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CLINICAL NEURODERMATOLOGY
A GUIDE TO UNDERSTANDING COMMON NEURODERMATOLOGIC DISORDERS

Malbora Xhelili [*], Monika Fida[**], Ilirjana Zekja,[***] Ermira Vasili,[****]Jera Kruja[*****]

* Neurologist, Regional Hospital Center "Shefqet Ndroqi", Albania

** University of Medicine, Faculty of Medicine, Tirana, Albania

*** Dermatologis, UHC "Mother Teresa", Dermatology Service, Tirana, Albania

**** Neurologist, UHC "Mother Teresa", Neurology Service, Tirana, Albania

***** University of Medicine, Faculty of Technical Medical Sciences, Tirana

Abstract

It is generally accepted that the skin is a mirror of human health. In addition, neurological conditions may be accompanied by characteristic skin changes that are diagnostically significant. Therefore, a thorough and accurate examination of the skin can provide important clues in the neurological diagnostic process. The wide range of skin lesions and the wide spectrum of symptoms can make a simple differential diagnosis difficult for non-dermatologists. Therefore, a multidisciplinary approach can be the key to a correct diagnosis. This article addresses this topic by discussing selected neurological disorders and describing and discussing the various skin manifestations associated with neurological signs and symptoms.

Keywords: *cutaneous manifestations, neurologic disorders, multidisciplinary approach, neurodermatology*

Introduction

Richard Edelson, MD, Aaron B. and Marguerite Lerner Professor of Dermatology cited: "You can identify so many systemic diseases by careful analysis of the skin". The central nervous system and the skin are closely connected. Many diseases affect both the nervous system and the skin at the same time. In these cases, the skills of dermatologists and neurologists complement each other. The neural crest produces melanocytes, an essential component of the skin, and has an embryonic origin similar to the neural tissue found in the brain and spinal cord. The dermal dermatomes receive sensory information from C fibers, alpha fibers, beta fibers, and delta fibers that terminate in the sensory organs of the skin. Eccrine sweat glands, subcutaneous vascular tone, and piloerection are regulated by the sympathetic and parasympathetic nervous systems. Many central and peripheral neurological disorders have dermatologic and neuroendocrine symptoms that may be clinically and physiologically significant.

Central and/or peripheral nervous system and the skin share the same source: the ectoderm. The discovery

of specific cutaneous manifestations can facilitate the neurologic diagnosis, and leading to further treatment regimens and/ or other investigations. Therefore, it is most important that a neurologist thoroughly examine your skin, hair, and nails. If unusual abnormalities are found on your skin or a more in-depth examination is needed, consultation with a dermatologist is recommended.

Neurodermatology is a branch of dermatology that focuses on the relationship between the nervous system and the skin. It treats skin conditions that have a neurological component, such as pruritus (itching), psoriasis, eczema, and some types of hives (urticaria), which can be aggravated by stress or other neurological factors.

Neurodermatology studies how the nervous system influences skin health and the development of skin diseases, and how skin diseases can affect the nervous system. Understanding these interactions can help us treat a variety of skin diseases more effectively, especially those that depend on or affect the nervous system.

There are about 300 diseases with neurocutaneous clinical manifestations.

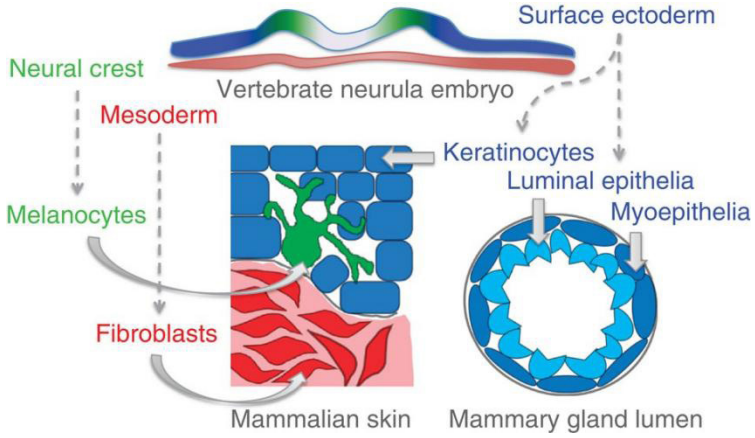
1.1. Pathogenesis and pathophysiology of neurodermatologic conditions

The ectoderm gives rise to the brain and spinal cord, the skin, peripheral nerves, pituitary and pineal gland, kidney marrow, cornea, nails hair, sweat glands, teeth and the mucous membrane of the nose.

