs in response to stress or cold exposure. In this phenomenon fingers and toes go white, blue, then red. Small vessel vasculitis may cause polyneuropathy or mononeuritis multiplex and is frequently associated with skin changes, which include a non-blanching purpuric rash, livedo reticularis and Raynaud's phenomenon.

5. Erythema chronicum migrans: It is characterised by an expanding, annular rash. In Lyme disease, 80% of patients develop a circular expanding, flat or slightly elevated lesion (erythema chronicum migrans) at the site of a tick bite, which is painless. Neurological symptoms develop in approximately 15–20% of cases [**1, 2**].

Diabetes Mellitus

Diabetes mellitus is the most common systemic endocrine disorder; an increasing number of patients are diagnosed each year. Neurologic complications of type 1 and type 2 diabetes mellitus are similar; the most common is peripheral neuropathy. Other important complications of diabetes result from accelerated atherosclerosis that places patients at high risk for cerebrovascular accidents, hypertension, and cardiovascular disease. Associated cutaneous manifestations of diabetes include necrobiosis lipoidica diabeticorum (NLD), acanthosis nigricans, and bullous diabeticorum. NLD occurs in 0.3% of patients, and one study by Little et al reported 0.8% prevalence in 82% of patients with type 1 diabetes. NLD is 3 times more common in women, and 60% of patients with NLD have diabetes. Screen patients with NLD for diabetes. Lesions start as sharply demarcated erythematous papules that become well circumscribed and annular and most commonly occur pretibially. Lesions progress to form shiny yellow-brown plaques with central atrophy and telangiectases. Control of diabetes does not necessarily result in remission of NLD. Treatment consists of occlusive dressing, topical steroids, aspirin, dipyridamole, pentoxifylline, and whirlpool therapy. Intralesional steroids have been used but can cause tissue breakdown. Reports have shown marked improvement using 0.05% tretinoin cream applied before bed. Topically applied bovine collagen also may enhance wound healing. New treatment strategies include cyclosporin A, infliximab, or tacrolimus, which can be used topically or systemically.

Acanthosis nigricans can be seen in a variety of disorders. More severe forms are associated with malignant disease, and milder forms can occur in obesity and in patients with insulin resistance, despite the absence of overt diabetes. Characteristic skin changes include velvety hyperpigmented plaques in the neck and axillary regions, and patients often complain of dirty skin. More severe forms of acanthosis nigricans can become generalized over the knuckles, extensor surfaces, and may involve mucosal surfaces. A rare cutaneous finding in diabetes is bullous diabeticorum. These tense bullae can arise spontaneously on the distal extremities. The bullae are subepidermal, with the plane of separation at the basement membrane zone above the basal lamina, and heal without scarring. They may be chronic and recurrent, especially in older patients. Only 100

cases have been reported in the past 70 years, but according to a report by Lipsky et al of 12 patients in an 8-year period, this disorder may be underdiagnosed [**1, 2**].

Lyme Disease

Lyme disease was first described in 1975 in Lyme, Connecticut. Currently, more than 90% of cases occur in the northern hemisphere. Lyme disease is a multisystemic disorder caused by the spirochete Borrelia burgdorferi transmitted by a tick bite. During the bite, the risk of transmission increases with the duration of the tick's attachment. The degree of engorgement seen in the tick is a rough measure of the risk of transmission. Cutaneous manifestations occur in 65-80% of patients. Erythema chronicum migrans (ECM) begins as a small papule, commonly at the site of the tick bite. The lesion progresses centrifugally over weeks and can become large. Central clearing gives the lesion the typical bull's-eye appearance. The area can irritate the patient, and regional lymphadenopathy may develop. Secondary lesions have been reported and usually are multiple erythematous macules with central clearing, similar to ECM but smaller. A bluish-red solitary nodule as borrelial lymphocytoma may develop at the site of the tick bite or at a distant location such as the ear, nose, scrotum, or areola region. Acrodermatitis chronica atrophicans consists of atrophic, edematous, bluish-red plaques on the extensor aspect of the lower legs and elbows and most commonly occurs in women. These may resemble scleroderma or lichen sclerosus6. More than 50% of patients have a migrating peripheral neuropathy, usually occurring 2-3 months after the onset of infection. The term neuroborreliosis describes the many neurologic complications that occur, such as lymphocytic meningitis, cranial neuritis, facial palsy, ophthalmoplegia, trigeminal neuralgia, vestibular neuritis, and paralysis. Neurologic complications cannot be excluded on the basis of a negative cerebral spinal fluid antibody analyses. Late complications, occurring after 1 year, are chronic peripheral neuropathy, MS-like demyelinating disease, dementia, and extreme fatigue. Arthritis in one to a few large joints is a common manifestation and develops in as many as 70% of untreated patients. Patients with human leukocyte antigen D4 haplotype may be at increased risk for chronic arthritis resulting from Lyme disease. Carditis, conduction abnormalities, and heart blocks also may occur. Antibiotics are 90% curative in the early stages but become less effective as the disease progresses. Consider prescribing doxycycline (100 mg bid) or amoxicillin (500 mg tid) for 14-21 days, or 28 days if arthritis is present. For patients with carditis or neurologic complications, ceftriaxone (2 g IV qd) for 14-21 days is recommended. In pregnant patients, use amoxicillin (500 mg PO tid) for 21 days. If they are allergic to penicillin, use azithromycin (500 mg PO qd) for 7-10 days [**6**].

Arsenic Poisoning

Arsenic is a tasteless and odorless substance and often is used in insecticides, fabric dyes, the tanning of animal hides, and certain printing processes. Contaminated drinking water can be a common source of chronic exposure. At one time, arsenic was used medically to treat disorders such as psoriasis. Many cases of arsenic poisoning occur each year as a result of accidental or industrial mishaps, and its characteristics and availability make it a popular choice for intentional poisoning. Cutaneous manifestations include hyperpigmentation occurring in a guttate pattern with increased pigment in the areola and inguinal folds. Mees lines are transverse bands of leukonychia and can occur 2-3 weeks after an acute poisoning or in persons with chronic exposure. Associated neurologic effects include subacute sensorimotor polyneuropathy, convulsions and, in severely affected patients, coma and death. Treatment begins by removing the offending agent and by chelating with British antilewisite (BAL). BAL (2,3-dimercaprol) is a traditional chelating agent that has been used clinically in arsenic poisoning since 1949. In humans and experimental models, the antidotal efficacy of BAL has been shown to be most effective when administered immediately after the exposure [**1, 2**].

C- Neurocutaneous Disorders Associated with Meningitis and Encephalitis

Determining whether a patient has infective or non-infective meningitis/encephalitis can

drastically change early management. Many patients with an infectious aetiology develop skin signs before the causative organism is proven on culture or on serological testing.

