

Profile of Neurocutaneous Syndromes in Infancy and Childhood

Thesis

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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) 12 cases (29.3%), two cases (4.88%) of each (Sturge Weber Syndrome, Hypomelanosis of Ito, Incontinentia 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 characteristic 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 cutaneous 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. In Tuberous 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 Telangiectasia 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 Telangectasia 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*).