INCIDENCE AND CLINICOPATHOLOGICAL FEATURES OF NEUROCUTANEOUS DISORDERS

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CERTIFICATE

This is to certify that this dissertation entitled **"INCIDENCE AND CLINICOPATHOLOGICAL FEATURES OF NEUROCUTANEOUS DISORDERS"** is a bonafide work done by **DR.S.KAYALVIZHI MONEY,** Post Graduate in M.D. Dermatology, Venereology and Leprosy, Madras Medical College, Chennai- 600 003, during the academic year 2006-2008. This work has not been formed previously the basis for the award of any degree.

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DECLARATION

I, **DR. S. KAYALVIZHI MONEY**, solemnly declare that this dissertation titled **"INCIDENCE AND CLINICOPATHOLOGICAL FEATURES OF NEUROCUTANEOUS DISORDERS"** is a bonafide work done by me at Madras Medical College during 2006-2008 under the guidance and supervision of Prof. Dr. B.Parveen, M.D., D.D., Professor and Head, Department of Dermatology, Madras Medical College, Chennai-600 003.

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CONTENTS

INTRODUCTION

Neurocutaneous disorders are genetically determined disorders showing both cutaneous and neurologic involvement. The definition includes both hereditary and nonhereditary phenotypes but excludes acquired disorders.

Either they follow the established Mendelian modes of inheritance or they represent lethal mutations surviving by mosaicism, or they belong to the group of chromosomal disorders.

Some clinicians still use phacomatosis to categorize particular neurocutaneous diseases characterized by patchy lesions involving the skin and the nervous system. Unfortunately, this term has diminished rather than increased our understanding of these disorders because the group of phacomatoses has never been well defined. Today, this term should no longer be used for the classification of neurocutaneous diseases but may be applied, together with a specifying adjective, to some genetically determined diseases characterized by the presence of multiple nevi, such as phacomatosis pigmentovascularis.

REVIEW OF LITERATURE

Neurocutaneous disorders are genetically determined disorders showing both cutaneous and neurologic involvement.

Either they follow the established Mendalian modes of inheritance, or they represent lethal mutations surviving by mosaicism, or they belong to the group of chromosomal disorders. Genetic classification will confirm the well established differences between Autosomal dominant, Autosomal recessive and X-linked gene expressions[1].

The neurocutaneous syndromes can be classified as follows:

I. Autosomal Dominant Phenotypes:

1. Neurofibromatosis
2. Tuberous sclerosis complex
3. Waardenburg syndrome.

II. Autosomal recessive Phenotypes:

1. Xeroderma Pigmentosum
2. Elejalde syndrome
2. Oculo cutaneous albinism

III. X-linked male - lethal Phenotypes:

1. Incontinentia pigmenti.

2. Focal Dermal hypoplasia

IV. X-linked – Non lethal Phenotypes:

1. Albinism – Deafness syndrome.
2. Menkes disease

V. Lethal autosomal mutations surviving by mosaicism:

1. Sturge Weber Klippel Trenaunay syndrome
2. Schimmelpenning syndrome
3. Nevus comedonicus syndrome
4. Proteus syndrome

VI. Chromosomal disorders:

1. Klinefelter syndrome
2. Trisomy 21

VII Phenotypes still unclassifiable according to formal genetics:

1. Johnston syndrome
2. Satoyoshi syndrome

THE NEUROFIBROMATOSIS

The neurofibromatosis comprise several distinct genetic disorders that lead to the formation of tumours surrounding nerves and a variety of pathological features. The main two forms are:

1. Type -1 neurofibromatosis (85%)
2. Type-2 neurofibromatosis (10%)[2]

NEUROFIBROMATOSIS - 1

Syn : VON RECKLINGHAUSEN NEUROFIBROMATOSIS

Definition

NF -1 is an inherited neuroectodermal abnormality, characterised by the presence of six or more café-au-lait spots, axillary freckles, multiple neurofibromas and Lisch nodules.

History

Friedrich von Reckling Hausen in 1882 coined the term neurofibroma, who was the first to appreciate the neural character of the tumours. Virchow – reported positive family history.