1. Purpura and petechiae: A petechial rash in a sick child indicates meningococcal meningitis until proven otherwise.

2. Maculopapular rash: These lesions are characterised by blanching, flat macules and raised papules. Rocky Mountain spotted fever, a tick-borne rickettsial illness, presents with some type of rash in 90% of cases. Typically macules appear on the wrists, ankles and forearms 4 days after the tick bite. By day 6, approximately half of patients have developed a characteristic red spotted, petechial rash, which in most cases affects just the palms and soles. Leptospirosis also presents with a maculopapular rash in 50% of cases and, when occurring with jaundice and recent exposure to contaminated water, is highly suggestive.

Non-infectious causes including Behçet's disease, sarcoidosis, small vessel vasculitis and Sjögren's syndrome also result in skin changes. These changes not only guide the physician on further investigations but may prove invaluable if seeking a histological diagnosis. The neurologists should look for;

- Mouth/genital ulcers
- Erythema nodosum
- Lupus pernio: This lesions are characterised by raised indurated, purple, papules and plaques appearing on nose, ears, cheeks and fingers.
- Skin metastases

Patients with *Behçet*'s disease all develop mouth ulcers, whereas only 25% of those with sarcoidosis have cutaneous disease including erythema nodosum and lupus pernio. Sweet's syndrome is characterised by painful red papules and plaques, and frequently occurs with leukaemia [**1,2**].

D. Neurocutaneous Disorders of Viral Origin

1. Herpes Varicella Zoster

Varicella-zoster virus is a herpes virus that causes a primary infection of varicella. The virus is latent in cranial nerve and dorsal root ganglia and can reactivate years later as herpes zoster. More than 300,000 cases of zoster are seen in the United States every year. Crops of diffuse, painful, pruritic vesicles and papules that occur in a dermatomal distribution characterize zoster. The disease is self-limiting and usually resolves within 2-3 weeks. Cutaneous manifestations are present in almost all cases of zoster. The phrase "dewdrops on a rose petal" describes the appearance of the vesicles on an erythematous base. The affected dermatome is painful to the touch, and prodromal pain may precede the development of visible lesions. Although zoster can occur anywhere along the neural axis, thoracic dermatomes are affected most commonly, followed by the face. Southern blot analysis and in situ hybridization has detected the virus in human trigeminal and thoracic ganglia. Polymerase chain reaction (PCR) analysis further confirms the clinical findings of thoracic and trigeminal dermatomes as the most common site of reactivation [**7, 8**].

Zoster occurring in the ophthalmic division of the trigeminal nerve may result in keratitis, a potential cause of blindness. Immediately refer these patients to an ophthalmologist for slit lamp examination. Of patients with ophthalmic nerve zoster, two thirds have eye involvement, especially when vesicles occur on the side of the nose, indicating involvement of the nasociliary nerve (*Hutchinson* sign). Other complications can develop following varicella or zoster infections. *Ramsay-Hunt* syndrome is the reactivation of the virus in the seventh cranial nerve, causing one-sided facial weakness combined with lesions of the ipsilateral external ear, herpes zoster oticus, or zoster of the hard palate. Ophthalmoplegia, optic neuritis, and other cranial neuropathies may develop. Arm weakness and, less frequently, diaphragmatic paralysis may occur with cervical zoster. Leg weakness with bladder and bowel dysfunction may occur with lumbosacral zoster. Rarely, myelitis or encephalitis occurs after the development of skin lesions. Recently, studies have shown that infection of blood vessels by the virus causes encephalitis. Granulomatous arteritis results from large vessel arterial disease and occurs mainly in immunocompetent patients. Encephalitis resulting from small vessel disease occurs exclusively in immunodeficient patients. Long-term use of low-dose steroids

may cause an increased susceptibility to myelitis and encephalitis [**7, 8**].

Treatment of zoster includes the following: Analgesic and famciclovir, valacyclovir (1000 mg tid) or oral acyclovir (800 mg 5 times per d) for 7 days to decrease new lesions. Treatment is ideally started within 3 days of rash appearance. Zoster is common in older patients, especially those older than age 60 years. Of patients who have had chickenpox, 2% develop zoster. Patients who develop chickenpox younger than age 1 year are predisposed to develop zoster before age 60 years. Millions of children worldwide have received the varicella vaccine, and vaccination is recommended by the American Academy of Pediatrics. Vaccine prevents the primary infection; however, the virus remains latent, and vaccination does not prevent later development of zoster. Pediatric herpes zoster has been reported in children who received the vaccine or who had clinical chickenpox at a very young age. A vaccine (Zostavax) has been approved by the US Food and Drug Administration for the prevention of herpes zoster in individuals age 50 years and older. In a randomized, double-blinded controlled trial, the zoster vaccine reduced the burden of illness for individuals aged 60 years or older by 61.1%, decreased the incidence of postherpetic neuralgia by 66.5%, and reduced the incidence by 51.3%. In March 2011, the Food and Drug Administration (FDA) lowered the approved age for use of Zostavax to 50-59 years. Zostavax was already approved for use in individuals aged 60 years or older. Zostavax significantly reduced the risk of developing zoster by approximately 70%. The most common complication of zoster is postherpetic neuralgia. Pain often is debilitating and can persist indefinitely. A prognostic factor is age, and this complication usually does not occur in immunocompetent patients younger than 50 years. After age 60 years, more than 40% of patients develop postherpetic neuralgia. Optimal therapy for prevention has not been established. Although controlled trials have not shown oral antiviral drugs to be effective, such medications are administered empirically to patients older than 60 years. Studies of other therapeutic options have been initiated to discover how to prevent postherpetic neuralgia and include steroids, interferon alfa-n3, amantadine hydrochloride, adenosine monophosphate, and levodopa with benserazide. Different therapies have been tried to treat postherpetic neuralgia. Tricyclic antidepressants and anticonvulsants have provided relief to some patients. Steroids may help by reducing inflammation. Topical aspirin, capsaicin, and anesthetic agents may help relieve pain [**7, 8**].

2 - HIV and AIDS

NHIV and AIDS cause skin involvement in 90% of patients. This often precedes neurological symptoms, which in turn appear in 75% of cases. Skin lesions are due to opportunistic infections, tumours and adverse drug reactions.

1. Seroconversion: 50% of those infected with HIV develop acute retroviral syndrome 2–4 weeks after exposure. Following a short flu-like illness, a generalised maculopapular rash develops.

