

NEUROLOGY AND MEDICINE

Neurology and the skin

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Many disorders affect both the nervous system and the skin. The complementary—and some would say—diametrically opposite—clinical methods of the dermatologist and the neurologist can in these circumstances reduce an otherwise dauntingly large differential into a more tractable, smaller list. Often triangulation with these and other clinical findings is sufficient for accurate diagnosis, but in other cases, serological or genetic data must be considered before diagnosis is secure.

We have purposely avoided traditional groupings such as phakomatoses, and immunological, infectious, or genetic diseases. Such distinctions are becoming increasingly obscure. Instead, we have organised the roughly 300 disorders with manifestations both in the skin and nervous system into clinically relevant groupings, as they may be first encountered by a practicing physician: neurocutaneous disorders associated with impaired immunity; stroke; neuropathy; meningitis or meningoencephalitis; vesicular lesions; ecchymoses, non-palpable purpura, and petechiae; café au lait spots; amyloidosis; rheumatoid arthritis; cutaneous vasculitis; photosensitivity; and melanoma. For disorders mentioned only in the tables, or not at all, the reader is referred to the encyclopaedic text of Fitzpatrick *et al*¹ and more specialised compendia.^{2,3}

Neurocutaneous disorders of impaired immunity**AIDS**

Eighty five per cent of those affected with AIDS have skin lesions, the most common of which are infectious, the result of impaired cell mediated immunity. Even such banal infections as verruca vulgaris and molluscum contagiosum are problematic. Both types of viral infection are resistant to therapy. Giant mollusca may disseminate over the body. Tinea corporis and recurrent bacterial infections, especially *Staphylococcal aureus*, may occur. The most common cutaneous manifestation, however, is recalcitrant seborrheic dermatitis, a chronic inflammation typically of the scalp and face, but which can also involve the intermammary region of the chest, groin, and axilla. It is thought to result from infection by *Pityrosporum orbiculare*, a saprophytic organism. Usually, it can be successfully suppressed by continued use of topical ketoconazole.

Herpes zoster is an AIDS defining event for those who test positive for infection with HIV.

Five per cent to 10% of patients with HIV infection will develop herpes zoster radiculitis, with painful dermatomal shingles, which in rare patients disseminates over the entire body (fig 1).⁴ Kaposi's sarcoma has been associated with herpes type VIII. Unlike the classic indolent Kaposi's sarcoma detected in elderly Eastern European Askenazi Jews, this rapidly growing tumour is seen in young homosexuals, but not in AIDS associated with a parenteral mode of infection (drug misuse, inadvertent needle stick, etc). Rarely, disseminated infection with cryptococcus resulting in cutaneous lesions resembling molluscum contagiosum may be an AIDS defining event. Surprisingly, patients with this complication may have few or no systemic features.

Neurological disorders related to AIDs are reviewed elsewhere.^{4,5} Syphilis, discussed below, is another important neurocutaneous complication of AIDS.



Figure 1 Grouped vesicles on an erythematous base in a zonal distribution characteristic of a herpes zoster infection.

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Table 1 Neurocutaneous disorders associated with stroke

Disorder	Cutaneous
Amyloidosis VII	Cutis laxa
Behçet's disease	Erythema nodosum, genital and oral aphthous ulcers
Cerebral cavernous malformations	Rarely, angiomas
Diabetes mellitus	Necrobiosis lipoidica diabetorum, poorly healing ulcers
Endocarditis	Petechiae, Osler's nodes, splinter haemorrhages
Fabry disease	Angiokeratoma—clusters of punctate dark red to blue black non-blanching macules or papules; symmetric, starting at the umbilicus and knees, then buttocks and scrotum
Haemolytic-uraemic syndrome	Erythematous necrotic skin lesions
Hereditary haemorrhagic telangiectasia	Telangiectasias
Homocystinuria	Sparse hair, malar flush, livedo reticularis, diffuse hypopigmentation
Hypercholesterolaemia	Xanthomas, xanthelasma
Progeria (Hutchinson-Gilford)	Aged skin, alopecia, generalised hypotrichosis, sparse or absent eyebrows, scleroderma-like, thin skin, midfacial cyanosis
Neurocutaneous angioma	Large irregular haemangiomas, angiomas
Pseudoxanthoma elasticum	Pseudoxanthoma, multiple papules, peau d'orange skin, angioid streaks, subcutaneous calcification usually in blood vessels
Systemic lupus erythematosus	Photosensitivity, malar rash, telangiectasia, discoid lupus, patchy alopecia, mucosal ulcers, angioneurotic oedema, Raynaud's phenomenon, subcutaneous nodules, palpable purpura, gangrene, erythema multiforme (rare)
Takayasu's arteritis	Cutaneous necrotising venulitis—palpable purpura
Werner (Pangeria)	Scleroderma-like skin, graying hair and baldness, leg ulcers, progressive scalp alopecia, sparse body hair, telangiectasia, mottled pigmentation, loss of subcutaneous fat, subcutaneous calcification

OTHER NEUROCUTANEOUS DISORDERS WITH IMPAIRED IMMUNITY

Similar infections and tumours are common to other immunosuppression from a wide variety of causes such as chemotherapy, lymphoma, and in excess of 100 described heritable disorders in which the immune system is depressed, including severe combined immunodeficiency (Swiss or alymphocytic type agammaglobulinaemia) with susceptibility to fungal and viral as well as pyogenic infections; the X-linked Wiskott-Aldrich syndrome of eczema and thrombocytopenia; Chediak-Higashi syndrome of partial albinism and neuropathy related to mutations of a beige-related lysosomal trafficking regulator encoded on chromosome 1q42; the Griscelli syndrome of partial albinism with silvery hair and progressive leukodystrophy, related to mutations of myosin 5 encoded on 15q21; ataxia telangiectasia; Bloom syndrome discussed below; and others.³



Figure 2 Livedo reticularis involving the knees and thighs. There is also ulceration on the lower leg.

Neurocutaneous disorders associated with stroke (table 1)

ANTIPHOSPHOLIPID SYNDROME

The antiphospholipid antibody syndrome is characterised by antibodies that are thought to induce hypercoagulability by neutralising anionic phospholipids on endothelial cells and platelets. These antibodies are most commonly seen in systemic lupus erythematosus but also as a primary abnormality. The most common antiphospholipid antibody of pathophysiological relevance is directed against epitopes localised to the cardiolipin 2 glycoprotein I complex. Other antibodies show specificity for prothrombin and annexin V. In some instances, antiphospholipid syndrome has been shown to be a familial trait.⁶ The two most common tests employed for detecting antiphospholipid antibodies are the anticardiolipin enzyme linked immunosorbent assay (ELISA) and a functional assay employing the Russell viper venom test (RVVT). The associated cutaneous manifestations are livedo reticularis, most commonly on the lower extremities (fig 2); acrocyanosis, a Raynaud's-like phenomenon, and rarely, Degos malignant atrophic papulosis. The combination of livedo reticularis with multiple strokes resulting in dementia has been designated Sneddon's syndrome. Antiphospholipid antibodies are associated with several neurological syndromes,⁷ most of which result from focal ischaemia.⁸

FABRY'S DISEASE

Fabry's disease is an X-linked multisystem disorder resulting from deficiency of ceramide trihexosidase (also known as α -galactosidase) and resultant vascular deposition of lipid.^{3,9} Affected males are easily recognised by a purpuric skin rash for which the disorder was given its other name, angiokeratoma diffusum universale. There is a characteristic whorl-like corneal dystrophy of similar severity in heterozygotes as in hemizygous males,¹⁰ but affected females almost never have the characteristic skin rash. Without the rash, the diagnosis is often overlooked. The cutaneous manifestations of Fabry's disease are characterised by discrete angiokeratomas most prevalent between the knees and nipples.



