# Profile of Neurocutaneous Syndromes in Infancy and Childhood

Thesis

*Submitted for Partial Fulfillment of Master Degree in Pediatrics*

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# List of Abbreviations

| Abb. | Full term |
|---|---|
| ADHD | Attention Deficit Hyperactivity Disorder |
| AEDs | Antiepileptic Drugs |
| AML | Angiomyolipoma |
| AMLs | Angiomyolipomas |
| A-T | Ataxia-telangiectasia |
| B/L | Bilateral |
| CALMs | Café-au-lait macule |
| CNS | Central Nervous System |
| CT | Computerized Tomography |
| CVA | Cerebrovascular accidents |
| DNA | Deoxy riboneucleic acid |
| ECG | Electrocardiogram |
| EEG | Electroencephalogram |
| EMG | Electromyogram |
| ERG | Electroretinogram |
| F | Female |
| FLAIR | Fluid Attenuated Inversion Recovery images |
| GABA | Gamma Amino-butyric Acid |
| GI | Gastrointestinal |
| GTPase | Guanosin triphosphatase activating protein |
| HI | Hypomelanosis of Ito |
| HI | Hypomelanosis of ITO |
| HMEG | Hemimegalencephaly |
| HRCT | High-resolution chest computed tomography |
| IP | Incontinentia pigmenti |
| IP | Incontinentia pigmenti |
| IQ | Intelligence Quotient |
| IQR | Interquartile range |
| Kb | kilobases kb |
| KTS | Klippel trenauanay syndrome |
| LAM | Lymphangiomyomatosis |
| M | Male |
| MPNST | Malignant peripheral nerve sheath tumor |
| MRI | Magnetic Resonance Imaging |
| MRS | Magnetic Resonance Spectroscopy |
| mTOR | Mammalian target of rapamycin |
| NF | Neurofibromatosis |
| NF-1 | Neurofibromatosis type-1 |

# *List of Abbreviations* **cont...**

| Abb. | Full term |
|---|---|
| NF-2 | Neurofibromatosis type-2 |
| NIH | National Institutes of Health |
| PRR | Parry romberg syndrome |
| RPE | Retinal pigment epithelium |
| SD | Standard deviation |
| SEGAs | Subependymal Giant Cell Astrocytomas |
| SENs | Subependymal Nodules |
| SPSS | Statistical package for social science |
| SWS | Sturge-Weber syndrome |
| TSC | Tuberous Sclerosis Complex |
| UBOs | Unidentified Bright Objects |
| US | Ultrasonography |
| VEGFD | Vascular endothelial growth factor D |
| VEPs | Visual evoked potentials |
| VHL | Von Hippel-Lindau syndrome |
| XP | Xeroderma pigmentosa |

# Abstract

**Background:** Neurocutaneous syndromes are disorders that lead to growth of tumors in various parts of the body. They're caused by the abnormal development of cells in an embryo and characterized by the presence of tumors in various parts of the body (including the nervous system) and by certain differences in the skin, while some can be diagnosed at birth; others don't produce symptoms until later in life.

**Objectives:** To highlight the clinical presentations of the neurocutaneous syndromes, systemic manifestations & their neuroimaging profile to facilitate their diagnosis, management and counseling.

**Methods:** 41 infants & children presenting with various neurological and cutaneous manifestations who were attending the neuropediatric outpatient clinic of the Children Hospital (Abou El-Rish Hospital), Faculty of medicine, Cairo University, Egypt from October 2013 till June 2014. All cases were subjected to full clinical evaluation & neuroimaging (MRI brain), CT brain for 24 cases, MRS for 3 cases, CT abdominal pelvis for two cases, EEG for 18 cases, EMG for one case, Echocardiography for 16 cases, abdominal ultrasound for 13 cases, IQ assessment for 32 cases, X-ray on the spine &renal artery Doppler for one case, chromosomal study for 3 cases, serum IgA & α fetoprotein level for 2 cases.

**Result:** Nine types of neurocutaneous disorders were identified based on clinical criteria and imaging findings. Neurofibromatosis type-1 (NF-1) was the commonest type diagnosed in 18 cases (43.9%), (Tuberous Sclerosis Complex) I2 cases (29.3%), two cases (4.88%) of each (Sturge Weber Syndrome, Hypomelanosis of Ito, Incotinentia Pigmenti & Ataxia Telangiectasia),and one case 2.44% of each (Klippel Trenaunay Syndrome, Xeroderma Pigmentosum, and Parry Romberg Syndrome).