2. Established HIV (CD4 cell count 200–500/mm^3):

a. Bacterial infections: Folliculitis, cellulitis, impetigo, abscesses and bacillary angiomatosis

b. Fungal infections: Candidiasis, pityriasis versicolor and seborrhoeic eczema: Intractable seborrhoeic dermatitis may be the first cutaneous manifestation of HIV and often in patients with AIDS associated dementia or CNS disease.

c. Viral infections: Molluscum contagiosum, oral hairy leukoplakia, herpes zoster (shingles), viral warts, and herpes simplex may occur in patients with HIV positive.

d. Infestations: Norwegian scabies

T cell dysfunction and altered immunity allow opportunistic infections and promote tumour growth. Staphylococcal skin infections may seed haematogenously and cause spinal epidural abscess. Infection with Bartonella species may cause meningitis or encephalitis, and often manifests cutaneously as bacillary angiomatosis. Viral infections may also cause encephalitis and frequently cause skin disease in HIV. Herpes simplex infections lasting for more than a month are common and herpes zoster may be recurrent or multi-dermatomal. *Epstein Barr* virus causes oral hairy

leukoplakia while cytomegalovirus may cause a maculopapular rash and painful polyradiculopathy.

e. Other: Acne, atopic eczema, generalised pruritus and acquired ichthyosis can be seen in patients with AIDS.

3. AIDS (CD4 cell count <200/mm3): Tumours such as Kaposi's sarcoma and lymphoma of the skin: Kaposi's sarcoma is associated with human herpes virus 8 and in addition to cutaneous lesions may affect peripheral nerves and the CNS. Neurological symptoms are variable, depending on location and whether lesions cause infarction or haemorrhage. Cutaneous drug reactions are common in HIV, especially with antibiotics including sulphonamides [**9**].

E-Inherited Neurocutaneous Disorders

Many neurocutaneous disorders have a genetic basis but in the absence of a strong family history, neurologists need to be aware of the common cutaneous manifestations, especially in children presenting with seizures and learning difficulties. In some cases, patients do not present until adulthood [**1**].

1-Neurocutaneous Disorders with Autosomal Dominant Phenotypes

a. Neurofibromatosis Type 1

Half of new cases arise spontaneously with no family history. Symptoms usually start in childhood with learning difficulties, seizures and visual disturbance due to optic nerve tumours. The diagnosis can be made on the basis of skin lesions with at least two of the following: *café au lait* macules (6+), neurofibromata (2+) or plexiform neurofibromta (1+), axillary/inguinal freckling, optic glioma, Lisch nodules (2+), osseous lesion and first degree relative with NF1. Although detectable at birth, lesions usually increase in number but fade in colour with advancing age. Neurofibromatosis type 1 is an autosomal dominant disorder. The gene locus is on band 17q11.2, but spontaneous mutations occur in approximately 50% of patients. As the most common genetic disorder of the nervous system, NF1 affects approximately 1 in 3000 people. NF1 occurs with equal frequency in men and women without regard to race or ethnic background [**10**].

The National Institutes of Health (NIH) consensus criteria for the diagnosis of NF1 require 2 or more of the following:

• *Café au lait* macules larger than 5 mm in diameter in prepubertal individuals and larger than 15 mm in diameter in postpubertal individuals and numbering 6 or more

• Neurofibromas of any type or 1 plexiform neurofibroma and numbering 2 or more

• Axillary freckling (*Crowe* sign) or inguinal freckling

• *Crowe* sign, axillary freckling, in neurofibromatosis type I.

• Optic glioma

• *Lisch* nodules (iris hamartomas; see image below) in more than 90% of patients younger than 6 years and numbering 2 or more

• Dysplasia of the sphenoid or thinning of long bone cortex with or without pseudoarthrosis

• First-degree relative with NF1 [**10**]

These criteria are useful in the clinical diagnosis of NF1; however, some children younger than 8 years may not appear to have NF1 because of the late onset of the characteristic features used in the classification.

Café au lait spots are characterised by flat patches of hyperpigmentation. Neurofibroma is benign non-painful skin tumours that commonly arise during puberty. They can also occur subcutaneously in 20% as painful rubbery tumours. Plexiform neurofibromata are diffuse, deep growths along nerve plexuses or dorsal nerve roots, which often cause neuronal compression. Neurofibromas occur in almost all patients affected with NF1. Neurofibromas are benign tumors and almost always involve cutaneous, subcutaneous, or dermal tissues. They comprise Schwann cells, nerve fibers, fibroblasts, vascular elements, mast cells, and myxoid matrix. Neurofibromas are classified into 4 types. The most common type is cutaneous neurofibromas. These neurofibromas are nonpainful, soft, flesh-colored tumors that can range from a few millimeters to 2 centimeters in diameter. The underlying dermal defect allows reduction of the tumor with light pressure,

which is termed the buttonhole sign. Subcutaneous neurofibromas occur in 20% of patients and are painful, firm, rubbery tumors. Nodular plexiform neurofibromas comprise a large network of subcutaneous neurofibromas that occur along nerve plexuses or dorsal nerve roots. As a result of their location, these tumors cause severe neurologic deficits. Diffuse plexiform neurofibromas occur in approximately 5% of patients and are considered specific to NF1. They usually are congenital and may have overlying hyperpigmentation and hypertrichosis. These tumors are highly vascular and may involve deep structures that erode bone and extend to visceral areas. These tumors are like icebergs; what appears small on the outside may be extensive on the inside and involve vast regions of the mediastinum or retroperitoneum. Of plexiform neurofibromas, 5-6% can progress to malignant peripheral nerve sheath tumors or Triton tumors (a rare variant of malignant peripheral nerve sheath tumors), which are severely painful and carry a poor prognosis [**10**].

Chromosome 17 encodes the tumor suppressor neurofibromin. Neurofibromin suppresses the products of ras by enhancing its guanosine triphosphatase activity, thus reducing the requirement for nerve growth factor or neurotrophins. The loss of neurofibromin, which is expressed in neurons, Schwann cells, the adrenal medulla, and white blood cells, may contribute to tumor progression. Patients are at risk for developing numerous benign and malignant tumors. CNS neoplasms are of particular concern in patients with NF1. Optic gliomas are the most common CNS tumors, occur in approximately 15% of patients, and may result in blindness if left untreated. Other associated CNS neoplasms are astrocytomas, vestibular schwannomas (acoustic neuroma), and, less often, ependymomas and meningiomas. Non-CNS tumors associated with NF1 include neurofibrosarcoma, rhabdomyosarcoma, pheochromocytoma, Wilms tumor, nonlymphocytic childhood leukemia, and visceral neurofibroma. Neurofibrosarcoma is the main cause of death of NF1 patients younger than 40 years. It may develop de novo or from sarcomatous degeneration of a preexisting plexiform neurofibroma. It should be suspected in patients with new onset of symptoms or in patients with changing symptoms. At imaging, neurofibrosarcoma is characterized by a large heterogeneous tumor invading adjacent structures. Other complications of NF1 include congenital glaucoma, hydrocephalus, seizures, learning disabilities, psychosocial difficulties, and endocrine disturbances. Hypertension can occur in NF1 and may result from a pheochromocytoma or renal artery stenosis. Pheochromocytoma occurs in 0.1-5.7% of patients with NF1 and is more common in adults. Other endocrine disturbances, such as growth hormone deficiency, short stature, and precocious puberty, have been reported in patients with NF1. Case reports of NF1 and juvenile xanthogranulomas have been associated with juvenile chronic myelogenous leukemia. *Zvulunov* et al found a 30- to 40-fold higher than expected rate for the association of NF1 with juvenile xanthogranulomas and juvenile chronic myelogenous leukemia [**10**].