Figure 3 *Necrobiosis lipoidica diabetorum*: sharply demarcated, yellowish-brown indurated plaques with atrophy and telangiectasias characteristically, but not exclusively, associated with diabetes mellitus.

In addition to a painful small fibre neuropathy with autonomic involvement and abdominal crises, the early syndrome includes small infarctions in the retina and kidney that had previously led to death by the third decade. However, renal transplantation has permitted survival to a later stage of multiple infarctions of the CNS. Although women tend to survive longer than affected men, clinical involvement can be very severe, including debilitating autonomic neuropathy,¹¹ renal failure, cardiomyopathy,¹² and involvement of the CNS.¹³

Angiokeratomas can also be found in association with other heritable disorders.³

DIABETES MELLITUS: METABOLIC ENCEPHALOPATHY, NEUROPATHY, RETINOPATHY, AND STROKE

Diabetes is arguably the most common neurological disorder in the developed world. The cutaneous manifestations of diabetes mellitus include necrobiosis lipoidica diabetorum and

a non-specific diabetic dermatopathy. The last is characterised by reddish brown macules most commonly over the extensor surfaces of the lower extremities. The more characteristic lesion, however, is necrobiosis lipoidica diabetorum. This lesion, although not absolutely specific, generally occurs in patients with long-standing diabetes mellitus. Lesions consist of sharply demarcated, yellowish brown patches located most characteristically over the anterior surface of the lower legs (fig 3). A peculiar yellowish hue is characteristic, as well as the presence of telangiectasia. Ulceration of this lesion may occur.

Neurocutaneous disorders with neuropathy (table 2)

LEPROSY

In addition to diabetes mellitus, there are many neurocutaneous disorders associated with neuropathy. Although largely sparing developed nations, leprosy is perhaps the most common neurocutaneous disorder and peripheral neuropathy in the world. Vulnerability to infection with *Mycobacterium leprae* appears, in part, to be determined genetically.¹⁴ It had consistently affected some 10 to 12 million people until the introduction of multidrug therapy in the mid-1980s. By 1991 this number had dropped to about 5.5 million, including some 2 to 3 million who were seriously deformed.¹⁵ The characteristic abnormality is a hypaesthetic mononeuritis multiplex, with palpably thickened nerves, beginning with burning or shooting nerve pain and progressing to complete anaesthesia in affected areas, comparable with that resulting from syringomyelia or completed nerve transection. There is invariably a non-necrotising lymphocytic angiitis of the

Table 2 Neurocutaneous disorders associated with peripheral neuropathy

Disorder	Cutaneous
AIDS	Seborrheic dermatitis, verruca vulgaris, molluscum contagiosum, Kaposi sarcoma
Alcoholism	Telangiectasias, malar rash
Amyloidosis (primary)	Purpura skin folds or flat surfaces or eyelids, papules, sometimes alopecia, rarely bullae on skin or oral mucosa
Arsenic poisoning	Dry scaly desquamation, linear hyperpigmentation of nails, Mees lines
Chediak-Higashi	Partial albinism, silvery blond hair
Cronkhite-Canada	Alopecia, skin hyperpigmentation, onychodystrophy
Diabetes mellitus	Necrobiosis lipoidica diabetorum, poorly healing ulcers
Diphtheria (cutaneous)	Jungle sore
Dysautonomia, familial	Blotching, abnormal sweating, hypohidrosis
Fabry Disease	Angiokeratoma
Flynn-Aird disease	Skin atrophy, hyperkeratosis, chronic ulceration
Haemochromatosis	Bronze pigmentation
Histiocytic reticulosis	Purpura, jaundice, erythroderma
Impaired long-chain fatty acid oxidation	Congenital ichthyosis, ichthyosiform erythroderma
Leprosy	Hypopigmentation and hyperpigmentation, leonine facies, erythema nodosum leprosum, Lucio phenomenon: arteritis of skin, vitiligo
Linear sebaceous nevi of Jadassohn	sebaceous and epithelial nevi, linear nevus sebaceous
Lyme disease	Target lesions
Pellagra	Erythematous photosensitive rash, erythema, vesicles, glossitis, malar and supraorbital hyperpigmentation, rhagades
Poems syndrome	Hyperpigmentation, thickening, verrucous angiomas, hirsutism, Raynaud's phenomenon
Poikiloderma-spastic paraplegia	Poikiloderma: delicate, smooth, wasted skin
Refsum's disease	Ichthyosis
Refsum's disease with increased pipercolicacidaemia	Ichthyosis
Sarcoidosis	Hypohidrosis,, cicatricial alopecia; acute: erythema nodosum, vesicles, maculopapular rash; chronic lupus pernio, plaques, scars, keloids
Systemic lupus erythematosus	Photosensitivity, malar rash, discoid lupus
Thallium intoxication	Hair loss
Trichorrhexis nodosa	Ichthyosis, flexural eczema, photosensitivity, short wooly hair
Vitamin B12 deficiency	Black nail pigmentation (nail bed and matrix), oral aphthae
Werner (pangeria)	Scleroderma like skin, graying hair and baldness, leg ulcers, progressive scalp alopecia, sparse body hair, telangiectasia, mottled pigmentation; loss of subcutaneous fat, subcutaneous calcification
Xeroderma pigmentosum	Photosensitivity, early onset skin cancer (basal cell, squamous cell, and malignant melanoma), atrophy, telangiectasia, actinic keratosis, angioma, keratoacanthomas

nerves, either as a result of delayed hypersensitivity, or, in the case of multibacillary disease, direct infection of endoneurial cells by the mycobacterium. The organism grows preferentially in cool, exposed limbs and face, giving a different distribution than is seen in inflammatory mononeuritis multiplex. In addition to superficial nerves, commonly affected are motor function of the ulnar nerve and sensory function of the posterior tibial nerve.¹⁶

The cutaneous manifestations of leprosy are the reflection of the host immune response to *M leprae*. All forms of leprosy are associated with invasion of the organism into peripheral nerves. The tuberculoid form of leprosy, characterised by anaesthetic patches on the skin adjacent to thickened peripheral nerves, results from a vigorous cell mediated immune response with formation of granulomas. Severe destruction of peripheral nerves ensues. The lepromatous form of leprosy is characterised by widespread cutaneous nodular lesions (leonine facies) in which massive quantities of *M leprae* are found in the tissue. This form of leprosy, associated with an absent cell mediated response, also produces nerve destruction, but more insidiously. Reversal reactions induced by therapy (Dapsone) or a natural immune response to *M leprae* produce a very prominent inflammatory reaction from which damage to nerves can be severe.

Although there is correlation between cutaneous and nerve pathology, it is not absolute. Careful examination shows that some 4% of at risk people have sensory or motor nerve involvement without cutaneous signs of reversal reaction, erythema nodosum, or nerve tenderness.¹⁷ Furthermore, there can be discrepancies in nerve and skin biopsies, showing paucibacillary involvement in one, multibacillary form in the other.¹⁸

LYME DISEASE

Lyme disease (erythema chronicum migrans) is a chronic inflammatory disease caused by the spirochete *Borrelia burgdorferi*. It is transmitted by a tick bite (*Ixodes dammini*). No genetic vulnerability loci have been identified. About 85% of patients develop a very peculiar, distinctive, cutaneous inflammatory reaction at the site of the tick bite. Initially there is an inflammatory papule, which over a period of weeks spreads centrifugally. Central clearing occurs but a haemorrhagic, papular, vesicular lesion may remain at the site of the tick bite. Multiple lesions of erythema chronicum migrans occur if the disease process is untreated.