**Conclusion:** Skin examination is an essential part of clinical examination and is of great help in evaluating patients with various neurological manifestations e.g., macrocephaly, microcephaly, seizures & delayed milestones. Identification of their variable neurological systemic manifestations & their neuroimaging are important for their diagnosis, management genetic counseling.



**Key words:** Neurocutaneous syndromes, neuroimaging, neurofibromatosis.

# Introduction

The "phakomatosis" or (neuro-oculo-cutaneous syndromes, neurocutaneous disorders) are multisystem disorders that have charatristic central nervous system,ocular and cutaneous lesions of variable severity ***(Rook and Burns, 2004).***

The "phakomatosis" concept was formulated early in the twentieth century by the ophthalmologist van der Hoeve. The term, from the Greek φακός, phakos, "spot, lens", suffix-(o)ma (-ωμα) and the suffix -osis, also called "Mother's spot "or" Birth mark "was introduced by Jan van der Hoeve in 1920, before the distinct genetic basis of each of these diseases was understood ***(Enersen and Ole Daniel, 2007).***

The skin and the brain have a common ectodermal origin, so there are many genetic and acquired diseases that affect both tissues. However in some conditions, such as von Hippel-Lindau disease, ectodermal presentation is minimal ***(Neau et al., 2014).***

In NF the cutenous features include six or more café -au -lait macules, axillary or inguinal freckling, two or more iris lisch nodules and two or more neurofibromas or 1 plexiform neurofibroma. InTuberous Sclerosis more than 90% of cases show typical hypomelanotic macules that have been likened to ash leaf on the trunk and extremities. In Sturge Weber there is a cutaneous angioma called a port wine stain that is present at birth and usually covers at least one upper eyelid and the forehead. In Ataxia Telangactasia there are tiny, red, spider like veins in the corners of the eyes or on the ears and cheeks when exposed to sunlight ***(Williams et al., 2009).***

In NF the neurological features include learning disability affecting 30%of children with NF type 1 and seizures in 8%. In tuberous sclerosis there is epilepsy, cognitive impairment and autism spectrum disorders. In Sturge Weber Syndrome epilepsy is seen in 75-90% in patient mainly in the first year of life. The first manifestation of Ataxia Telangactasia appears in the second year of life when the child starts to walk. In Hypomelanosis of Ito seizures and mental retardation are the most common neurological abnormalities ***(Datta et al., 2008).***

NF1 is the most common of all the neurocutaneous syndromes. CNS lesions are frequent and imaging is valuable for diagnosis, treatment and follow-up of patient. Tumors of the central nervous system are frequent. Optic nerve glioma usually affects younger patients with clinical symptoms in one third of cases. Magnetic Resonance Imaging (MRI) shows fusiform enlargement with variable enhancement of the optic nerve. These tumors are usually non-aggressive with good prognosis. Other gliomas and astrocytomas can occur as well, usually midline in location, which also generally have good prognosis ***(Jacques and Dietemann, 2005).***

Nerve sheath tumors are an inherent characteristic of NF1 and may develop as cutaneous, subcutaneous and plexiform neurofibromas ***(Ferner, 2007).*** Plexiform neurofibromas may cause radicular symptoms. They more frequently involve the lumbosacral plexus. Neurofibromas are homogeneous oval shaped tumors that may extend into the spinal canal ***(Jacques and Dietemann, 2005).***

Among patients with neurofibromatosis type-1 (NF1), however, malignant peripheral nerve sheath tumors are the leading cause of

mortality, with an incidence of 4.6-13% ***(Evans et al., 2002; Rasmussen et al., 2001).***

They may develop de novo or from sarcomatous degeneration of a pre-existing plexiform neurofibroma. Osseous lesions have been described including progressive thoracic scoliosis, vertebral anomalies, long bone anomalies, and rib anomalies. Vascular lesions may occur resulting in arterial hypertension and aneurysm formation ***(Jacques and Dietemann, 2005).***

In Tuberous Sclerosis MRI may show cortical tubers, subependymal nodules, giant cell astrocytoma, and linear white matter abnormalities. Computed tomography (CT) scanning may be required to adequately show calcifications, which are most commonly seen in subependymal nodules. In addition to these typical findings, MRI may also detect cerebellar tubers subtle cortical dysplasia, transmantle dysplasia, hemimegalencephaly (HMEG), focal megalencephaly, and cortical infoldings ***(Leventer et al., 2008).***

Neuroimaging (CT-scan/angio-magnetic resonance imaging [MRI]) provides the diagnosis of Sturge Weber syndrome, when it shows ipsilateral leptomeningeal angioma ***(Maruani, 2010).***