b. Neurofibromatosis Type 2

Neurofibromatosis type 2 is an autosomal dominant disorder caused by mutation in the schwannoma tumor suppressor gene on bands 22q11-13.1. This gene codes for schwannomin/merlin proteins, which are membrane-organizing proteins and may affect tumor suppressor activity at the cell membrane level. Evidence for interfamilial clinical variability and spontaneous mutations exists in 50-70% of patients. NF2 is less common than NF1, occurring in 1 in 35,000 live births without regard to sex, race, or ethnic background. The neurologic hallmark of NF2 is the development of bilateral vestibular schwannomas that are not associated with NF1. Skin lesions are less frequent in NF2 although some patients have skin tumours that resemble neurofibromata and café au lait spots. Freckling is unusual. The NIH Consensus Developmental Conferences provide guidelines for use of the term neurofibromatosis type 2. They suggest the term vestibular schwannoma in place of the term acoustic neuroma to reflect the anatomic site of the tumor. Evidence suggests that 2 subtypes of NF2 exist, which are (1) a milder variant (*Gardner*) resulting from missense and splice-site germ-line mutations and (2) a severe variant (*Wishart*) resulting from frameshift and

nonsense mutations. Onset of the disorder frequently appears at age 15-30 years [**11**].

Diagnostic criteria for NF2 include the following:

• Bilateral vestibular schwannomas (visualized with CT scan or MRI)

• A first-degree relative with the disease plus a unilateral vestibular schwannoma before age 30 years

• Any 2 of the following: neurofibroma, meningioma, glioma, schwannoma, or juvenile posterior subcapsular opacity [**11**]

Cutaneous manifestations in NF2 are less common than NF1. Of patients with NF2, two thirds have a skin manifestation. Neurofibromas occur less commonly than in NF1. Plexiform neurofibromas are unusual, and café au lait macules tend to be fewer and lighter in pigmentation; only 8% of NF2 patients have more than 3 macules. Axillary or inguinal freckling is not present. Cutaneous and subcutaneous flat or spherical schwannomas often occur on peripheral nerves. Most commonly, schwannomas are superficial raised papules with overlying pigment and hair. Subcutaneous spherical nodular schwannomas occur on peripheral nerves of the limbs and trunk and often can be palpated [**11**].

The most common neurologic finding is the presence of vestibular schwannomas; however, schwannomas may occur on any of the cranial nerves except for the olfactory nerve. Pressure on the vestibulocochlear and facial nerve complex can cause symptoms of hearing loss with intermittent tinnitus, unsteady gait, and facial weakness. Advise patients to avoid swimming under water, especially alone, because of the association with underwater disorientation. Other tumors of the CNS occur in NF2, such as intracranial and spinal meningiomas, astrocytomas, and ependymomas. Ocular manifestations include juvenile posterior subcapsular lenticular opacity, retinal hamartomas, optic disk glioma, and optic nerve meningioma. Lisch nodules are not associated with NF2 [**11**].

c. Tuberous sclerosis

Tuberous sclerosis also has an autosomal dominant pattern of inheritance but two-thirds of cases arise spontaneously. Seizures, learning difficulties and autism develop in early childhood. Skin involvement occurs in 75% of patients and is also early. Tuberous sclerosis is an autosomal dominant disorder in approximately 50% of patients; in the remaining 50% of patients, the disorder occurs as a result of spontaneous mutation. In 1908, Vogt first described tuberous sclerosis as a triad of mental retardation, epilepsy, and adenoma sebaceum; however, this triad is present in less than one third of patients. The term epiloia indicates epilepsy, low intelligence, and adenoma. In tuberous sclerosis, 2 gene loci have been identified, TSC1 and TSC2. TSC1 has been mapped to band 9q34, which codes for a 130-kd protein (termed hamartin) and is a probable tumor suppressor gene. TSC2 has been mapped to band 16q13.3 and codes for an amino acid protein (termed tuberin), which has a region of homology with the GTPase-activating protein GAP3. GTPase regulates cell proliferation, and current studies suggest tuberin may mediate this activity. The genetic heterogeneity produces subtle differences in the phenotype. This may be explained by the function of hamartin and tuberin as part of the same intracellular pathway. Prevalence has been estimated to range from 1 case per 5,800 population to 1 case per 10,000 population, occurring equally between males and females of all races. Expression is highly variable among families [**12**].

In tuberous sclerosis, angiofibroma, Shagreen patches, Ash leaf macules and periungual fibroma are seen as cutaneous manifestations. Cutaneous manifestations associated with tuberous sclerosis may be present at birth. In approximately 87% of patients, congenital hypopigmented macules are found. These ash-leaf macules are the earliest and most characteristic finding and can be accentuated on Wood lamp examination. Polygonal macules are the most common type. Another type is Confetti macules, which are 1 to 3 mm, hypopigmented, and spotlike macules commonly located on the pretibial area. Melanocytes are present in the macules; however, their transfer and synthesis are impaired. Shagreen patch, a connective tissue nevus, may occur on the trunk, most often in the lumbosacral region. Shagreen patch is a 1- to 10-cm, flat, flesh-colored plaque with an orange peel appearance. Facial angiofibromas are diagnostic of tuberous sclerosis and usually appear in children aged 4-10 years. These typically are

firm, smooth, red-to-pink papules consisting of hyperplastic blood vessels and collagen, occurring on the nasolabial folds, cheeks, and chin. Successful treatment of facial angiofibromas has been reported with podophyllin, but this should be considered experimental. Subungual and periungual fibromas are firm flesh-colored fibromas in the nail matrix or bed that result in destruction of the nail plate. *Koenen* tumors are common in tuberous sclerosis, and surgical excision is curative. Other associated cutaneous findings include fibrous plaques on the face, *café au lait* macules, and port-wine hemangiomas [**13**].