The neuroectoderm forms the neural tube and neural crest. The neural tube forms the central nervous system (CNS: brain and spinal cord) and controls most functions of the body and mind, including body movement, thought, and homeostasis.

The peripheral nervous system (PNS) contains nerves and ganglia outside the CNS and is divided into the somatic nervous system and the autonomic nervous system. The main function of the PNS is to connect organs to the CNS and is made up of the neural crest. The neural crest also gives rise to Schwann cells, chromaffin cells of the adrenal medulla, the inner ear, cornea, odontoblasts, melanocytes, pharyngeal arches, and the meninges of the brain and spinal cord.

The surface ectoderm gives rise to, among other things, the epidermis, ectoderm, hair, nails, anterior pituitary, and apical ectoderm ridges. The functions of the surface ectoderm include hormonal regulation and homeostasis by the adenohypophysis, which acts as a barrier to external interference.



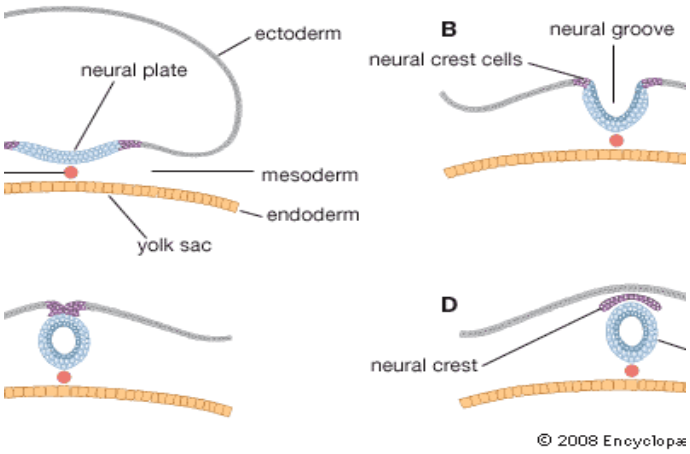


Figure 1. Pathogenesis and pathophysiology of neurodermatologic conditions (Ref.) The ectoderm gives rise to the brain and spinal cord, the skin, peripheral nerves, pituitary and pineal gland, kidney marrow, cornea, nails hair, sweat glands, teeth and the mucous membrane of the nose.

Ectodermal differentiation towards the neural crest and neural tube route correlates with protein members of fibroblast growth factors (Fgf) which acts to modulate Bmp proteins (bone morphogenic proteins) simultaneously negatively. At the same time, expression of Bmp and Wnt signals blocks FGF signals on ectodermal cells and permits it to continue towards a non-neural ectodermal lineage, including the epidermis.

2. Cutaneous manifestations and neurologic diseases

There are above 300 syndromes that manifest with both neurologic signs and symptoms and characteristic skin lesions. Some are listed in Table 1. Above we will discuss further some of the most common diseases in our practice.

Neuropathic pain and itch

Patients with skin manifestations associated with peripheral neuropathy often present for dermatologist's consultation. Skin lesions of peripheral neuropathy may be secondary to a medical condition such as chronic renal failure, or a manifestation of neuropathy itself. Generalized neuropathic itch/pain has also been described in cases of CNS- involvement such as: brain and spinal tumors, multiple sclerosis and stroke. Localized neuropathic itch is seen in: notalgia paraesthetica, brachioradial pruritis, Herpes Zoster, Trigeminal trophic syndrome.

Notalgia paresthetica is a unilateral chronic neuropathic dysesthesia typically seen in older females and is characterized by secondary cutaneous lesions due to scratching. This cutaneous dysaesthesia is caused by impingement of the posterior rami of T2–T6 nerve roots. The skin may be normal or pigmented.