Borrelia burgdorferi affects the joints, the heart, and the nervous system. The typical presentation is of a painful patchy mononeuritis multiplex in association with mild lymphocytic meningitis. The mononeuritis can take the form of cranial neuropathies, particularly of the facial nerve, or a painful radiculopathy, or brachial or lumbar plexitis.¹⁹ Less often, there can be a myositis. Involvement of the CNS can mimic roughly some common neurological disorders. Patchy demyelination sometimes suggests an atypical distribution of multiple sclerosis. Myelopathy with radicu-

lopathies has crudely approximated motor neuron disease in some patients. Such rare occurrences as well as incidental seropositivity in patients affected with these common diseases, including stroke, have suggested associations, none of which have been established.²⁰

In chronically affected patients there can also be a non-vasculitic mononeuropathy multiplex, perhaps mechanistically identical to the acute form. Some untreated patients develop an indolent, indistinct diffuse encephalopathy. This nondescript chronic syndrome has become seriously overdiagnosed, in part because of the problems inherent in serological diagnosis of an immunologically complex spirochete, endemic in some areas and rare in others. Inappropriate diagnosis may well contribute to the belief that there is a subgroup of patients with chronic Lyme disease unusually refractory to antibiotic treatment, in contradistinction to the responsiveness of classic neuroborreliosis.^{21 22} Difficulties with serological diagnosis abound.

Neurocutaneous disorders with meningitis or meningoencephalitis

In addition to Lyme disease, there is a wide variety of neurocutaneous disorders associated with inflammation of the meninges, often with associated cranial or peripheral neuropathies. Dermatological findings are particularly helpful in diagnosing aseptic meningitides or those associated with indolent organisms.

BEHÇET'S DISEASE: MENINGOENCEPHALITIS AND SINUS THROMBOSIS

This is an inflammatory dermatosis of unknown aetiology. There is a high prevalence of Behçet's syndrome in people from the Mediterranean, Middle East, China, and Japan. There is an increased frequency of HLA-B5 (Bw51 split) in affected people. There is evidence that the primary association with Behçet's syndrome is not in the HLA-B1 gene itself, but with the newly discovered MICA gene.²³

Behçet's syndrome is characterised by recurrent aphthous stomatitis, genital ulcers, uveitis, erythema nodosum, and thrombophlebitis. Recurrent aphthous stomatitis occurs in 98% of patients with Behçet's syndrome and is often the initial manifestation. As many as 90% of patients with Behçet's syndrome have a relapsing iridocyclitis, anterior and posterior uveitis, or retinal vasculitis. Optic atrophy may occur and blindness may result. Pathergy (the development of pustulation at the site of trauma) is a characteristic feature. Vesicles, pustules, folliculitis, pyoderma, and acneiform eruptions, as well as necrotising vasculitis have also been described.

Neurological manifestations are the least frequent but most feared aspect of this disorder, affecting 2.2% of those in a recently reported series.²⁴ Most often, this takes the form of a recurrent or chronic aseptic meningitis. In about 10% of patients there is a meningoencephalitis or meningomyelitis, which may respond to early and aggressive treatment with steroids, immunosuppressive drugs, and colchicine. There is a high incidence of dural sinus



Figure 4 Chancre of primary syphilis.

thrombosis, affecting about 25% of all those with neuroBehçet's syndrome.²⁵ Psychiatric disturbances and isolated trigeminal neuralgia have also been described.

SARCOIDOSIS: CRANIAL NEUROPATHIES AND ASEPTIC MENINGITIS

Sarcoidosis is a chronic granulomatous disease of unknown aetiology. Some 20% to 35% of patients with systemic sarcoidosis have cutaneous disease. The cutaneous features include skin coloured papules, nodules, and annular lesions. The annular lesions are most common in people of African descent. In addition to being skin coloured, the lesions of sarcoidosis may be brownish red or violaceous. They are often detected on the face, especially around the nostrils. On occasion, they may become confluent, forming erythematous plaques.

The angioliupoid form of sarcoidosis is a rare cutaneous lesion occurring most often in women. These lesions are soft, well demarcated, orange-red or reddish brown, with a livid hue secondary to prominent telangiectasia. Lupus pernio is characterised by large, bluish red, dusty, violaceous infiltrated nodules and plaques, which generally appear on the cheeks, ears, fingers, and nose. On rare occasions, sarcoidosis may present as an erythrodermic lesion characterised by red scaling patches extending and merging into brownish red, confluent areas. Ulceration is rare, but most commonly seen in those of African descent.

Clinically recognisable disease of the nervous system occurs in 5% to 10% of patients with sarcoidosis.²⁶ In half of these patients, neurological signs were the presenting feature.²⁷ The most common findings were cranial neuropathies, chiefly of the facial nerve. Also encountered were parenchymatous lesions of the nervous system including the hypothalamus, hydrocephalus, peripheral neuropathy, and myopathy.



Figure 5 Characteristic copper coloured lesions over the palms in secondary syphilis.

SYPHILIS

After a period of diminishing prevalence, there has been a 10-fold rise in the incidence of primary and secondary syphilis, some 20/100 000 in the United States and 360/100 000 in parts of Africa. Inflammatory CSF is found in 10%-20% of those with primary syphilis, 30% to 70% of cases of secondary syphilis (2-4 months after infection), and falling to 10%-30% of cases of latent syphilis. In these early stages mild meningism can be associated with cranial nerve involvement, particularly of the optic, facial, and acoustic nerves.²⁸

The cutaneous manifestations of syphilis characteristically are initiated by a primary chancre most commonly on the genitalia, but sometimes on the lips or in the throat. This is a painless, indurated, rubbery lesion generally occurring within 2 weeks of infection (fig 4). It is also characterised by painless swelling of the draining lymph node (bubo). Serological testing (Venereal Disease Research Laboratory test) may be negative during the early phase, but invariably becomes positive within 1 month of infection. The fluorescent *Treponema* antibody test, however, is generally positive within 2.5 weeks of the onset of infection. The primary chancre may go untreated or unrecognised (most common in women with a cervical primary chancre) allowing the secondary phase of syphilis to occur. This can occur while the primary chancre is still present. It is characterised by mucous membrane patches and a patchy alopecia, as well as copper coloured lesions on the palms and soles (fig 5).

In adults, it is only during the early meningeal phases of the illness that cutaneous abnormalities are present. About 10% of those with early syphilitic meningitis have a rash. Cutaneous abnormalities resolve by the time of the later stages of neurosyphilis: meningovascular, which peaks after 4 to 7 years; general paresis, 10-15 years; and tabes dorsalis, 15-25 years. There is considerable overlap in the times of incidence. Cutaneous nodules or plaques of late syphilis are distinctly rare.²⁹

Prenatal syphilis is lethal in utero or shortly after birth in about half the cases. Early prenatal syphilis, with manifestations occurring before the age of 2, corresponds to secondary syphilis, whereas the signs of late prenatal syphilis do not appear until after the age of 2, rarely as late as 30. Half of early cases have cutaneous manifestations, typically copper red macules and papules on the palms, soles, and perineum. Fissures of the lips or anus "rhagades" affect 75% of affected infants. Less

often, there are bullae or a bright red nasal discharge “snuffles”.²⁹ As in secondary syphilis of adults, meningoencephalitis is the most common neurological presentation. Neurologists must be wary of the “pseudoparalysis of Parrot”—failure to move a limb because of a painful osteochondritis at the epiphysis of a long bone.