Neurologic symptoms often are the first presenting sign and begin as focal or generalized seizures. Infantile spasms, tonic-clonic seizures, and complex partial and myoclonic seizures are the most common forms. Of children with infantile spasms, 10% have tuberous sclerosis. Cortical tubers are characteristic to tuberous sclerosis. These are potatolike nodules of glial proliferation occurring anywhere in the cortex, ganglia, or ventricle walls. Other CNS findings include mental retardation, subependymal hamartomas, paraventricular calcifications, and giant cell astrocytomas. Over time, subependymal nodules and cortical tubers can become calcified. Tuberous sclerosis is a multisystemic disease. Retinal hamartomas (phacomata) are white streaks on the retina seen on funduscopic examination. Renal involvement usually begins in infancy, and 75% of patients have angiomyolipomas. Simple renal cysts may appear spontaneously. Oral pathology consists of enamel pits and gingival fibromas. Effects on the musculoskeletal system are seen in phalangeal cysts and periosteal thickening. Lung cysts may occur. Rhabdomyomas occur in 50% of patients, usually in infancy, and may regress spontaneously with age. Pulmonary lymphangiomyomatosis, a proliferation of smooth muscle cells, can occur in women with tuberous sclerosis. A few reports exist of infants with a white forelock who later were diagnosed with tuberous sclerosis [**13**].

d. Nevoid Basal Cell Carcinoma Syndrome

Nevoid basal cell carcinoma syndrome is an autosomal dominant disorder with a gene locus at bands 9q22-31 and a variable expressivity. The disorder begins at birth with obvious frontal bossing, hypertelorism, bifid ribs, and bone abnormalities of the spine and fingers. As the child ages, jaw cysts, palmar pitting, and basal cell carcinomas become apparent. Nevoid basal cell carcinoma syndrome results from mutation causing an inactivation of the patched gene, a tumor suppressor gene, in the hedgehog pathway. Epidemiologic studies have demonstrated that sunlight, and particularly UV radiation, are key risk factors for developing basal cell carcinomas. This explains the low frequency of these lesions in African Americans, owing to the protective action of melanin pigmentation. Multiple basal cell carcinomas present as tan-brown papules on the face, neck, and trunk. Palmoplantar pits are 2- to 3-mm erythematous pits occurring on the palms and soles. Other cutaneous findings are epidermoid cysts and milia [**14**].

Key neurologic abnormalities are calcification of the falx cerebri, hydrocephalus internus, agenesis of the corpus callosum, medulloblastoma, and occasionally, mental retardation. Common features include odontogenic keratocysts, jaw cysts (usually occurring in the maxilla), ovarian fibromas, fibrosarcoma, strabismus, and congenital blindness. An unusual finding of combined hamartoma of the retina and retinal pigment epithelium also has been reported [**14**].

e. Variegate Porphyria

Variegate porphyria is an autosomal dominant acute hepatic porphyria, due to a deficiency of protoporphyrinogen oxidase activity, the penultimate enzyme in the heme biosynthetic pathway. The disease is termed variegate because it can manifest with neurological symptomatology, cutaneous photosensitivity, or both. Variegate porphyria has been recently cloned and mapped to the protoporphyrinogen oxidase gene on bands 1q22-23. The disorder is termed South African porphyria because it occurs frequently in white South Africans of Boer descent with an incidence of 1 case per 330. Genealogic studies show that all are descendants of Gerrit Jansz and Ariaantje Jacobs who married at the Cape of Good Hope in 1688. Similar founder effects explain the high prevalence of variegate porphyria in Finland, and links have been hypothesized to the houses of Stuart,

Hanover, and Prussia. Symptoms begin in the second or third decade of life as a result of a deficiency of protoporphyrinogen oxidase, the enzyme that catalyzes the oxidation of protoporphyrinogen IX to protoporphyrin IX in the heme pathway. This results in the accumulation of protoporphyrinogen, porphyrins, and porphyrin precursors [**15**].

Cutaneous manifestations are present in 80% of patients. The extent of skin findings varies (hence the name) and is identical to findings in porphyria cutanea tarda. Vesicles, bulla, and ulcers are found primarily on light-exposed skin. Increased skin fragility with chronic scarring, milia on fingers and hands, hyperpigmentation in photodistributed patterns, sclerodermoid plaques, dystrophic calcifications, photo-onycholysis and hypertrichosis are common [**15**].

Acute attacks are seen in approximately 50% of patients and cause neuropsychiatric, gastrointestinal, and cardiovascular manifestations as a result of the increase in porphobilinogen (PBG) and aminolevulinic acid (ALA). Acute attacks also are associated with other hepatic porphyrias, such as acute intermittent porphyria and hereditary coproporphyria. During attacks, symptoms include delirium, colicky abdominal pain, dark urine, axonal neuropathy that can mimic Guillain-Barré syndrome, seizures, coma, tachycardia, and hypertension. Attacks in all 3 porphyrias are precipitated by increases in hepatic ALA synthase, eg, by drugs that increase cytochrome P450 or by starvation dieting. Laboratory analysis in variegate porphyria can be helpful. ALA and PBG can be found in the urine only during acute attacks and fluoresce a pink-to-red color. Accordingly, the Watson-Schwartz test for PBG is positive only during acute attacks. Stool porphyrin levels are elevated markedly (including between attacks), with protoporphyrin in greater proportion than coproporphyrin. Plasma porphyrin levels are elevated, and fluorescence at 626 nm is diagnostic [**15**].

f. LEOPARD Syndrome

LEOPARD (lentigines, electrocardiographic conduction abnormalities, ocular hypertelorism, pulmonary stenosis, abnormal genitalia in males, retardation of growth, and sensorineural deafness) syndrome is an autosomal dominant disorder with high penetrance and variable expressivity. Gorlin first described the condition. This disease was also known as multiple lentigines syndrome, cardiocutaneous syndrome, Moynahan syndrome, lentiginosis profuse, and progressive cardiomyopathic lentiginosis. About 200 patients have been reported worldwide, but the real incidence of LEOPARD syndrome has not been assessed. Mutations in the PTPN11 gene, are known to be mutated in persons with *Noonan* syndrome, has been demonstrated in patients with LEOPARD syndrome [**16**].

The most prominent cutaneous findings in LEOPARD syndrome are the lentigines that begin at birth and increase with age. These lentigines are multiple 1- to 2-mm, flat, dark-brown patches in a general distribution, sparing mucous membranes. Areas of hypopigmentation in places where previous lentigines existed also may be a key feature. Unlike freckles, the lentigines have an increased number of melanocytes and large pigment granules that are unrelated to sun exposure. Some patients lack lentigines, which makes the diagnosis difficult. Other key dermatologic findings include café noir and café au lait spots. Hypotonia is common in the newborn and can result in delayed psychomotor development. Mild learning difficulties are reported in about 30% of the cases. Sensorineural deafness occurs in 15-25% of reported cases and can be profound. Once the diagnosis is made, screen the child for sensorineural deafness and start appropriate therapy as soon as possible to avoid later difficulties with speech and phonation. Mild mental retardation, disturbed EEG wave activity, and diffuse encephalopathy also may be present [**16**].

g. *Von Hippel–Lindau* syndrome

Von Hippel–Lindau syndrome, a rare autosomal dominant condition associated with hemangioblastoma in the cerebellum, spinal cord, kidney and retina, can be associated with café au lait spots [**17**].

h. *Osler-Weber-Rendu* disease (Hereditary hemorrhagic telangiectasia)

Patients with *Osler-Weber-Rendu* disease have multiple telangiectasias on the face, hands, palmoplantar, and subungual regi-

ons. Epistaxis is common in approximately 80% of patients, and neurologic complications include vascular lesions of the brain and/or spinal cord. The mutated genes are HHT1 and HHT2; both endoglin and activin are tumor growth factor-beta receptors that play a role in vessel wall integrity. Piebald trait with neurologic defects presents as a white forelock and depigmented patches with spots of hyperpigmentation on the anterior body, sparing the hands and feet. Patients have cerebellar ataxia, varying degrees of mental retardation, and possible hearing loss [**18**].