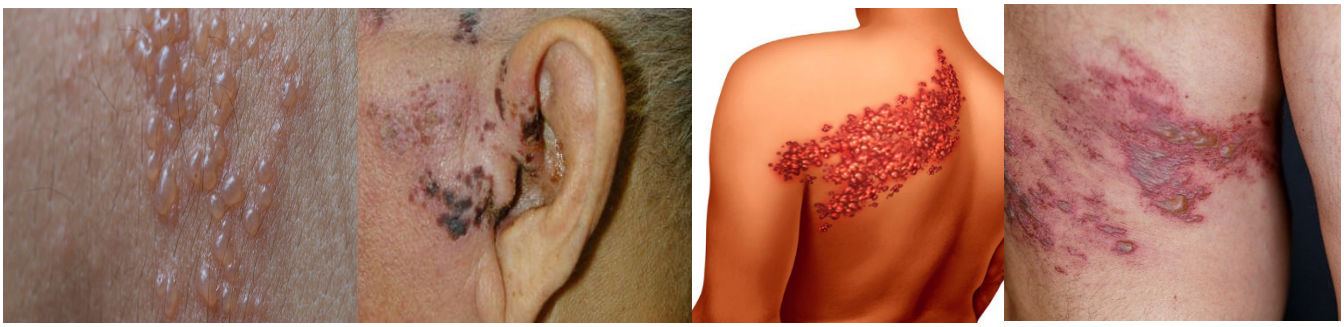
Brachioradial pruritis is a localized bilateral neuropathic dysesthesia affecting the dorsolateral aspects of the upper extremities and is caused by cervical radiculopathy, exacerbated by exposure to ultraviolet radiation (UVR).

Trigeminal trophic syndrome is a rare form of cutaneous dysaesthesia that is thought to occur after central or peripheral damage to the trigeminal nerve. Ulcers involve the ala nasi, spreading to the adjacent lip and cheek. This syndrome is often seen in trigeminal neuroablation and Gasser ganglion- alcohol injection.

Neurocutaneous syndromes associated with:	
Impaired immunity	AIDS, Chediac- Higashi Syndrome, Griscelli Syndrome
Stroke	Antiphospholipid Syndrome, Fabry Disease, Diabetes Mellitus, Vasculitis, Thrombo-occlusive vasculopathies
Neuropathy	Leprosy, Lyme Disease
Neuroinfections	Behcet Syndrome, Sarcoidosis, Syphilisis
Vesiculae	Herpes Varicella Zoster
Echimosis,Petekie, purpura	Thrombotic thrombocytopenic purpura (TTP)
Café au laits spots	Neurofibromatosis type 1 and 2, Tuberous Sclerosis, von Hippel-Lindau Syndrome, Turcot Syndrome, McCune Albright Syndrome
Amyloidosis	Cutis laxa type- 5 and -8, multiple cranial neuropathy
Rheumatoid Arthritis	Multiplex mononeuritis, cervical myelopathy, necrotising CNS vasculitis
Sclerodermia	Brachial plexopathy, Trigeminal neuralgia, Parry- Romberg Syndrome
Palpable purpura	Cutaneous vasculitis, Sjogren Syndrome, Polyarteritis Nodosa, Henoch-Schonlein purpura
Photosensitivity	LES, Dermatomiositis, Xeroderma pigmentosum, Pellagra, porfiria
Melanoma	Brain metastases
Rosacea	Parkinson's Disease, Essential tremor
Seborrheic Dermatitis	Parkinson's Disease, Epilepsy
Vasculitis	Thrombo-occlusive vasculopathies

Table 1. Some cutaneous manifestations of neurologic diseases

Herpes Varicella Zoster



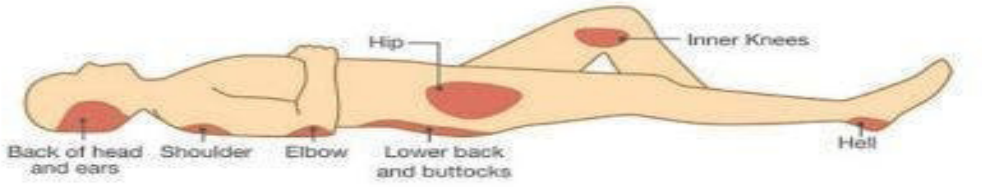
HVZ cause some severe neurologic complications such as: postherpetic neuralgia, aseptic meningitis, stroke, Bickerstaff encephalitis, cerebellar ataxia, transverse myelitis, Guillain-Barre syndrome, Ramsay-Hunt syndrome, Elsberg syndrome, cranial polyneuropathy. Patients with herpes zoster have a rash in one or two adjacent dermatomes. The rash most commonly appears on the trunk along a thoracic dermatome, usually not crossing the midline. The rash develops into clusters of vesicles and usually heals in 2 to 4 weeks.