Etiology

The mode of inheritance is autosomal dominant with 100% penetrance. Sporadic cases result from a high gene mutation rate. The prevalance is 1 : 2500 – 3500. No gender or racial preferences. The gene for NF1 is located on chromosome 17. NF-1 gene has now been cloned and encodes a protein named neurofibromin, which is expressed

predominantly in neurons, Schwann cells, oligodendrocytes and leucocytes, keratinocytes and melanocytes. Neurofibromin shows similarity to the GTP ase – activating protein - and is capable of downregulating Ras activity.

Mast cells are increased in neurofibromas which may be involved in the development and growth of these tumours by producing several growth factors such as histamine and tumour necrosis factor α (TNF α).

CLINICAL FEATURES

According to the National Institute of Health Consensus Development Conference Statement is based on 2 or more of the following criteria[3].

1. Six or more café-au-lait macules over 5mm in greatest diameter in prepubertal and over 15mm in post pubertal.
2. Two or more neurofibromas of any type or one plexiform NF.
3. Freckling in the axillary or inguinal regions.
4. Optic glioma
5. Two or more Lisch nodules
6. Sphenoid dysplasia or thinning of long bone cortex with or without pseudoarthrosis
7. A first degree relative with NF-1 by the above criteria

CUTANEOUS FEATURES - Café-au-lait Macules (CALM)

Sharply defined light brown macules and patches with smooth borders. Earliest

to appear. Found all over the body except scalp, eyebrows, palms and soles. They vary in size.

Neurofibromas

1. Cutaneous neurofibroma or mollusca fibrosa: are soft, lilac, pink, sessile or pedunculated tumours, mostly on the trunk and limbs, on gentle digital pressure, the lesions herniate into the dermis – 'button holing'. In women they are prominent in the areola.
2. Plexiform neurofibromatosis : Pathognomonic for NF-1 (occurs in <1%), Diffuse elongated fibroma along the course of a nerve, frequently involving the trigeminal or upper cervical nerves. They feel like a "bag of worms."
3. Elephantiasis neurofibromatosa is associated with over growth of the subcutaneous tissue and of the skin, produces gross disfigurement. Dark pigmented patches over plexiform neurofibroma may be present. If the tumour extends to the midline, it may indicate that the tumour involves the spinal cord. Neurofibromas may also involve viscera and blood vessels which may lead to constipation, bleeding obstruction. Plexiform neurofibromas can be a precursor lesion for malignant peripheral nerve sheath tumour .[4]

3. Freckling

Freckles are small, tan brown macules that are 1–3mm in diameter, diagnostic only when present in the axilla and groin. Crowe's sign[5] indicates axillary freckling. Palmar freckling[6] can be a sign of neurofibromatosis.

Other Diagnostic Cutaneous Features[7].

Hypopigmentation is of 3 types – those resembling ash leaf macules, small punctate macules and local areas of hypoplasia that can appear blue red (Pseudo atrophic macules). Giant pigmented hairy naevi, cutis verticis gyrate, angiomas, hypertrichosis, hyperpigmentation, and rarely piebaldism are associated with NF-1. The typical order in which clinical features appear are 1) Café-au-lait macules 2) Axillary freckling, 3) Lisch nodules, 4) neurofibromas (according to NIH, National Institute of Health Criteria). Pruritus is a prominant but non specific cutaneous finding in 10% of cases due to increased mast cells in the skin.

NON CUTANEOUS FEATURES

I. Ocular

Lisch nodules - Pigmented melanocytic iris hamartomas are dome shaped, translucent brown spots, bilateral and asymptomatic, most common manifestation of NF-1[8], occurs in more than 90% of patients and does not occur in segmental type of NF.

II. Neurological Manifestations

Occurs in 40% of patients. Most common is optic glioma. Optic glioma - is an Astrocytic tumour of the optic nerve occurs in 15% of patients with NF1, 80% are asymptomatic. The common features are epilepsy, cerebrovascular accident, headache, intellectual, behavioural, emotional disturbances. 30% have learning disabilities[9] and poor school performance. The common intracranial tumours reported are astrocytomas and schwannomas.

III. Skeletal Manifestations

They are kyphoscoliosis (2%)[10], sphenoid wing dysplasia often results in pulsating exophthalmos, congenital pseudoarthrosis (common in tibia or radius) (0.5%). vertebral scalloping, macrocephaly, short stature (growth hormone deficiency is reported). Thinning of cortex resulting in pathological fractures.