OTHER NEUROCUTANEOUS DISORDERS WITH MENINGITIS OR MENINGOENCEPHALITIS

In addition to Behçet’s disease and neurosarcoidosis, aseptic meningitis with uveitis can occur in infantile multisystem inflammatory disease and in the rare Vogt-Koyanagi-Harada syndrome. In the last, a prodromal meningoencephalitis precedes uveitis and the final phase with the characteristic dermatological findings of alopecia, poliosis, and leukoderma with symmetric patches of vitiligo involving the head, neck, shoulders, and eyelids.³⁰

There is a large differential for meningitis or meningoencephalitis with cutaneous manifestations (table 3).

Neurocutaneous disorders with vesicular lesions

HERPES VARICELLA ZOSTER

The varicella zoster virus causes two distinct syndromes: a primary infection (chickenpox) and a recurrent infection (shingles) after reactivation of virus that has lain dormant in the dorsal root ganglia for years after the primary infection.³¹ The most common nervous system complication of primary infection is a self-limiting cerebellar ataxia and aseptic meningitis, that typically occurs around 21 days after the eruption of cutaneous vesicles. About 0.1% to 0.2% of infected children develop encephalitis.

About 2% of patients with childhood chickenpox will reactivate the virus to develop shingles, usually in the 6th through to the 8th decade. Excruciating dermatomal pain, typically in thoracic or high lumbar dermatomes precedes by 2–3 days the development of a maculopapular rash that quickly matures into a vesicular eruption that may take 2–4 weeks to resolve completely. Postherpetic neuralgia, however, may persist indefinitely. Reactivation of the virus in the distribution of the VIIIth cranial nerve results in a characteristic mononeuritis: Ramsay Hunt herpes zoster oticus. Deep local pain is followed several days later by vesicles in the external auditory meatus, and later hearing loss, with or without vertigo.³²

In some patients there is symptomatic meningitis. Reactivation of the virus in the ophthalmic branch of the trigeminal nerve results in herpes zoster ophthalmicus. Vasculitic stroke is most common with eruptions in the distribution of the first division of the trigeminal nerve, but may occur from shingles elsewhere.³³ In rare circumstances there may be transverse myelitis or granulomatous angiitis of the CNS. The risk of widespread dissemination is greater in the immunocompromised host, but is rarely fatal.

Ecchymoses, purpura, and petechiae

Ecchymoses, petechiae, and purpura result from extravasation of blood into the skin or subcutaneous tissues. Such bleeding can occur after significant trauma in people who are otherwise well. However, subcutaneous haemorrhages occurring after trivial trauma indicate either a coagulopathy or disorder of platelets or blood vessels. All of these may concurrently affect the nervous system, platelet disorders perhaps less so than the others.

CHILD ABUSE: THE SHAKEN BABY SYNDROME

Physical abuse—delivered either by a frustrated caregiver trying to stop an infant’s crying, or by someone deliberating trying to inflict harm—is the leading cause of serious head injury in infants,³⁴ accounting for 95% of serious intracranial injuries. Intracranial pathology may occur in the setting of bone fractures and the mucocutaneous manifestations described above. However, the “shaken baby syndrome” can occur in the absence of skeletal or cutaneous manifestations of trauma. Infants present comatose or convulsing with retinal haemorrhages and anaemia from intracranial extravasation of blood into the subdural or subarachnoid space. The clinical triad of the “tin ear syndrome”: unilateral ear bruising, ipsilateral cerebral oedema, and retinal haemorrhage is said to be pathognomonic, but bilateral subdural haematomas are seen most often.³⁵ In more severe cases there may be lacerations or other intraparenchymal brain lesions. Up to 60% of children either succumb or become profoundly mentally retarded, blind, or tetraparetic with residual encephalomalacia, porencephalic cysts, and chronic subdural fluid collections.³⁶ Less often rhabdomyolysis and myoglobinuric renal failure ensue.

The differential diagnosis for the neurocutaneous manifestations includes haemophilia and vitamin K deficiency of infancy. Multiple bone fractures after trivial trauma can occur in osteogenesis imperfecta type 3 or 4 (resulting from mutations in the genes encoding collagen 1A or 2A)³ Wormian bones in these disorders can simulate the multiple skull fractures which are now considered almost pathognomonic for child abuse. Careful radiographic examination of bones usually permits distinction of osteogenesis imperfecta from child abuse.^{37 38}

THROMBOTIC THROMBOCYTOPENIC PURPURA

Thrombotic thrombocytopenic purpura is a rare acute or subacute disorder that chiefly affects young women, sometimes in association with systemic lupus erythematosus, Sjögren’s disease, or scleroderma. Petechiae are less frequent than in the unrelated disorder, idiopathic thrombocytopenic purpura, in which there is no involvement of the nervous system. Jaundice can result from the severe haemolysis that is a hallmark of this disease. A severe encephalopathy with seizures, focal deficits,³⁹ and coma occur in about 90% of patients that succumb to the disease, usually as a result of cerebral or renal involvement. However, patients successfully treated with plasmapheresis will go on to complete neurological recovery.⁴⁰