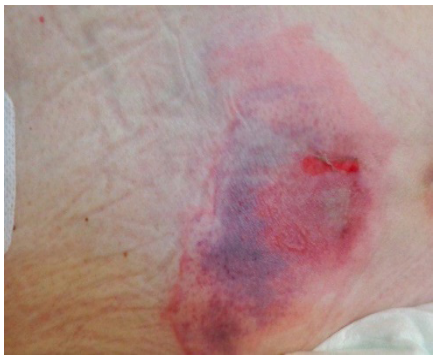
Figure 2. (a) (b) (c) Vesicles in HVZ on the trunc along a thoracis dermatome. (d) Ramsay-Hunt Syndrome, as a result of facial nerve involvement. Reference. Steiner I et al. "The neurotropic herpes viruses: herpes simplex and varicella-zoster". The Lancet

Autonomic dysfunction and the skin

Autonomic dysfunction occurs in disease of peripheral small fibers (e.g. diabetes, vasculitis, HIV), disease affecting autonomic ganglia, and CNS disease (e.g. Parkinson disease, multiple system atrophy). Diabetes is one of the commonest causes of autonomic neuropathy.

The motor system and the skin





Muscle weakness with abnormalities in gait or musculoskeletal deformity may lead to skin problems. The common skin lesion we have in practice are pressure sores caused by immobility.

Figure 3. (a) Pressure sores in stroke patiens (b) Common sites of pressure ulcers in patients with severe neurologic deficits. Reference: Tleyjeh I, et al. Infectious complications of pressure ulcers. http://www.uptodate.com/home. Accessed Dec. 16, 2016

Neurofibromatosis type 1 (von Recklinghausen Disease)

Neurofibromatosis type 1 (NF1), a RAS- opathy, is one of the commonest AD inherited conditions.

Diagnostic criteria:

Two or more of these clinical features establish the diagnosis:

• Six or more café au lait spots (macules or patches).

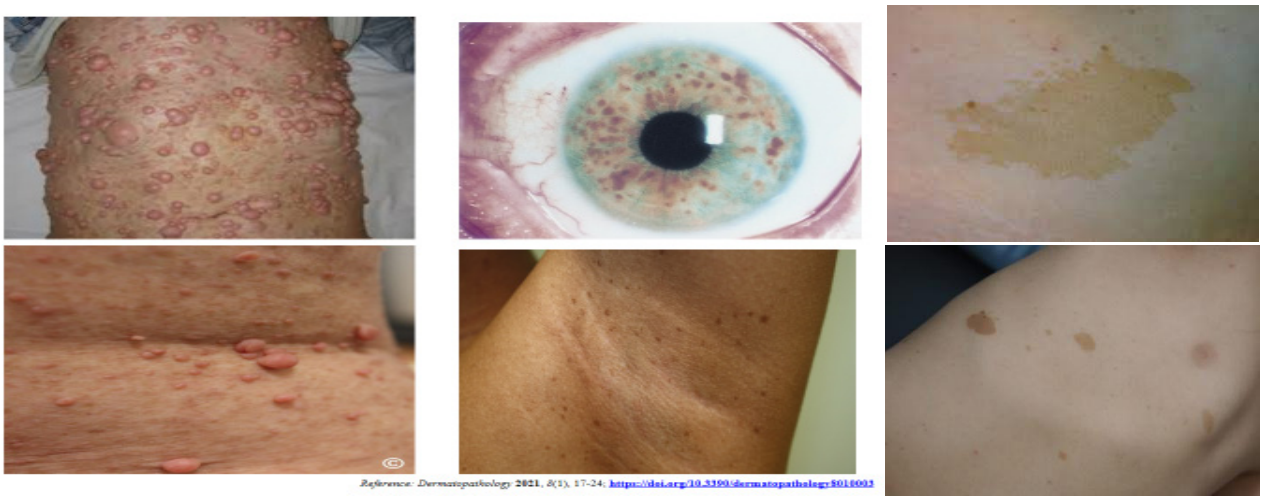
• Axillary or inguinal freckles, 1–3mm in diameter, develop later than café au lait spots.

• Two or more neurofibromas. Dermal neurofibromas also appear later than café au lait spots. Neurofibromas are soft and may become pedunculated. Patients may develop thousands of disfiguring neurofibromas.

• An optic pathway glioma.

• Two or more Lisch nodules (melanocytic hamartomas of the iris). The yellowish-brown nodules within the iris appear before neurofibromas and will confirm the diagnosis.

• Sphenoid wing dysplasia or thinning of the cortex of long bones, with or without pseudarthrosis.