IV. Oral Lesions

Occurs in (5 – 10%) of cases as Unilateral macroglossia, papillomatous tumours of palate, tongue, buccal mucous membranes and lips.

V. Endocrine abnormalities[11]

They are precocious puberty, acromegaly / gigantism, Addison's disease, hyperparathyroidism, gynaecomastia and phaeochromocytoma.

VI. Renal[12]

The common renal manifestation are renovascular hypertension[13] due to (a) renal artery stenosis, b) phaeochromo cytoma, c) coarctation of aorta. Renal tubular defect resulting in osteomalacia. Lower urinary tract symptoms are due to obstruction and Wilms tumour.

VII. Pulmonary Changes (10-20%)

1. Firbrosing alveolitis, 2. Interstitial fibrosis

VIII. Gastro Intestinal (25%)[14]

Constipation (dysfunction of colonic musculature/colonic NF). Recurrent Haemorrhages or obstruction or intussuception, frequently occurs in stomach and

jejunum.

IX. Malignancies Associated with NF-1(3-5%)[15]

They are neurofibrosarcoma (1.5-15%), rhabdomyosarcoma, retino blastoma, malignant melanoma, Wilms tumour, several types of leukemia, malignant schwannoma with melanocytic differentiation.

X. Other Association of NF-1

Gynaecomastia, Neurofibromatosis of the vulva[16], Neurofibromatosis type I and Mycosis fungoides[17] and associated with glioblastoma in a case of multiple sclerosis[18], NF-1 and Mc Cune – Albright syndrome occuring in the same patient[19], Juvenile Xantho granuloma, late onset NF in a liver transplant recipient[20],. Coexisting Von Recklnighausens neurofibromatosis and von Hippel – lindau's disease[21], common variable immuno deficiency[22] with NF-1, congenital absence of the inferior rectus muscle[23] and NF-1 with retinal vein occlusion[24] in one case of NF-1 are reported.

RICCARDI'S Classification System of NF[25]

NF	Inheritance	Main Clinical – Features
NF1	Autosomal dominant Gene 17q 11.2 (AD)	Café-au-lait spots (CLS), axillary or inguinal freckles, Lischnodules, NF, opticglioma, bone changes.
NF2	AD, Gene 22q12.2	Bilateral vestibular (acoustic) schwannoma, multiple CNS Tumours – meningiomas, ependymomas, spinal astrocytomas, cataracts, retinal hamatoma.
NF3	AD (or)	Features of NF1 and NF2 including some CLS,

	Sporadic	freckling, NF, CNS or paraspinal tumours, no vestibular shawannoma or lisch nodules.
NF4	Sporadic	Atypical NF. Mostly occur as a variant of type II
NF5	Sporadic or A.D somatic mutation of NF1 with or without germ cell mutation	Segmental NF[26] - NF-1 that is localized to one quadrant /one side of the body – arises from post zygotic somatic mutation and is not heritable. It can occur as bilateral segmental NF with or without CLS
NF6	AD	Multiple CLS, without neuro fibroma. It must occur in two generation to be diagnosed.
NF7	Sporadic	Adult onset cutaneous NF with onset at end of 3rd decade or later. Lisch nodules are absent. NF also appears after immunosuppresion[22].
NF8		Case which are definitely NF but do not fit into any of the other categories.

Histopathology[27]

The histologic spectrum of neuro fibromas in NF-1 is as follows:

Types

I. Extra neural Variants:

(i) Cutaneous extraneural variant (Extra neural sporadic cutaneous neurofibromas ESCN)

(ii) Deep, diffuse (extraneural) variants.

II. Intraneural Variants:

(i) cutaneous or deep circumscribed variant

(ii) Plexiform variants.

Histological Types

1. Extra neural sporadic cutaneous neurofibromas (ESCN)

These tumours are faintly eosinophilic, and are circumscribed but not encapsulated showing thin spindle cells with elongated, wavy nuclei which are regularly spaced among thin wavy collagenous strands. It can be homogenous (closely packed) or loosely spaced in a clear matrix. There are large number of mast cells and nerve fibres.

2. Extraneural deep diffuse variant

The matrix is either delicately fibrous and faintly acidophilic or more coarsely, fibrous and brightly acidophilic. Nerves within the lesion usually are small, internally symmetrical and hypercellular and the perineuria are hyperplastic.