Table 3 Meningitis or meningoencephalitis with cutaneous manifestations

Disorder	Cutaneous	Neurological
Adams-Oliver aplasia cutis congenita type III	Scalp defect at the vertex, hypoplastic nails, tortuous scalp veins, cutis marmorata telangiectatica, haemangioma	Acute bacterial meningitis from skull defect
AIDS	Seborrhoea, herpes zoster, tinea corporis, <i>S Aureus</i> , molluscum contagiosum, Kaposi sarcoma, cryptococcosis	Transient meningitis during seroconversion
Amyloidosis V (Meretoja)	Cutis laxa	Cranial and peripheral neuropathies
Behçet's disease	Erythema nodosum, genital and oral aphthous ulcers (not as painful as recurrent aphthae) 1-5 ulcers <10 mm, 4-14 days duration, papules, purpura, pustules, dermatographia, pyoderma	Chronic or recurrent meningitis, meningoencephalitis, dural sinus thrombosis
Blastomycosis	Hyperplastic granulomatous microabscesses	Very rarely: chronic meningitis or cerebral abscess
Brill-Zinsser epidemic typhus	Macular rash	Meningoencephalitis
Chagas disease	Romana's sign, inflammation of lacrimal glands, erythema multiforme	Encephalitis
Coccidiomycosis	Erythema nodosum, draining sinus, subcutaneous cellulitis	Meningitis common; sometimes from parameningeal focus in vertebral osteomyelitis
Cryptococcosis	Macules and nodules in only 10-15% of affected individuals	Chronic meningitis
Haemophilus influenza	Typically single indurated area on face, neck, upper chest, or arm	Acute purulent meningitis
Histiocytic reticulosis (autosomal recessive)	Purpura, jaundice, erythroderma	Chronic aseptic meningitis, neuropathy
Infantile multisystem inflammatory disease	Evanescence rash, uveitis	Papilledema, optic atrophy, mental retardation, aseptic meningitis
Leptospirosis	Scleral conjunctival injection; maculopapular rash of trunk in 50% of cases, jaundice	Subacute meningitis
Leukaemia	Erythema nodosum, Sweet's syndrome (acute febrile neutrophilic dermatosis—painful raised red plaques commonly on face and extremities)	Meningeal leukaemia is common form of relapse, especially in all
Listeria	Generalised erythematous papules or petechiae in infants; veterinarians with tender red papules of hands	Subacute meningitis
Lyme borreliosis	Target lesion	Early aseptic meningitis, polyneuropathy, delayed demyelinating disease
Lymphoma	Erythema nodosum	Subacute meningitis, cerebral or vertebral metastasis
Lymphoma, cutaneous (T cell)	Scaly erythematous patches, leonine facies, poikiloderma, hypopigmented and hyperpigmented patches with atrophy and telangiectasia	Subacute meningitis, vertebral metastases
Meningococcaemia	Typically small and irregular petechiae with smudged appearance, usually on extremities and trunk; initially can mimic a viral exanthem	Fulminant meningitis
Murine typhus	Axillary rash, macular rash of upper abdomen, shoulders, chest	Headache, encephalopathy, and nuchal rigidity without meningitis
Neurocutaneous melanosis	Melanosis; large multiple pigmented skin nevi (> 20 cm), no malignant melanoma other than CNS; primary CNS melanoma in over 50% of cases	Meningeal enhancement secondary to melanosis of pia-arachnoid; cranial nerve palsies, Dandy Walker malformation, suprasellar calcification;
Reticulosis, familial histiocytic	Purpura, jaundice, erythroderma	Chronic meningitis, peripheral neuropathy
Rocky mountain spotted fever	Characteristically progressing rash begins (1) on the fourth day of fever with pink macules on wrists, ankles, forearms; (2) after 6 to 18 hours, on palms and soles, then centrally (3) after 1-3 days deep red macules; (4) after 2-4 days, non-blanching petechiae	Vasculitic meningoencephalitis, choreoathetosis, deafness, hemiplegia
Sarcoidosis	Dry skin, hypohidrosis, decreased sweating, cicatricial alopecia; acute: erythema nodosum, vesicles, maculopapular rash; chronic: lupus pernio, plaques, scars, keloids	Chronic meningitis with cranial neuropathies, distal neuropathy and proximal myopathy; leukopathy, hypothalamic involvement
Sjögren's syndrome	Purpura, Raynaud's phenomenon, xerostomia, candidiasis, dental caries	Aseptic meningitis, dorsal ganglionopathy with sensory ataxia, dural sinus thrombosis
Syphilis	Primary: chancre; secondary maculopapular non-pruritic scaling rash (acral), hair: patchy alopecia, condyloma lata, mucous patches, erythema multiforme, hyperpigmentation on healing; split papules, palm and sole lesions	Aseptic meningitis in secondary phase; late meningovascular syphilis; tabes dorsalis
Tuberculosis	Cutaneous tuberculosis is rare; primary tuberculosis chancre; warty tuberculosis verrucosa cutis from reinfection, postprimary lupus vulgaris, scrofuloderma, erythema nodosum, erythema multiforme	Chronic meningitis; Pott's disease of vertebrae; CNS tuberculomas
Varicella-zoster (chickenpox)	Vesicles with oral lesions	Meningitis with cerebellar ataxia
Vogt-Koyanagi-Harada	Vitiligo type macules, poliosis and alopecia in convalescent third phase	Meningoencephalitis in first phase of illness, preceding uveitis
Yersinia pestis (bubonic plague)	Erythema multiforme, bubos then petechiae and ecchymoses	Meningitis can complicate all three types: bubonic, bubonic-septicaemic, pneumonic

Cafe au lait spots

NEUROFIBROMATOSIS TYPE 1

Neurofibromatosis is the most common single gene disorder to affect the nervous system, affecting about 1/3500 people.⁴¹ The NIH consensus criteria⁴² for the diagnosis of neurofibromatosis type 1 (von Recklinghausen's neurofibromatosis) require at least two of the following: (1) the presence of six or more café au lait macules with a diameter of 5.0 mm in children younger than 6 years and >15 mm in older people (fig 6); (2) two or more neurofibromas of any type or one plexiform neurofibroma; (3) axillary or inguinal region freckling;

(4) optic pathway glioma; (5) two or more Lisch nodules (whitish tumours of the iris); (6) dysplasia of the sphenoid bone or thinning of the cortex of long bones with or without pseudoarthrosis; and (7) a first degree relative exhibiting these changes.

Among the most pressing management issues in neurofibromatosis type 1 are those pertaining to tumours, usually histologically benign.⁴¹⁻⁴³ Neurological involvement most often results from benign neurofibromas arising in the root entry zone, causing radiculopathy or compression of the spinal cord. Plexiform neurofibromas, which can be



Figure 6 Two café au lait macules on the skin of a patient with neurofibromatosis. These are adjacent to two small neurofibromas.

nodular or diffuse, arise from nerve trunks. Diffuse plexiform neurofibromas are usually congenital and undergo transformation in about 4% of cases into⁴⁴ malignant peripheral nerve sheath tumours that are severely painful, tender, and hard. The more common dermal neurofibromas are usually innocent, permitting conservative management in asymptomatic people. Incidence of non-neural tumours is also increased, albeit to a modest degree, especially rhabdomyosarcomas of the urogenital tract and myelogenous leukaemia.⁴⁵

In addition to involvement of the peripheral nervous system, there is also involvement of the CNS. Increasing awareness of CNS pathology led to abandonment of the old name for this disorder—peripheral neurofibromatosis—for the current neurofibromatosis type 1). Of the central tumours, gliomas of the optic pathway are the most frequent, occurring in about 15% of those affected. Astrocytomas, and, less often, ependymomas and medulloblastomas also occur.

Not all neurological manifestations result from tumours.⁴⁴ Indeed, the most frequent neurological manifestation of neurofibromatosis type 1 is a learning problem.⁴⁶ Other manifestations unrelated to tumour are megalencephaly, scoliosis, and hydrocephalus.⁴⁴ Hypertension can result either from pheochromocytomas or fibromuscular dysplasia of the renal arteries. Rarely, there can be a peripheral neuropathy, fibromuscular dysplasia, or fusiform aneurysm of an intracranial artery.

Brain MRI often demonstrates T2 bright lesions—“unidentified bright objects” or UBOs. Typically they arise in the basal ganglia, brainstem, and cerebellum⁴⁷ and do not show mass effect. However, they can only be distinguished reliably from low-grade astrocytomas by careful follow up. Thought by some to represent aberrant myelination or gliosis, the majority of these can be distinguished from hamartomas by their spontaneous resolution by adulthood, after a peak incidence between 8 and 16 years. These are for the most part clinically silent, although their presence in multiple sites has correlated with cognitive disturbance in some studies⁴⁸ though not others.⁴⁹

Neurofibromatosis type 1 is caused by mutation of an unusually large gene (spanning 350 kb of genomic DNA) on chromosome 17 which encodes a novel tumour suppressor, neurofibromin. Neurofibromin is thought to inactivate the tumour suppressor Ras by enhancing its GTPase activity and thus reduc-

ing or eliminating the requirement for nerve growth factor or neurotrophins.⁵⁰ About a third of affected people have no family history.⁵¹ New mutations can occur in any of several locations in this very large gene. Because so many of the mutations are novel, DNA based diagnosis is currently not clinically practicable in many instances. However, a protein truncation assay can detect about 70% of all mutations⁵² and can be useful in conjunction with other tests.⁴³ Other mutations in the neurofibromin gene give rise to the Watson pulmonary stenosis syndrome,⁵³ in which there is also macrocephaly, axillary freckling, intellectual dullness, and axillary freckling, but in which Lisch nodules are uncommon and the neurofibromas visceral or retroperitoneal.