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First-degree relative with NF1 diagnosed by the presence of two or more of the above criteria.

Figure 4. Skin manifestations of NF1. a) café au lait spot b) neurofibromas c) Lisch nodules (melanocytic hamartomas of the iris) d) café au lait spot e) dermal fibroma f) axillary freckles

Reference: Dr Amanda Oakley, Dermatologist, Hamilton, New Zealand, November 2015. DermaNet

Neurofibromatosis type 2

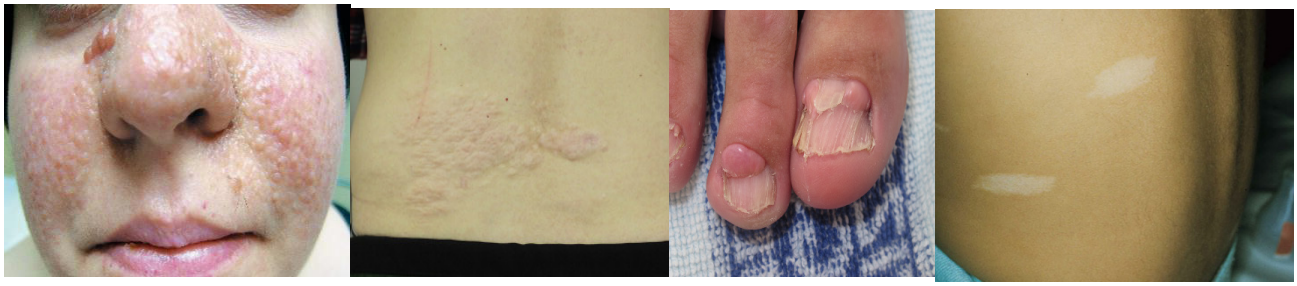
Neurofibromatosis type 2 (NF2) is a rare condition inherited as an AD disorder (incidence about 1 in 40 000). The diagnosis is confirmed, if the individual has bilateral vestibular schwannomas or a family history of NF2 in a first-degree relative plus a unilateral vestibular schwannoma diagnosed by age 30 or any two of: meningioma, glioma, schwannoma, juvenile posterior subcapsular lenticular opacities/ juvenile cataracts. NF2 patients have less skin lesions than NF1. In some rare cases, *are see*afé au lait spots are seen.

Tuberous sclerosis complex (Bourneville disease)

TSC a rare genetic disease that causes non-cancerous (benign) tumors to grow in the brain and several areas of the body, including the spinal cord, nerves, eyes, lung, heart, kidneys, and skin. The triad of symptoms Vogt triad, including epilepsy, sebaceum adenoma and mental retardation.

Mucocutaneous signs:

- Hypopigmented macules (≥3) on the trunk and limbs. Congenital, in a confetti-like pattern.
- Ash leaf patch in 90% of the cases.
- Forehead plaques (may be present at birth) on the scalp, face, or neck.
- Facial angiofibromas (‘adenoma sebaceum’) on nasolabial folds and cheeks in 75% of the patients
- Shagreen patch in 20-30% of the cases.The orange-red patches develop most often on the lower back
- Periungual fibromas (Koenen tumors) in 15-20% of the cases.



- Subcutaneous occipital angiofibromas.

Figure 4. Skin manifestations in Tuberous Sclerosis Complex a) Hipopigmented macule (ash leave spot) b) Angiofibroma faciale (Pringle nodules) c) Shagreen Patch d) Ungual fibromas (Koenen tumours)

Reference:Diagnosis of Tuberous Sclerosis Complex in Adulthood based on Late Presenting Cutaneous Manifestations Shalabi D, Sethi M, Lee H, Cha J and Nikbakht N*

Epidermal naevus syndromes (ENS)

These neurocutaneous syndromes share cutaneous, neurologic, skeletal, and ophthalmologic findings. CNS abnormalities include: infantile spasms, seizures, hemiparesis and intellectual disability. Skin manifestations include: verrucous epidermal naevus, sebaceous naevus, scalp aplasia cutis and café au lait macules. Schimmelpenning syndrome is the most well-known epidermal nevus syndrome. Other ENS are phakomatosis pigmentokeratotica, Becker nevus syndrome, Proteus syndrome.

Capillary malformations

Facial port wine stains, a red congenital red patch that grows over time, is characteristic. Sturge-Weber Syndrome, an encephalotrigeminal syndrome characterized by facial port wine stains, ipsilateral leptomeningeal angioma, epilepsy, abcucens nerve palsy, stroke-like episodes, hemiparesis and intelectual disability. The haemangioma present on the surface of the brain is in the vast majority of cases on the same side as the birth mark and gradually results in calcification of the underlying brain and atrophy of the affected region.