3. Deep circumscribed (intra neural) variant and plexiform variant

Here, the axial bundles of symmetrically arranged nerve fibres, are remnants of the axial bundle of the nerve of origin. The schwann cells are hyperplastic and tightly placed. Ultrastructurally, the cells of neurofibroma resemble those of perineural cells/schwann cells as well as fibroblasts. Special stains used are Silver stain and Bodian stain. Immuno histochemical markers that are used are S-100 protein (+), CD57 antigen (leu-7), Myelin basic protein

(MBP), NSE (Neuron – Specific enolase), GFAP (Glial fibrillary acidic protein and EMA (Epithelial membrane antigen).

Variants

There are 3 variants. Schwann cells with enclosed axons, are an integral part of NF. Perineural variants are rather, uniformly & densely fibrous, and their cells are bi or tri polar with rigid processes. Endoneurial variants are characterised by thickened perineurium with few axial bundles and isolated cells, in an expanded, mucinous endoneurial component. In Schwannaian variants, thickened perineurium with few axial bundles and spindle cells are spaced among asymmetrical collagen bundles.

Histopathology of

Café-au-lait macules

Shows a total increase in the amount of melanin in melanocytes and keratinocytes by silver stain. Melanocyte count is higher than in normal individuals. Giant melanosome, 'Macro melanosomes' are present. (Autophagosome merged with a secondary lysosome)

Lisch nodules

Consists of condensation of spindle cells on the anterior iris surface. Immuno histochemically positive for S100 and vimentin.

Freckles

Hyperpigmented basal layer. No elongation of rete ridges. No increase in

melanocyte concentration.

TUBEROUS SCLEROSIS COMPLEX (TSC)

Synonyms : EPILOIA, BOURNEVILLE'S DISEASE

Definition

Tuberous sclerosis complex (TSC) is an autosomal dominant disease attributable to mutations in one of the two different genes. Lesions are characterized by systemic hamartomas involving mostly the skin, nervous system, heart, eyes and kidneys.

History

Virchow (1860) :Was the first person to describe the brain lesions in TS. Bournville (1880) :Showed relation between the skin and brain lesions Vogt (1908): Described the classic triad of Adenoma sebaceum, epilepsy & mental retardation. Van der Hoeve: Introduced the term phakomatosis Phakos is the Greek word means lentil, flatplate or spot.

Epidemiology

Occurs in 3-10 / 100000. All races and both sexes are affected and has world wide distribution.

Etiology

Inheritance is by: 1. Single autosomal dominant gene with variable expression of 40%, 2. Sporadic cases due to new mutations. (60%).

2 specific genes are involved, namely :

I. TSC 1 (Chromosome 9q34), it encodes for a protein ('HAMARTIN') [28]. It accounts for 30-50% of all familial cases.

II. TSC 2 (Chromosome 16p13) : It encodes for a protein "TUBERIN"[28] which in homologous to GTP activating protein Rap1 is involved in regulation of cell proliferation & differentiation (similar to Ras oncogene in neurofibroma). When tumour suppressor role is lost, tumour formation occurs. Also, loss of heterozygosity in TSC 2 gene leads to tumour production.

Clinically

The most commonly observed manifestations are of skin, CNS followed by ocular, cardiac and renal.

In 1998, the diagnostic criteria from the consensus report of the National Tuberous Sclerosis Association were modified and divided into 2 groups: major and minor criteria as followed.

Revised Diagnostic Criteria for Tuberous Sclerosis Complex[29]:

Major features:

- Facial angiofibromas or forehead plaque
- Nontraumatic ungula or periungual fibroma
- Hypomelanotic macules (3 or more)
- Shagreen patch (connective tissue nevus)
- Multiple retinal nodular hamartomas
- Cortical tuber

- Subependymal nodule
- Subependymal giant cell astrocytoma
- Cardiac rhabdomyoma, single or multiple
- Lymphangiomyomatosis
- Renal angiomyolipoma

Minor features:

- Multiple randomly distributed pits in dental enamel
- Hamartomatous rectal polyps
- Bone cysts
- Cerebral white matter radial migration lines
- Gingival fibromas
- Nonrenal hamartoma
- Retinal achromic patch
- "Confetti" skin lesions
- Multiple renal cysts.