2. Neurocutaneous Syndromes with Autosomal Recessive Phenotypes

Autosomal recessive phenotypes typically are more severe than those with autosomal dominant traits and commonly are associated with enzyme deficiency [**1, 2**].

a. Ataxia-telangiectasia

Ataxia–telangiectasia (AT; *Louis-Bar* syndrome) is an autosomal recessive condition characterised by progressive ataxia, variable immunodeficiency and telangiectasia, which occur over the cheeks, eyelids, neck, ears, backs of hands and conjunctivae. Ataxia-telangiectasia is an autosomal recessive disorder characterized by progressive cerebellar ataxia, oculocutaneous telangiectasia, abnormalities in cellular and humoral immunity, and recurrent viral and bacterial infections. The gene for AT has been localized to bands 11q22-23 and is termed the ATM gene. The disorder occurs with equal frequency in males and females and in approximately 1 in 80,000-100,000 live births [**19**].

Patients present with distinctive cutaneous manifestations. Telangiectasias develop when patients are aged 3-6 years and are noted first on the bulbar conjunctiva and ears. Later, they appear on the flexor surface of the arms, eyelids, malar area of the face, and upper chest. Granulomas, café au lait macules, graying hair, and progeria can occur. The presenting symptom is cerebellar ataxia beginning in the second year, when the child begins to walk. Choreic and athetoid movements, progressive nystagmus, slurred speech, dystonia, dysarthria, oculomotor apraxia, impassive facies, decreased deep tendon reflexes, and distal muscular atrophy develop gradually. Intelligence may be normal in early childhood but progressively deteriorates. Immunodeficiency results in an inability to mount sufficient immune response. Recurrent viral and bacterial infections occur in 80% of patients and are the most common cause of death resulting from respiratory failure. Patients lack helper T cells, but suppressor T cells are normal. Immunoglobulin A (IgA) is absent in 75% of patients, immunoglobulin E (IgE) in 85%, and immunoglobulin G (IgG) is low. Alpha-fetoprotein and carcinoembryonic antigen are elevated and may be useful in the diagnosis. Endocrine disorders associated with AT include ovarian agenesis, testicular hypoplasia, and insulin-resistant diabetes.The ATM gene is a nuclear protein important in the detection and repair of damaged DNA. Defects in the gene result in an increased susceptibility to malignancy. Malignant neoplasms occur in 10-15% of AT patients; most common are lymphoreticular neoplasm and leukemia [**19**].

b. *Sjögren-Larsson* Syndrome

Sjögren-Larsson syndrome (SLS) is a rare autosomal recessive disorder characterized by a triad of intellectual disability, spastic diplegia or tetraplegia, and congenital ichthyosis with associated ocular features, which include pigmentary changes in the retina. Linkage to arm 17q has been reported in Swedish pedigrees. *Lacour* et al show linkage of chromosome 17 in families from different ethnic origins; thus providing evidence of a single gene locus. SLS is caused by mutations in the ALDH3A2 gene, causing a deficiency in fatty alcohol oxidoreductase, which catalyzes the oxidation of medium- and long-chain fatty acids. The disorder begins at birth with generalized ichthyosis and erythroderma. As the child ages, the scale becomes darker without erythema and is more pronounced around the umbilicus, neck, and flexures, typically sparing the face. Hyperkeratosis of the palms and soles and marked pruritus are common. Atypical retinal pigment degeneration in the macula (glistening dots) usually is seen after the first year [**20**].

Neurologic symptoms and signs appear during the first 1-2 years of life and consist of delay in reaching motor milestones due to spastic diplegia or, much less commonly,

spastic tetraplegia. Approximately half the patients are nonambulatory, and most others require braces or crutches to walk. Seizures occur in about 40% of patients. Cognitive deficits are equally divided among those with mild, moderate, or profound retardation, but rare patients have been found with normal intellect. Delayed speech and dysarthria are common. A distinctive ophthalmologic finding is the presence of retinal crystalline inclusions, so-called glistening white dots, surrounding the fovea. Although all SLS patients do not have the retinal inclusions, their presence is pathognomonic for SLS. Photophobia and myopia are also often present. Brain MRI reveals white matter disease and MR spectroscopy identifies an unusual lipid peak in myelin [**20**].

c. Multiple sulfatase deficiency

This is a neurodegenerative disorder that progresses to death early in childhood. Children with this disorder are unable to degrade various sulfatases like steroid sulfatase, which results in mild ichthyosis. Neurologic complications result from myelin deterioration, causing unsteady gait, deterioration in speech, and blindness [**21**].

d. Hartnup disease

Hartnup disease is a disorder of amino acid transportation with resulting decreased absorption of tryptophan. Cutaneous manifestations include photosensitivity and the pellagra-like skin changes of photodistributed erythema and scale. Progressive cerebellar ataxia and psychiatric disturbances are common. Urinalysis shows aminoaciduria and tryptophan derivatives [**22**].

e. Tangier disease

It is a rare autosomal recessive deficiency syndrome. The disease results from a deficiency of high-density lipoproteins, causing orange-yellow papules, xanthomatous papules, and recurrent neuropathy [**23**].

3. Other Inherited Neurocutaneous Syndromes

a. Incontinentia Pigmenti

Incontinentia pigmenti (IP; Bloch-Sulzberger syndrome) is an X-linked dominant disorder lethal to male patients. The disorder has been linked to the gene locus Xq28 in a number of studies. Recently, mutations in the NEMO/IKKy have been found to cause expression of the disorder. Few affected males have been documented, and most had Klinefelter syndrome (47,XXY). The disorder was described as early as 1906; *Bloch* and *Sulzberger* were credited with fully describing IP in 1928. Skin lesions arranged in a linear pattern, ocular defects, dental, and neurologic abnormalities characterize IP. More than 700 cases have been reported, with a 97% female predominance [**24**].

Characteristic cutaneous findings begin at birth and occur in 4 stages. In stage 1; The vesicular stage occurs from birth to 2 weeks. Infants present with inflammatory vesicles and bullae in a linear pattern on the extremities, trunk, and scalp. Recurrent crops of erythematous macules and papules may erupt for weeks. Skin biopsy at this stage reveals increased eosinophils. In Stage 2: The verrucous stage occurs from 2-6 weeks, with hyperkeratotic streaks, pustules, and papules occurring exclusively on the extremities. In Stage 3: The hyperpigmentation stage occurs from 3-6 months and is characterized by marbled swirls of hyperpigmentation along Blaschko lines. In Stage 4: The hypopigmentation stage occurs in adult women, when follicular atrophy and hypopigmentation replace hyperpigmented swirls. Of patients, 50% present in stage 1 at birth and 90% by age 2 weeks. Stage 2 lesions occur in approximately 70% of patients. In a small percentage of patients, the hyperpigmentation is present at birth. Other cutaneous findings include scarring alopecia in 30% of patients, nail dystrophy in 5-10%, and peg teeth in 66%. Subungual tumors, keratotic tumors, and more rarely, squamous cell carcinoma also have been reported [**24**].