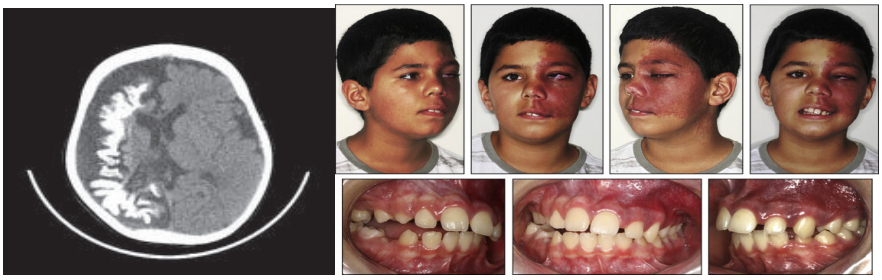


Figure 5. a) Facial port wine stains in Sturge-Weber syndrome b) Brain haemangioma and ipsilatral brain atrophy

Reference: a) Sturge Werber Syndrome, ScienceDirect, Matthew D. Shirley et al b) Thomas-Sohl,etal"Sturge-Weber syndrome: A review". Pediatric Neurology2004

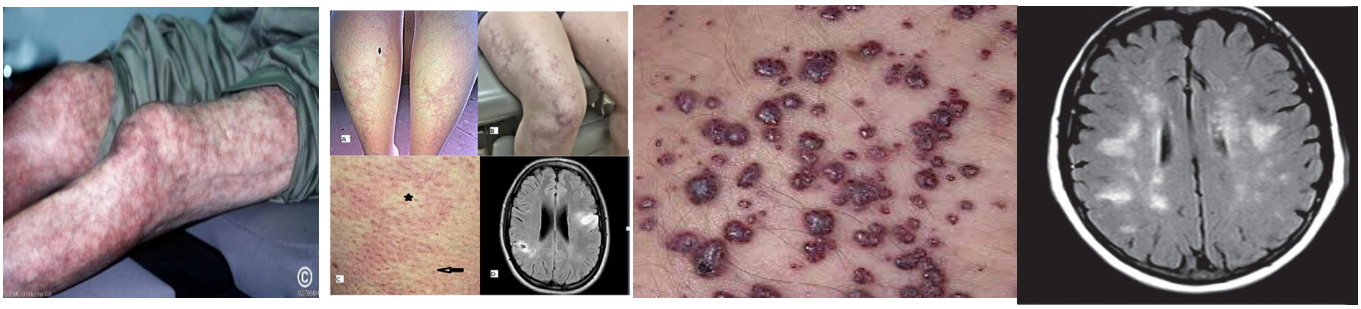
Neurocutaneous syndromes of impaired immunity

- AIDS manifests with cutaneous signs in 80% of the cases. In 5-10% of the cases patients have Herpes Zoster radiculitis.
- *Chediac Higashi Syndrome* (CHS) is characterized of partial albinism and neuropathy.
- *Grischelly Syndrome*: partial albinism with silvery hair and progressive leukodistrophy

Sneddon Syndrome (SS)

Sneddon Syndrome is a rare genetic syndrome that affects small- and medium-sized blood vessels, causing brain ischaemia in young ages. It is characterized by the triad of: livedo reticularis, dementia, recurrent stroke. Other neurologic signs include: vertigo, TIA, epilepsy and depression. *Figure 6*

Fabry Disease



Fabry disease, also known as Anderson–Fabry disease, is one of a group of conditions known as lysosomal storage diseases. Symptoms and signs include acroparesthesia, neuropathy, stroke symptoms, diffuse angiokeratomas, anhidrosis, Raynaud's disease-like symptoms. *Figure 6*