Definite TSC : Either 2 major features or 1 major feature plus 2 minor features.

Probable TSC: 1 major feature and 1 minor feature

Possible TSC: Either 1 major feature or 2 or more minor features.

CLINICAL FEATURES : Cutaneous – Seen in 60 to 70%

1. Facial angiofibroma (80 to 90%) starts at around 3-10 years. 80 to 90% starts at around 3 to 10 years. Firm, discrete, red brown, telangiectatic papules, 1 to 10 mm

in size, extending from nasolabial furrows to the cheeks and chin. They are rarely present in the forehead and scalp. Unusual types - Cauliflower like, segmental forms with unilateral distribution[30]. Rarely solitary angiofibroma is reported as an abortive form of TSC. Multiple facial angiofibroma like lesions have been observed in multiple endocrine neoplasms. (Multiple Endocrine Neoplasia Type1)

2. Ash leaf macules (85%). They are ovoid or lance ovate shaped macules present at birth (earliest marker) [31,32].Also seen in a confetti like or segmental distribution and easily detectable by wood's lamp. They are commonly seen in trunk and limbs.
3. Shagreen patch (25 to 50%) commonly located in lumbosacral region[33], irregularly thickened , slightly elevated, skin colored plaque with a "pig skin', 'elephant hide', or 'orange peel appearance.
4. Periungual fibromas (Koenen's tumours)[34] 15 to 20% smooth, firm, flesh colored excrescences emerging from the nail folds. It appears after or around puberty. These fibromas lead to thinning and destruction of the nail plate. They are 5 to 10mm in size.

Other cutaneous lesions

Gingival, palatal & lip fibromas, firm fibromatous plaques over the fore head / scalp, soft fibromas in neck & axilla (5.7%), port wine stain, café-au-lait macules, poliosis. Enamel pits (common in adults) which are conical and cylindrical shaped, 80-500 microns in size is a constant and pathognomic sign.

Systemic Manifestation : CNS

Seizures[35] – seen in all cases with mental retardation. Earliest and most frequent complaint in TSC. They may be temporal lobe epilepsy, persistent infantile spasm like seizures (21.2%), tonic clonic seizures (37.1%), intractable seizures. Mental deficiency (60 to 70%) with or without behavioural disorders, psychiatric manifestations like schizophrenia and depression can be seen. Tumours : Sub ependymal giant cell astrocytoma, cortical tubers, sub ependymal nodules. Forehead plaque may be a cutaneous marker of CNS involvement in TSC[36].

II. Renal manifestations

The common renal manifestations reported are renal angiomyolipoma[37], renal artery stenosis, aneurysmal dilatation of internal carotid artery and renal arteries and polycystic kindneys (12%). Hypertension in children with TSC can be due to renal parenchymal lesions (cysts and angiomyolipomas). Other rare reported features are unilateral anglomyolipoma and renal failure. Malignant epitheloid renal angiomyolipoma in a patient with TSC is reported. In some cases, this is related to a contiguous gene syndrome because mutations span both the TSC2 gene and the adjacent polycystic kidney disease gene (PKD).

III. Pulmonary Manifestation[38]

Pulmonary lymphangioleiomyomatosis, proliferation of smooth muscle cells is common in women. Micronodular multifocal pneumocyte hyperplasia, lung cysts and recurrent intra pleural cysts are common. Acute pulmonary embolism from cardiac

tumours are reported. Others are micronodular pneumocyte hyperplasia of the lung, spontaneous pneumothorax, chylothrox due to underlying pulmonary disease.

IV. Ocular Manifestation 50%

Occur in 50%. Retinal phacomas are seen. Pigmentary and other retinal abnormalities can occur. Symptoms are rare. There may be scotomas or amaurosis. Hypopigmented spots in the iris also occur.

V. Cardiac Manifestation

Benign rhabdomyomas of the heart are common and may be associated with conduction defects. 80% of all children presenting with Rhabdomyoma have TSC. Fetal cardiac rhabdomyomatosis is a prenatal marker for the detection of latent TSC[39].