CNS findings occur in more than 30% of patients; seizures are the most common. Other findings include cerebral ischemia, cerebral edema, brain atrophy, and gyral dysplasia. Gross neurologic findings associated with IP include mental retardation, spastic paralysis, cortical blindness, and paresis. Ocular manifestations occur in 25-35% of patients and include strabismus, cataracts, retinal detachments, optic atrophy, retrolental mass, and vitreous hemorrhage. In particular, note the retinal vascular abnormalities with secondary blindness [**24**].

b. *Sturge-Weber* Syndrome

Sturge–Weber syndrome occurs sporadically and is associated with a red–purple area of skin discolouration as wine stain, usually over the ophthalmic division of the trigeminal nerve. Underlying the skin lesion, the leptomeninges contain multiple angiomata and over time the adjacent cortex becomes calcified and may cause seizures. Sturge-Weber syndrome is not an inherited disorder, but it has been reported to show prevalence among relatives. Sturge-Weber syndrome is characterized by congenital facial port-wine stains and leptomeningeal vascular angiomatosis. Sporadic malformations most commonly occur in the leptomeninges, facial capillaries, and ocular vessels. Leptomeningeal angiomatosis can present clinically as epilepsy, mental retardation, and hemiplegia [**25**].

Newborns with port-wine stains have a 5-8% risk of *Sturge-Weber* syndrome. In patients with Sturge-Weber syndrome, the port-wine stain usually involves the ophthalmic and maxillary division of the trigeminal nerve. The macule is deep red, irregular-shaped, and of vascular origin. The lesion's size varies, and it may involve the eyelid, face, and trunk. Although striking, the size of the nevus does not predict the degree of neurologic impairment. Neurologic complications can begin as early as age 5 months with partial motor seizures later progressing to more generalized seizures. Most neurologic complications, such as spastic hemiparesis, sensory defects, and homonymous hemianopia, appear later in childhood and are contralateral to the nevus. At approximately age 6-7 years, skull radiographs reveal curved double outlines of the parietooccipital cortex, which is the classic tram-track calcification. Mental retardation is present in approximately 55-92% of cases [**25**].

F. Neurocutaneous Syndromes With Photosensitivity

Pellagra

Pellagra is caused by dietary deficiency of niacin, resulting in the 4 D 's: diarrhea, dermatitis, dementia, and eventually, death. Niacin can be ingested or synthesized from large quantities of dietary tryptophan. In the early 1900s, pellagra was prevalent, and during the years 1928-1929, it became the eighth-to-ninth highest cause of death in the United States. Because of intensive fortification efforts in the United States, pellagra has become uncommon; however, it remains a public health issue in Africa, India, and China, and recent outbreaks were reported in Angola at an asylum camp dependent on food distribution [**26**].

Pellagra continues to occur in the United States and commonly is associated with alcoholism and isoniazid therapy. Other possible causes include carcinoid tumors, Hartnup disease, hookworms, and medications such as azathioprine and 5-fluorouracil. Recognizing the clinical manifestations associated with pellagra is important, since the disorder is easily treated. The condition has been reported in fad dieters and persons infected with HIV. Cutaneous manifestations occur in a photodistributed pattern. Hand erythema in a glove distribution is one of the first signs, and patients may complain of pruritus and burning, especially after sun exposure. Early facial lesions are erythematous scaly papules and pustules and may resemble the malar rash seen in lupus erythematous. As the disorder progresses, lesions become hard, dark, and thick plaques with painful fissures. Note that a striking demarcation exists between affected and normal skin. A symmetric ring of lesions around the neck as known Casal necklace is a late finding [**26**].

Episodes of mania, aggressive behavior, and severe mood swings may occur. Neurologic symptoms may be predominant in late stages of the disease. Patients may experience paresthesia, muscle weakness, and headaches. Death occurs within 4-5 years if the patient remains untreated. Focus treatment on dietary correction and daily supplements of 100-300 mg of nicotinic acid. Once therapy has begun, skin lesions begin to heal within 24 hours [**26**].

G.Neurologic Disorders With Important Dermatologic Findings

1.Reflex Sympathetic Dystrophy

Reflex sympathetic dystrophy (RSD) is a poorly defined disorder often difficult to diagnose. Symptoms of intolerable pain (out of proportion to clinical picture) develop follo-

wing an injury. In 50% of patients, the initial injury is a fracture, usually of the distal extremity. The sympathetic nervous system is believed to be a mediating factor in the early stages of the disorder, but the exact role is unclear [**27**].

RSD can be divided into 3 stages, and each stage is characterized by dermatologic and neurologic findings. In early or acute stage, patients are in severe pain, which often is described as a burning throbbing sensation. The key finding is pain beyond that expected for the injury sustained. The pain can be induced easily by minor stimuli such as blowing air, stress, and certain textures. In approximately 20% of patients, associated skin findings are edema, erythema, and warmth. In second or dystrophic stage occurs approximately 3 months after the injury and can last as long as 6 months. Pain begins to spread from the initial site and can occur spontaneously. Skin becomes cool, clammy, and pale. A faint cyanosis, decreased capillary refill, and/or livedo reticularis can be present. If the affected area involves the nails, they can become dry and brittle. Hair in the area may become darker and grow faster. In third or atrophic stage, This occurs approximately 8 months after the initial injury and can be chronic. Patients may experience constant burning and increasing pain, resulting in disruption of sleep. Depression and anxiety may develop. Tissue damage progresses, and the skin appears shiny, dry, and mottled. Atrophic changes occur, and the patient may lose hair in the areas of previous increased growth. Ridging of the nails and *Beau* lines may be present. Diffuse osteoporosis (*Sudeck* atrophy) may occur because of increased absorption of bone [**27**].

Diagnosis is primarily clinical; therefore, cutaneous manifestations can help the diagnosis in patients without classic findings. Some advocate sympathetic nerve block as a diagnostic test. In chronic stages, a bone scan can reveal osteoporosis and a 3-phase scan often reveals abnormal absorption of bone. Treatment begins with prevention. Promptly immobilize patients with distal injuries. Once diagnosed, no single effective therapy exists, and patients respond differently to proposed treatments. Patients may benefit from intensive physical therapy, sympathetic blockade, calcitonin, or alpha-blockers and beta-blockers. Kemler et al reported spinal cord stimulation to be safe and effective in decreasing pain associated with RSD. According to van Hilten et al intrathecal baclofen, a type B GABA-receptor agonist, has relieved pain and decreased spasms and dystonia in some patients [**27**].