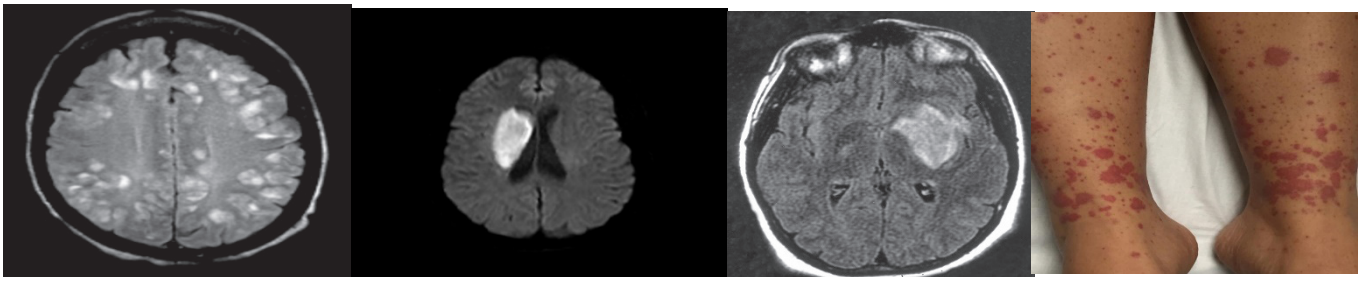
Figure 6. Sneddon Syndrome a) livedo reticularis and b) Stroke in SS patient c) Skin lesions in Fabry Disease d) Multiple infarctions of CNS in Fabry Disease

References: a)b)Caplan LR. Sneddon's Syndrome. Caplan's Stroke c) and d) Eng et al. Fabry disease: guidelines for the evaluation and management of multi-organ system involvement. Genet Med. 2006

Henoch-Schonlein Purpura (HSP)- IgA vasculitis

HSP is a systemic inflammation of small vessels caused by an acute perivascular deposition of immunoglobulin A (IgA) and activation of neutrophils. Neurologic signs include: intracranial hemorrhage with confusion, convulsions, weakness, visual changes, and reduced level of consciousness IgAV is the most common vasculitis in childhood. The incidence decreases with age, but in adults the severity increases with age. Skin findings are usually the first sign of IgAV, with a palpable symmetrical purpura, localized mostly in legs *Figure 7*

Ataxia-telangiectesia (Louis- Bar syndrome).



Ataxia Telangiectasia

(AT)—also known as Louis-Bar syndrome, cerebello-oculocutaneous telangiectasia, or immunodeficiency with ataxia telangiectasia—is a rare inherited childhood neurological disorder that affects the part of the brain that controls motor movement (intended movement of muscles) and speech. This syndrome is characterized by vermian atrophy, ventriculomegaly, ischaemic and hemorrhagic lesions of the brain. Skin lesions include: dry skin, scleroderma, gray hair, impetigo, blepharitis, seborrhoeic dermatitis, non-infectious granuloma and basal cell carcinoma.

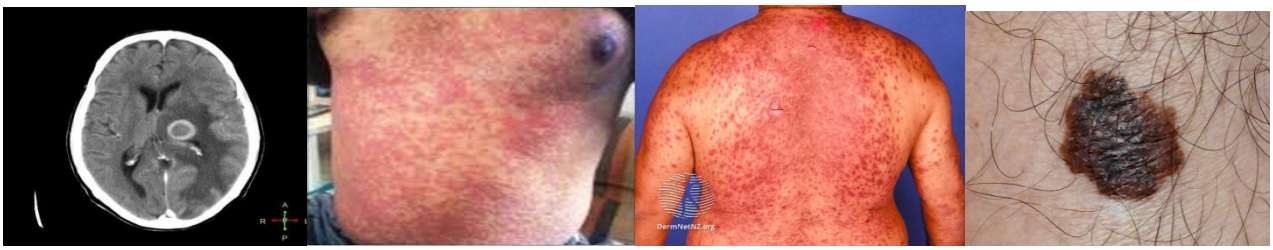
Figure 7. a) HSP skin lesions b) CNS hemorrhage in a patient with HSP c) and d) Brain MRI in a SLE patient

Reference**:** Saadatnia M, Sayed-Bonakdar Z, Mohammad-Sharifi G, Sarrami AH. The necessity of stroke prevention in patients with systemic lupus erythematosus. J Res Med Sci 2012

Systemic Lupus Erythematosus (SLE)

SLE is a chronic autoimmune disease with a multisystemic clinical presentation. In 70% of the cases there is neurological involvement with convulsions, psychosis, diffuse encephalopathy, optic neuropathy, stroke, mononeuritis multiplex, distal axonal neuropathy, miopathy, Miastenia Gravis, etc.

Brain metastasis in Melanoma



Researchers estimate as many as 40% to 60% of those with late-stage melanoma will develop brain metastases, often resulting in death.