NEUROFIBROMATOSIS, TYPE 2 (NF2): BILATERAL ACOUSTIC NEUROFIBROMATOSIS

The neurological hallmark of this clinically and genetically distinct disorder is the appearance of bilateral vestibular schwannomas, tumours that are not associated with neurofibromatosis type 1.^{54 55} The diagnostic criteria for definite neurofibromatosis type 2 are either bilateral vestibular schwannomas or a first degree relative with the disease plus a unilateral vestibular schwannoma appearing before the age of 30 or any two of the following: meningioma, glioma, schwannoma, and juvenile posterior subcapsular lenticular opacity/juvenile cortical cataract.⁴³ Neurofibromatosis type 2 was formerly named central neurofibromatosis because the café au lait spots and dermal neurofibromas characteristic of neurofibromatosis type 1 are less abundant and often absent. However, the terms central and peripheral are unfortunate and have been abandoned, in as much as both neurofibromatosis type 1 and type 2 each have central and peripheral manifestations.⁵⁶ Two thirds of patients with type 2 have some sort of skin lesion, but café au lait spots are less frequent than in type 1. Only 8% of patients with neurofibromatosis type 2 have more than three café au lait spots. In a large clinical study palpable subcutaneous tumours attached to large nerves were found in 43% of patients,⁵⁷ violaceous subcutaneous neurofibromas in 27%, and well circumscribed pigmented and often hairy patches of skin in 48%. There are no Lisch nodules but posterior capsular cataracts are typical. In addition to the characteristic vestibular schwannomas, there can be meningiomas, gliomas, and generalised neuropathy. This autosomal dominant disorder occurs less often than does neurofibromatosis type 1. It is caused by mutations in the MERLIN gene on chromosome 22, which also seems to be involved in the pathogenesis of some cases of what had initially been described as neurolemmomatosis^{58 59} and is now called schwannomatosis.⁶⁰ In this disorder, there are multiple schwannomas, but no other manifestations of neurofibromatosis type 2 in most family members.⁶¹ There may also be a distinct form of schwannomatosis unrelated to neurofibromatosis type 2.⁶²



Figure 7 Shagreen patch over the back of a patient with tuberous sclerosis. This is a hamartoma resulting from subepidermal fibrosis.

OTHER NEUROCUTANEOUS SYNDROMES ASSOCIATED WITH CAFE AU LAIT SPOTS AND TUMOURS

Café au lait spots are also seen in other neurocutaneous tumour syndromes, which can be easily distinguished both clinically and genetically. In tuberous sclerosis the distinguishing cutaneous manifestations are not café au lait spots but adenoma sebaceum, periungual angiokeratomas, Shagreen patches (fig 7), and hypopigmented ash leaf spots, best appreciated under Wood's ultraviolet lamp.⁶³ The neurological manifestations vary from severe mental retardation and infantile spasms to normal intelligence. Cardiac and olfactory hamartomas are characteristic of severely affected infants. Large hamartomas called tubers are often found on neuroimaging and can only be distinguished from astrocytomas, also associated with tuberous sclerosis, by serial scanning. The characteristic tumours are ganglioneuromas that give a candle guttering appearance to the ventricular wall. Other associated lesions are ependymomas, Wilms' tumour, retinal phakomas, clinically silent renal cysts, and angioliipomas, as well as, less often, renal cell carcinoma.^{3 64} This autosomal dominant disorder is genetically heterogeneous: tuberous sclerosis I is caused by mutations of the hamartin gene on chromosome 9q34, and tuberous sclerosis II, with a higher risk of mental retardation, by mutations of the tuberin gene on chromosome 16p13.3.^{3 65} Previous reports of additional tuberous sclerosis 3 and 4 loci on chromosomes 11 and 12 have proved incorrect.³

Café au lait spots are sometimes found in some of the many autosomal recessive neurocutaneous disorders associated with defective DNA repair. Some early compendia had associated ataxia telangiectasia with café au lait spots.⁶⁶ However, the association is not with the classic disorder but with what had been called ataxia telangiectasia variant VI. This genetically distinct disorder is now known as the Nijmegen breakage syndrome of microcephaly with (usually) normal intelligence, immunodeficiency, and lymphoreticular malignancies.^{3 67} Facial telangiectasias are also typical in Bloom syndrome,^{3 68} in which susceptibility to infections and neoplasia result from mutations in DNA ligase I encoded on chromosome 15q26.1. There is dolichocephaly and light sensitivity, with mild learning disability as the only neurological manifestation. Leukaemia is a fatal complication of the genetically heteroge-

neous Fanconi syndrome^{3 69} in which mental retardation is associated with microcephaly, deafness, thumb anomalies, and pancytopenia.

Rarely, café au lait spots as well as hypopigmented patches are seen in the von Hippel-Lindau syndrome: autosomal dominant retinal angiomas; hemangioblastomas of the cerebellum and spinal cord; renal and pancreatic cysts and carcinomas; as well as pheochromocytomas.^{3 70 71} However, cutaneous manifestations are decidedly rare in this common autosomal dominant disorder that results from mutations in a gene on chromosome 3p26-p25. This gene encodes a novel tumour suppressor protein that both regulates exit from the cell cycle and the expression of several hypoxia-inducible genes, including vascular endothelial growth factor.³ More often, café au lait spots have been seen in Turcot's syndrome,^{3 72} a rare autosomal dominant syndrome of brain tumours, usually medulloblastomas, colon cancer associated with polyposis, thyroid carcinoma, and bone cysts. These phenomena result from certain germ line mutations of the adenomatous polyposis coli gene.³

NEUROLOGICAL DISORDERS ASSOCIATED WITH CAFE AU LAIT SPOTS BUT NOT TUMOURS

Very large, unilateral and segmental café au lait spots are characteristic of McCune Albright polyostotic fibrous dysplasia. Although it was commonly understood that the rough border of these cutaneous lesions distinguished them from the smoother contour seen in neurofibromatosis, this does not permit the reliable distinction afforded by the rest of the syndrome.^{3 73} The osseous and endocrine abnormalities result from somatic mosaicism for constitutively lethal mutations the GNAS1 gene (guanine nucleotide binding protein, α -stimulating activity polypeptide 1), that encodes a GTP binding subunit of adenylate cyclase. Neurological manifestations are limited to brainstem compression and syringomyelia resulting from severe basilar invagination.⁷⁴

Café au lait spots are associated with mental retardation in several clinically distinguishable syndromes: the rare West-erhof syndrome in which growth retardation is associated with congenital hypopigmented and hyperpigmented patches,⁷⁵ as well as in children with ring 14 and ring 17 chromosomal anomalies. Microcephaly but usually normal intelligence are typical of Russell-Silver dwarfism, a growth retardation syndrome with a characteristic lateral body asymmetry.^{3 76}

Finally, it is important to remember that autosomal dominant transmission of café au lait spots can be seen in the absence of other abnormalities.³ Some,⁷⁷ although not all⁷⁸ such cases result from mutation in the neurofibromin gene.