VI. Other disorders associated with TSC

Benign tumours have been found in the liver, thyroid, testes and gastrointestinal tract. Pituitary –adrenal dysfunction, thyroid disorders and premature puberty, primary localized gigantism and diffuse cutaneous reticulohistiocytosis have been reported.

HISTOPATHOLOGY[27]

- Angiofibroma : hyperplastic blood vessels with increased dermal collagen (synthesis & turnover), atrophic sebaceous glands and immature hair follicles.
- Shagreen patch: 2 types (histopathological). Sclerotic mass of very broad collagen bundles in an interwoven pattern (common), Uniform mass of collagen

with fibroblasts.

- Periungual fibromas: Distal part: Loose collagen & many blood vessels. Proximal part: Dense collagen bundles with few capillaries.
- Ash leaf macule: normal number of melanocytes, defective melaninisation due to decreased tyrosinase activity.

XERODERMA PIGMENTOSUM

Definition:

Xeroderma Pigmentosum is a rare autosomal recessive disease characterized by photosensitivity, pigmentary changes, premature skin ageing, neoplasia and abnormal DNA repair. Some patients with XP also have neurological complications.

History:

The initial report of this disorder was made by Hebra and Kaposi in 1874[40] and the term Xeroderma pigmentosum, meaning pigmented dry skin, was introduced in 1882. Cleaver (1968)[41] reported defective DNA excision repair in UV irradiated fibroblasts in patients with XP.

Epidemiology:

XP is distributed worldwide, frequency being 1:250,000, inherited autosomal recessively with equal sex ratio.

Aetiology and Pathogenesis :

There are at least eight different subtypes that are recognized, designated as complementation groups A-G and XP variant. 80% of patients with XP show a defect in the initiation of DNA excision repair of UV photoproducts. Repair replication is reduced in all cell types.

Nucleotide excision repair[42]. This process, whereby damaged DNA is removed and replaced with new DNA using the intact strand as a template, involves the products of some 30 genes[43].

The names of the XP genes have superseded those of the corresponding excision repair cross-complementing genes. The initial step in the process involves recognition of the damaged DNA by the XP-C with its partner HR23B. This results in the recruitment of the dual function transcription factor TFIIH, composed of at least six subunits including XP-B and XP-D proteins, which have helicase activity. These helicases open out the structure at the damaged site. XP-A verifying the positions of other proteins on damaged structure. XP-G and XP-F cut DNA on either side of damage. New DNA is joined with old DNA by ligase. XP-E binds specifically to UV irradiated DNA and assists in the early recognition.

Drug and Chemical Hypersensitivity[44] **:**

A number of DNA damaging agents other than UV radiation have been found to yield hypersensitive responses with XP cells. These agents include drugs (psoralens, chlorpromazine), cancer chemotherapeutic agents (cisplatin, carmustine), and chemical

carcinogens (benzopyrene derivatives). These agents induce DNA damage whose repair involves portions of the DNA repair pathways that are defective in XP.

XP Variant[45] :

20% of XP patients called XP variants, have normal NER but have a defect in an alternative repair process, known as post replication or daughter – strand repair. XP variants have a defect that manifests as a reduced molecular weight of newly synthesized DNA in UV-irradiated cells.

The majority of patients are in group C, and they show no neurological disease. Patients in group A tend to develop neurological disease before the age of 7 years, group D tend to develop neurological damage after 7 years[46].

Skin photosensitivity :

Some cases of the typical form show a papular and vesicular reaction, mainly to light in the 290 – 320nm range[47]. The minimal erythema dose is lower than normal at most wavelengths.

XP and Neoplasia:

Cultured dermal fibroblasts from XP patients exhibit increased UV-induced mutagenesis. Neoplasms in sun exposed areas of XP patients are due to the result of UV induced mutations. Mutations bearing a UV signature in the p53 and PTCH genes[48]. UV exposure also triggers a complex series of signal transduction pathways that result in immunosuppression of the skin, which may be an important factor[49].

CLINICAL FEATURES:

Cutaneous Features[50]:

The skin is normal at birth. Onset is between 6 months and 3rd year of life. Rate of progression is unpredictable. Freckling and increasing dryness on light –exposed surfaces are usually the earliest manifestations; they may follow and acute sunburn or more persistent erythema. The freckles appear first on the face and hands and later on other exposed parts. Telangiectasias and small angiomas appear. Small, round or irregular, white, atrophic spots are soon added. Some follow crusted vesiculobullous lesions. Superficial ulcers, healing with difficulty, leave disfiguring scars, and contractures may produce ectropion.