Figure 8. a) skin melanoma b) brain metastasis in a patient with melanoma c) Anticonvulsivant Hypersensitivity Syndrome d) Stevens Johnson/TEN in a patient taking lamotrigine Reference: a) and b) Zakrzewski J. et al. Clinical Variables and Primary Tumor Characteristics Predictive of the Development of Melanoma Brain Metastasesc) d)Anticonvulsant hypersensitivity syndrome: incidence, prevention and management. Knowles SR, Shapiro LE, Shear NH.Drug Saf. 1999 Dec;21

Stroke

The neurocutaneous disorders associated with stroke are listed in *Table 2.*

Post- stroke pruritis is a common finding in stroke patients. It is characterized by a very intense pruritis days- weeks after stroke, usually contralateral with the lesion. It is treated with emollients, carbamazepine and amytriptiline.

Disorder	Cutaneous
Amyloidosis VII	Cutis laxa
Behçet's disease	Erythema nodosum, genital and oral ulcers
Cerebral cavernous malformations	angiomas
Diabetes Mellitus	Necrobiosis lipoidica diabeticorum, poorly healing ulcers
Endocarditis	Petechiae, splinter haemorrhages, Osler nodes
Fabry Disease	Angiokeratoma
Haemolytic-uraemic syndrome	Erythematous necrotic skin lesions
Hereditary haemorrhagic telangiectasia	Telangiectasia
Homocystinuria	sparse hair, livedo reticularis, diffuse hypopigmentation
Hypercholesteloraemia	Xanthomas, xanthelasma
Progeria (Hutchinson- Gilford)	Aged skin, alopecia, thin skin, absent eyebrows
Neurocutaneous angioma	Large irregular haemangiomas, angioma
Pseudoxhanthoma elasticum	Pseudoxanthoma, multiple papules, peau d'orange skin
Systemic lupus erythematosus	Photosesitivity, malar rush, telangiectasia, patchy alopecia, mucosal ulcers, angioneurotic oedema, palpable purpura, subcutaneous nodules, gangrene, Raynaud's phenomenon, erythema multiforme

Takayasu's arteritis	Cutaneous necrotising venulitis- palpable purpura

Table 2. Some neurocutaneous disorders associated with stroke

Reference: Neuroscience Research, SmithKline Beecham Pharmaceuticals, New Frontiers Science Park North. Department of Dermatology, The Johns Hopkins University School of Medicine

Cutaneous reaction to neurologic drugs

There is a considerable number of drugs used in neurology that cause adverse skin effects, especially antiepileptic drugs. Some of them are listed below:

i. Acne or acne-like pustular eruptions- phenytoin, phenobarbital, lithium
ii. Dermatomyositis-like- IFN-β
iii. IV Ig may precipitate pompholyx (vesicles on palms and soles) and eczema.
iv. Erythema gyratum repens- • Azathioprine, IFN-α
v. Halo naevi may be induced by immune-modifying drugs, including infliximab, IFN-β1a, adalimumab, tocilizumab.
vi. Azathioprine hypersensitivity syndrome resembles Sweet syndrome, with fever, neutrophilia, and papules/plaques with dense infiltrate of polymorphonuclear cells. Signs mainly on extremities, unlike Sweet syndrome
vii. Anticonvulsivant Hypersensitivity Syndrome- Phenitoin, lamotrigine *Figure 8*
viii. Stevens Johnson/TEN – Carbamazepine, lamotrigine *Figure 8*
ix. Skin hyperpigmentation: levetiracetam
x. Alopecia- IF

Conclusions

The article explores the intricate relationship between the skin and the nervous system. Central and/or peripheral nervous system and the skin share the same source: the ectoderm. The discovery of specific cutaneous manifestations can facilitate the neurologic diagnosis, and leading to further treatment regimens and/or other investigations. Therefore, it is most important that a neurologist thoroughly examine your skin, hair, and nails. If unusual abnormalities are found on your skin or a more in-depth examination is needed, consultation with a dermatologist is recommended.

Neurodermatology studies how the nervous system influences skin health and the development of skin diseases, and how skin diseases can affect the nervous system. Understanding these interactions can help us treat a variety of skin diseases more effectively, especially those that depend on or affect the nervous system. A multidisciplinary approach with dermatologists, neurologists, psychiatrists and histopathologists can be the key to a correct diagnosis

Note from authors: This literature review is based on two recent books on Clinical neurology neurodermatology chapter. The figures are cited separately at the end of the figure- description.

Conflicts of interest: None

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