Amyloidosis

Amyloidosis refers to extracellular deposition of insoluble protein fibrils. The pattern of cutaneous, neurological, or visceral involvement is to some extent related to the type of protein that is being deposited.⁷⁹ Slightly raised

cutaneous papules clustered in skin folds of the axilla or perineum are characteristic of amyloidosis (AL type), resulting from deposition of fragments of immunoglobulin light chains. There is a painful small fibre peripheral neuropathy, with prominent autonomic involvement. A similar small fibre neuropathy in the absence of cutaneous lesions is associated with autosomal dominant mutations of the transthyretin gene.⁸⁰

In familial amyloidosis type VII cutis laxa is associated with an episodic encephalopathy and amyloid deposition in leptomenigeal and retinal blood vessels.⁸¹ In amyloidosis type V, cutis laxa and lattice corneal dystrophy are associated with multiple cranial neuropathies, but not autonomic dysfunction.⁸² Erysipelalike erythema and benign recurrent meningitis similar to Mollaret's⁸³ are the neurocutaneous features of familial Mediterranean fever, associated with mutations in the pyrin gene⁸⁴ an autosomal dominant disorder that leads to amyloid deposition in the kidneys.

Rheumatoid arthritis

The characteristic cutaneous findings in rheumatoid arthritis are subcutaneous nodules. In some patients there may be painful intracutaneous papules of the finger pulp, bright red "liver palms", or a vivid washable yellow discoloration of the skin from inspissated sweat. Rheumatoid nodules characteristically occur at sites of trauma: extensor surfaces of forearms, ears, and posterior scalp.

The most serious neurological complication commonly encountered in rheumatoid arthritis is a high cervical myelopathy, most often attributed to horizontal atlantoaxial instability, but recently discovered to be as frequent in patients with vertical translation of the dens and a normal atlantoaxial interval.⁸⁵ Systemic necrotising arteritis indistinguishable from polyarteritis nodosa affects fewer than 1% of people with rheumatoid arthritis. Nevertheless, it is among the most common causes of mononeuritis multiplex associated with necrotising vasculitis, second only to classic polyarteritis nodosa.⁸⁶ Peripheral nerve involvement results from occlusion of the vasa nervorum. Less often there can be a necrotising vasculitis of the CNS.⁸⁷

Scleroderma

The defining cutaneous abnormality of progressive systemic sclerosis is sclerodactyly, but all patients also have Raynaud's phenomenon. About two thirds have proximal scleroderma, telangiectasias, or digital pitting scars of the fingers. About half exhibit calcinosis. Although scleroderma is thought to be the least likely of the connective tissue disorders to be associated with neurological dysfunction, a systematic survey found the frequency of both peripheral and CNS involvement in scleroderma to be comparable with that in systemic lupus erythematosus and Sjögren's syndrome, although the types of pathology differ.⁸⁸ In that survey one third of patients with scleroderma had peripheral involvement, including trigeminal neuralgia and brachial plexopathy. Most CNS

pathology in patients with scleroderma occurred in those who had systemic features overlapping with those of Sjögren's syndrome or systemic lupus erythematosus.

An unusual form of localised scleroderma is seen in the Parry-Romberg syndrome of progressive hemiatrophy of the face with contralateral focal epilepsy and trigeminal neuralgia.⁸⁹

Palpable purpura: cutaneous vasculitis

Raynaud's phenomenon is also the most common cutaneous manifestation of Sjögren's syndrome, a very heterogeneous rheumatic disease associated with characteristic dryness of the eyes and mouth. This common disease affects 3% to 5% of elderly women, some 30% of whom have anti-La(SS-B) or anti-Ro(SS-a) antibodies. Peripheral neuropathy occurs in about 10% of those with Sjögren's syndrome. The most distinctive neurological manifestation of Sjögren's syndrome is a sensory ataxia associated with lymphocytic infiltration of the dorsal root ganglia.⁹⁰ Other neurological manifestations have been attributed to Sjögren's syndrome but the strength of these associations has yet to be determined.⁹¹⁻⁹³ There is cutaneous vasculitis manifesting either as palpable purpura of the lower extremities or urticaria-like vasculitic lesions in as many as 25% of anti-Ro(SS-a) antibody positive patients with Sjögren's syndrome. Palpable purpura, the hallmark of cutaneous vasculitis can also be seen in other vasculitides⁷ including polyarteritis nodosa, Henoch-Schönlein purpura, essential cryoglobulinemia, some cases of giant cell arteritis, and Churg-Strauss allergic granulomatosis,⁹⁴ as well as the autosomal dominant syndrome of retinal vasculopathy with cerebral leukodystrophy.⁹⁵

Photosensitivity

Exaggerated sensitivity of the skin to sunlight is a feature of several neurocutaneous disorders of diffuse aetiology: two autoimmune disorders, systemic lupus erythematosus and dermatomyositis; nutritional deficiency of niacin; as well as several heritable disorders of intermediary metabolism or DNA repair.

SYSTEMIC LUPUS ERYTHEMATOSUS

Systemic lupus erythematosus is a chronic relapsing and remitting multisystem inflammatory disorder thought to result from impaired control of autoimmunity. The genetics of lupus is complex, susceptibility being associated with certain HLA class II alleles³; homozygosity for deficiency of several complement genes as well as a demonstrated but uncharacterised susceptibility locus on chromosome 1.⁹⁶

Photosensitivity is the most common cutaneous manifestation of systemic lupus erythematosus, usually manifested as a malar rash. Less often there is a discoid rash and oral ulceration. Neurological complications are frequent and diverse in systemic lupus erythematosus, affecting 70% of those with the disease.^{7 88} Events predominate in the CNS. This may in part be an artefact of disease definition. Psychosis and seizures are each elements of the American



Figure 8 Diffuse erythema on the dorsal hand of a patient with photosensitive dermatomyositis. Typical hand lesions of dermatomyositis are injections of the cuticle nail fold, erythema over the PIP, DIP, and MCP joints (Gottron's sign) or inflammatory papules over these joints (Gottron's papules).

Rheumatological Association's diagnostic scheme, whereas polyneuropathy and myositis are not. A diffuse encephalopathy is a frequent manifestation, as is optic neuropathy. The initial presentation of systemic lupus erythematosus is often a psychosis that develops months before other aspects of the disorder. Both large and small vessel strokes occur, either as a manifestation of vasculitis, embolisation from Libman-Sachs endocarditis, or secondary to a coagulopathy. There may be an associated antiphospholipid syndrome, as described above. Distal axonal neuropathy, mononeuritis multiplex, myopathy, and myasthenia gravis occur less often.