Benign tumours like keratoacanthomas and actinic keratoses, malignant tumours like basal cell carcinoma, squamous cell carcinoma. melanomas, angiosarcoma and fibrosarcoma may occur.

Occular lesions:

Eyes are affected in 80% of XP patients. Photophobia and conjunctivitis are common early symptoms. Ectropion, destruction of the lower lids, symblepharon, ulceration, pigmented macules, vascular pterygium, corneal opacities and epitheliomas of the lids, conjunctiva or cornea may develop.

Neurological Complications:

Neurological abnormalities occur in approximately 20% of XP patients, with one or more of the following: mental retardation, areflexia or hyporeflexia, spasticity, ataxia, sensorineural deafness, seizures dysphasia and abnormal electroencephalographic

findings. DNA repair mechanisms are essential for maintaining the normal function of neurons, and progressive damage, perhaps caused by ingested or endogenous chemicals, might cause premature death of susceptible neurons.

The most severe form, known as the De Sanctis-Cacchione syndrome[51], involves the cutaneous and ocular manifestations of classic XP with additional neurologic and somatic abnormalities, including microcephaly, progressive mental deterioration, low intelligence, hyporeflexia or areflexia, choreoathetosis, ataxia, spasticity, Achilles tendon shortening leading to eventual quadraparesis, dwarfism, and immature sexual development.

Associations are short stature, Cockayne's Syndrome,[52] SLE[53] and Pilomatricoma.[54]

HISTOPATHOLOGY

Resembles senile skin. Epidermis is thinned and flattened and the dermal collagen shows basophilic degeneration. Irregular proliferation of rete pegs, heavily laden with pigment, is a distinctive feature. Electron microscopic studies[55] show shrinkage of kerationocytes and their nuclei. Melanocytes are also abnormal, with polymorphic melanosomes, and there may be giant pigment granules in melanocytes or keratinocytes. The dermal fibroblasts appear to behave like macrophages. In hypopigmented macules the melanocytes are scanty, but Langerhans cells are numerous[56].

WAARDENBURG SYNDROME

Definition

It is an autosomal dominant neural crest cell disorder, phenotypically characterized by hearing impairment and disturbance in pigmentation. It has a variable penetrance of its constituent anomalies[57].

Type 1 : Classical form, with dystopia canthorum occurs due to mutation of the PAX-3 gene on chromosome 2q35. Sensory neural deafness is due to lack of melonocytes in inner ear and defective development of striae vascularis.

Type II : Similar features but, lacks dystopia canthorum. Mutation in MITF gene.

Tpye III : (Klein–Waardenburg syndrome) associated with limb abnormalities and dystopia canthorum, due to mutation of the PAX3[58] gene on chromosome 2q35.

Type IV : Caused by mutations in the genes for endothelin-3[59], endothelin –B and SOX 10. Variant – associated with Hirschsprung's disease also called as Shah – Waardenberg syndrome[60].

Ultra structurally, the amelanotic skin shows absence of melanocytes[61]. In the pigmented areas, there are abnormalities of the melanocytes and melanosomes.

CLINICAL FEATURES[62]

The abnormalities are present at birth. The most constant features of the syndrome is lateral displacement of the inner canthi and the lacrimal puncta, prominent nasal root, and medial eyebrows, congenital deafness and heterochromic irides. White forelock with

premature graying of hair. Some cases show piebaldism.

NAEVUS COMEDONICUS

Synonyms : COMEDO NAEVUS

Definition : First described in 1895. The comedo naevus is a linear lesion comprising numerous keratin filled pits sometimes with acneiform pustules.

AETIOLOGY

It is an uncommon developmental defect of the pilosebaceous apparatus, which can be associated with various developmental abnormalities of the skeletal system, the CNS, skin and eye. This reflects mosaicism for a variety of mutations that can predispose to acne. The lesion occurring in the palms, soles and glans penis could arise from an ectopic pilosebaceous unit or eccrine duct.

HISTOPATHOLOGY

Deep and wide invaginations of epidermis filled with concentric lamellae of keratin. Rudimentary hair follicles, sebaceous glands and trichilemmal cysts can be seen in such lesion. Interfollicular changes typical of common verrucous epidermal nevi is sometimes seen.