2. Seborrheic Dermatitis

Seborrheic dermatitis is a common disorder in the general population but has increased incidence in certain neurologic disorders. Erythematous greasy scales and yellow plaques on the scalp, eyebrows, nasolabial folds, ears, and sternal area are characteristic. Blepharitis is a common finding. The etiology is unknown, but studies have described Pityrosporum ovale as the causative agent. Pityrosporum ovale is lipophilic yeast, and patients with seborrheic dermatitis have significantly higher amounts of it, as well as increased skin lipids. Some associated disorders are as follows: Patients with Parkinson disease can have severe cases of seborrheic dermatitis, usually involving the scalp and face. Facial paralysis resulting from stroke or injury can result in seborrheic dermatitis, usually occurring on the corresponding side. Other disorders including quadriplegia, poliomyelitis and syringomyelia have an increased incidence of seborrheic dermatitis. Immunocompromised patients like HIV patients are especially at risk. Seborrheic dermatitis is more common and more severe in persons infected with HIV, particularly in those with CD4 counts below 400 cells/μL, than in uninfected persons, and it may regress with highly active antiretroviral therapy. In HIV-infected patients, lesions are widespread and markedly inflamed and oozing. The skin condition is rare in African blacks; when it occurs in this population, it raises concern about HIV infection. Seborrheic dermatitis has been reported to be associated with several conditions, including neuroleptic-induced parkinsonism, familial amyloidosis with polyneuropathy, and trisomy 21, but these associations have been poorly documented. Hyperinsulinism also has been associated with seborrheic dermatitis and supports the mycologic origin of the disorder [**28**]. In seborrheic dermatitis, effective treatments are available. Selenium sulfide, ketoconazole,

and tar shampoos control symptoms well. Corticosteroid scalp solutions can help decrease the inflammation that commonly occurs. Calcineurin inhibitors, such as tacrolimus ointment, work well for treatment of the face. Warm compresses and gentle cleaning with mild baby shampoo help relieve blepharitis. Mild steroids, and in infection, steroids in combination with antimicrobial preparations, are effective. Ultraviolet B phototherapy is sometimes considered as an option for extensive or recalcitrant seborrheic dermatitis, but it has not been studied in randomized trials [**28**].

3. Malignancy

Melanoma is undoubtedly the most likely of any skin malignancy to metastasise to the brain. Primary intracranial melanoma can arise from the leptomeninges or dura mater, and accounts for less than 1% of melanomas. Any incidental skin lesion suspicious of melanoma should be urgently referred to a dermatologist [**1**].

Dermatomyositis is associated with malignancy in 20% of patients; skin disease is the initial manifestation in around a third of these. Muscle disease is more variable but importantly, both manifestations tend to occur before any signs of malignancy. In dermatologic examination, there are photosensitivity ecpecially in sun exposed areas, heliotrope rash as periorbital purple discolouration and swelling, *Gottron*'s papules as purple flat topped plaques over the knuckles, elbows or knees, urticarial lesions as itchy rash, usually over the face and neck, subcutaneous calcification as firm subcutaneous papules or nodules, commonly associated with trauma and best seen over the elbows, knees, buttocks and hands, and nail fold telangiectasia [**2**].

Central nervous system involvement occurs in around 10% of patients with non-Hodgkin's lymphoma. In non-Hodgkin's lymphoma ichthyosis as dry, thickened, scaly or flaky skin, paraneoplastic pemphigus as stomatitis and blistering on the trunk and limbs, and also acquired hypertrichosis lanuginosa as rapid growth of long, fine, lanugo-type hair, particularly on the face could be observed [**1**].

Skin changes often mirror changes in hormone levels and may be the first indication of pituitary disease. In acromegaly, the skin becomes oily with excess hair growth. Also skin tags and deep, hard skin creases are noted [**1**].

Thyroid dysfunction may result in myxoedema, the skin being cool and doughy with hair loss, or in thyrotoxicosis when it is warm, flushed and moist. In Cushing's disease there may be skin atrophy, bruising, acne and striae. Hypopituitarism leads to dry, scaly, hairless and finely wrinkled skin [**1**].

4. Drug reactions

Adverse drug reactions causing rashes are not uncommon in neurology, especially when prescribing antiepileptic drugs. *Stevens–Johnson* syndrome, toxic epidermal necrolysis and antiepileptic hypersensitivity syndrome are non-allergic hypersensitivity reactions which may occur following carbamazepine, lamotrigine, phenobarbital, phenytoin, sodium valproate or primidone, especially if used in combination. Presentation is usually within the first 60 days and may occur in 5% of patients starting carbamazepine or lamotrigine. There is a strong association between the HLA B*1502 allele in Asian patients3 who often develop Stevens–Johnson syndrome and toxic epidermal necrolysis with carbamazepine; genotyping is advocated in some centres [**1, 2**].

Stevens–Johnson syndrome presents acutely with fever, sore throat and burning eyes. Mucous membranes, especially around the mouth, eyes and lips, become blistered. This is followed by a widespread erythematous rash, which within hours becomes confluent and sheets off to leave eroded surfaces similar to burns. Other organs may also be involved and patients often develop hepatitis, nephritis, pneumonitis and myocarditis. More widespread involvement (>30% of body surface area) results in toxic epidermal necrolysis, which can be fatal if complicated by dehydration or secondary sepsis. Early identification and immediate withdrawal of the suspected drug improves outcome, and dermatological advice should be sought while supportive treatment is instigated. In antiepileptic hypersensitivity syndrome, patients have systemic and cutaneous features of *Stevens–Johnson* syndrome and toxic epidermal necrolysis but without mucosal involvement or skin desquamation. Other serious cutaneous and syste-

mic acute drug reactions associated with antiepileptics include acute fixed drug reactions, phototoxic reactions and porphyric exacerbations. Maculopapular rashes and urticaria are more common and resolve once the drug is stopped. Intravenous immunoglobulin is commonly used to treat neurological conditions and may cause skin problems. A blistering eczematous reaction, usually on the palms, may spread to involve the whole body 8–10 days after starting treatment. This can take up to a month to resolve although topical and oral steroids can expedite recovery. Alopecia and urticaria have also been reported [**1, 2**].

Summary

Neurologists should examine a neurological patient, have a careful look at their skin. For young patients with stroke, think about possible causes of vessel damage, bleeding or disturbed blood flow. For patients with meningitis/encephalitis neurlogist should ask whether this be infective or part of a systemic illness or, in the case of neuropathy, could this be nutritional. Neurological symptoms frequently result in a new diagnosis of HIV infection and neurologists should do skin examination. They should also remember that significant proportion of patients with neurocutaneous syndromes have no family history and may present in adulthood. Rashes are common in patients starting antiepileptic drugs and occasionally may be very serious indeed.

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