DERMATOMYOSITIS

Dermatomyositis is a distinctive disorder in which myositis and dermatitis usually coexist, but both are sufficiently distinctive to permit accurate diagnosis in the absence of the other. The characteristic dermatological manifestation is photosensitivity. In addition to the characteristic heliotrope rash of the eyelids, a photosensitive erythematous rash often develops over sun exposed areas: malar, the "shawl" of the neck and shoulders, and the exposed anterior "V" of the chest. Unlike in systemic lupus erythematosus, there is a tendency for the eczematous rash to localise over knuckles, malleoli, and other joints (fig 8). In about two thirds of paediatric cases, there is also subcutaneous calcification. There can also be periorbital and perioral oedema and cicatricial alopecia. Sometimes the characteristic cutaneous photosensitivity occurs in the absence of myositis.⁹⁷

Contrary to popular thinking, dermatomyositis is not "polymyositis with a rash." Both disorders are rare with a combined annual incidence of 1/100 000. Although a subacute or insidious steroid responsive proximal myopathy is common to both, dermatomyositis is distinct from polymyositis. Histologically, dermatomyositis is a vasculitis, with perimysial and perivascular infiltration by CD4+ T cells and B cells, unlike the endomysial infiltration by CD8+ T cells and macrophages typical of polymyositis.⁹⁸⁻⁹⁹ Furthermore, each disease is associated with a characteristic HLA genotype

and a different spectrum of autoantibodies.¹⁰⁰ Both disorders can be part of overlap mixed connective tissue disorders, but an increased frequency of malignancy is a feature of dermatomyositis, particularly of adult onset. Among the more striking is a 16-fold to 32-fold increase in the rate of ovarian cancer.¹⁰¹

PORPHYRIA

Heritable disorders of porphyrin metabolism are clinically divisible into two general types: the cutaneous porphyrias, most of which have no neurological involvement, and the hepatic porphyrias, most of which have no cutaneous involvement. The hallmarks of hepatic porphyrias are metabolic crises with delirium, abdominal pain, and sometimes an axonal neuropathy, the rapid evolution of which can clinically simulate Guillain-Barré syndrome.^{3 102} Only two of the porphyrias exhibit both cutaneous and neurological features. Variegate (South African) porphyria typically results in severe photosensitivity with bullae, scars, erosions, and leather-like thickening of sun exposed skin. Infrequently, photosensitivity with some blistering is found in coproporphyrin. In both of these disorders, neurological crises are triggered by a wide variety of drugs including barbiturates, carbamazepine, valproic acid, and ergot alkaloids.¹⁰²

PELLAGRA AND HERITABLE NEUROCUTANEOUS DISORDERS WITH SIMILAR RASH

Pellagra is a chronic wasting neurocutaneous disorder characterised by dermatitis, dementia, and diarrhoea. It results from niacin (a B vitamin that can be synthesised from large quantities of dietary tryptophan) deficiency. Both niacin and tryptophan are in short supply in maize. The rash is characteristically symmetric, hyperkeratotic, hyperpigmented, and desquamated in sun exposed areas.¹⁰³

A similar rash occurs intermittently during bouts of metabolic encephalopathy in two distinct autosomal recessive disorders: Hartnup disease,³ a mild disorder resulting from altered transport of tryptophan and other neutral amino acids that affects some 1/14 000 people¹⁰⁴ with emotional instability and intermittent ataxia that occasionally progresses to stupor, and hydroxykynureninuria¹⁰⁵ a very rare, severe affliction of tryptophan metabolism in which episodic metabolic crises are superimposed on a congenital encephalopathy with marked hypertonemia and deafness. A pellagra-like rash can also occur in the carcinoid syndrome, in which tryptophan is catabolised at abnormally high rates.

XERODERMA PIGMENTOSUM AND OTHER DISORDERS OF DNA REPAIR

Xeroderma pigmentosum³ is a rare condition affecting about 1/100 000 people. However, the insights provided by this and related autosomal recessive neurocutaneous syndromes make their heuristic value greater than their frequency. The hallmark of xeroderma pigmentosum is extreme sensitivity to sunlight with progressive atrophy of the skin, irregular

pigmentation, telangiectasias, keratoacanthomas, actinic keratosis, and high onset of skin cancer, including melanoma, basal cell, and squamous cell carcinomas. It is genetically heterogeneous, as was originally suspected from complementation studies of DNA repair with fibroblasts from affected patients. Patients in some complementation groups,¹⁰⁶ although not others, have progressive degeneration of the nervous system: characteristically spastic ataxia, often associated with microcephaly, peripheral neuropathy, dementia, choreoathetosis and sensorineural deafness. Some of these patients had previously been described as having the De Sanctis-Cacchione syndrome, a term that has outlived its usefulness and is best abandoned. One form of xeroderma pigmentosum (complementation group G) is allelic with phenotypically distinct Cockayne syndrome,^{107, 108} characterised by a triad of precocious senility beginning in infancy, salt and pepper retinopathy with optic atrophy and sensorineural deafness, as well as photosensitive dermatitis. Neurological deficits in Cockayne syndrome include dementia, peripheral neuropathy as well as ataxia. Cockayne syndrome is itself genetically heterogeneous. Other complementation groups of xeroderma pigmentosum (B and D) are allelic with trichothiodystrophy, a syndrome with brittle hair and nails, as well as photosensitive ichthyotic skin and mental retardation.¹⁰⁹

However, photosensitivity is not a feature of all neurocutaneous disorders associated with defects in DNA repair. In ataxia telangiectasia,^{3, 66} cutaneous findings are limited to the diagnostic oculocutaneous telangiectasias that appear after the development of oculomotor apraxia and ataxia.¹¹⁰ Severe progressive neurodegeneration leads to choreoathetosis and peripheral neuropathy. Neurodegeneration only occurs in homozygotes for mutations in the ATM gene on chromosome 11q22.3, which encodes a DNA binding protein kinase.³ Both heterozygotes and homozygotes for ATM mutations are unusually sensitive to ionising radiation, a clinically relevant problem given the high incidence of lymphoma in homozygotes, and breast cancer in heterozygotes.

Melanoma

Of the three major types of skin tumour—basal cell carcinoma, squamous cell carcinoma, and melanoma—only the last typically involves the nervous system by metastases. There has been a dramatic 300% increase in the incidence of melanoma over the past 40 years, resulting in over 6700 deaths annually in the United States.¹¹¹ If allowed to grow vertically, melanoma has a high rate of metastasis, initially to regional lymph nodes, and then by haematogenous spread to lung, liver, bone, and brain. Brain metastases from malignant melanoma usually are multiple, unlike the solitary metastases typical of colon, breast, or renal cancer.

Excessive exposure to sunlight is clearly the strongest aetiological factor, but genetic predisposition has been found. In addition to the increased (but not exclusive) vulnerability of

fair skinned people, there is evidence for other genetic susceptibility factors.¹¹² Primary tumours of the CNS are seen in increased frequency in family members of probands with cutaneous melanoma.¹¹³ The melanoma-astrocytoma syndrome segregates as an autosomal dominant trait.¹¹⁴ Melanomas are also seen in association with more complex neurocutaneous syndromes, such as xeroderma pigmentosum. In the rare neurocutaneous melanosis syndrome malignant transformation of a hypermelanotic leptomeninges leads to death in childhood.¹¹⁵

Summary

As knowledge of pathophysiology grows, so does the refinement of diagnoses. Sometimes increased knowledge permits consolidation and unification. Unfortunately, at our present level of understanding, it usually demands proliferation of diagnostic categories. As tedious as this diagnostic splintering may seem, such is the price currently exacted of both the investigator and the clinician who seek to optimise management.

Increased diagnostic refinement often requires inquiry into matters outside the bounds of one's specialty. Most often we turn to the radiologist or to the laboratory to narrow the differential diagnosis generated from the history and neurological examination. As we have shown, a useful intermediate step is extension of the physical examination to organs such as the skin, which are not the traditional preserve of the neurologist. That any text could confer the sophistication required for expert dermatological diagnosis is an unrealistic expectation. However, we hope that this review will encourage careful examination of the skin, hair, and nails by the neurological practitioner, with consideration of referral to a dermatologist when greater expertise is required.

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