Types: There are two other autosomal disorders featuring widespread comedones.

1. **Familial diffuse comedones :** Commonly called as ‘nevus comedonicus’. The comedo-like lesions appear in a diffuse bilateral distribution.
2. **Familial dyskeratotic Comedones :** Here comedones are less extensive and

demonstrate dyskeratosis histologically.

CLINICAL FEATURES - Cutaneous

Comedo naevi comprises of groups of pits filled with black keratinous plugs resembling black heads. There may be one or several lesions may be very extensive common sites – face, neck, trunk and upper arm, palms, soles and glans penis may be occasionally involved. Scalp is rearely affected. Lesions are rarely present at birth but more often appear during childhood or adolescence.

Associations : Trichilemmal[63] cyst, benign and malignant tumours, ipsilateral cataract, skeletal malformations, extensive naevus flammeus, transverse myelitis and perforating elastoma.

Complications : Chronic inflammation, suppurations fistula formation and hypertrophic scarring (nevus acneformis)

EPIDERMAL NAEVUS SYNDROME

Synonyms : Feurstein – Mims syndrome; Schimmelpenning's syndrome; Organoid Naevus syndrome; Jadassohn's naevus phakomatosis.

Definition : The epidermal nevus syndrome is a disease complex of epidermal nevi and developmental abnormalities of different organ systems, like skeletal, CNS, ocular, dental and cardiovascular system as well can be involved.

Etiology : It is likely that the syndrome reflects genetic mosaicism for one or more lethal autosomal dominant genes.

I. Cutaneous Associations.

The verrucous epidermal naevi and sebaceous naevi are variants of a single pathological process, differing in the site of lesion. Other cutaneous abnormalities are naevi flammei, hypochromic naevi, café-au-lait macules, congenital melonocytic naevi and spitz naevi. Naevi can involve mucosae of the mouth, anus or genitalia. Naevus sebaceous syndrome association in 3 patients is reported[64].

II. Dental Anomalies

Enamel hypoplasia, hypodontia, malformations of the teeth, maxillary giant cell granuloma.

III. Skeletal Abnormalities

Kyphosis, scoliosis, cystic and lytic changes[65], hypertrophy and atrophy, short limbs, syndactyly, vitamin – D resistant rickets[66] with bone and muscle weakness.

IV. Neurological abnormalities[67]

Occurs in 50% of patients. More frequent in patients with sebaceous naevi on the head and neck. 50% of patients have seizures especially infantile spasms. 50% has mental retardation, 20% have spastic hemiparesis and spastic tetraparesis.

CNS structural abnormalities

Commonest : Ipsilateral gyral malformations, complete or partial hemimegalencephaly, vascular malformations, hemiatrophy, posterior cranial fossa anomaly, lateral ventricle enlargement, porencephaly, agenesis of corpus callosum,

hamartoma and cranial nerve palsies.

Eye :

35-70% are involved. Commonest feature is eye lid involvement of epidermal naevus causing trichiasis or difficulty in lid closure. Others are Coloboma of eyelid, iris and retina, retinal dysplasia, conjuctival lipodermoids, choristomas[68], cortical blindness, micro / macrophthalmia, anophthalmia, corneal opacities and cataracts.

Other associated anomalies

Carcinomas : Benign and malignant transformations, systemic malignancies like nephroblastoma, salivary gland carcinoma, carcinoma of stomach and esophagus, carcinoma of breast, astrocytoma, glioma, mandibular ameloblastoma, transitional cell carcinoma of the bladder, rhabdomyosarcoma of the bladder and intrathoracic teratoma are reported.

GIANT CONGENITAL MELANOCYTIC NAEVUS

Neurocutaneous melanosis is defined by the presence of neurologic symptoms and increased number of melanocytes in central nervous system combined with the presence of large cutaneous naevus. A giant congenital nevus is a nevus greater than 20cm. The most common location is on the back, head, neck and extremities. Malignant melanoma (4.5% - 8%) can arise from a giant congenital naevus within first decade of life.

- **Symptoms :** Headache, vomiting, failure to thrive, weakness, gait abnormalities,

bowel and bladder dysfunction. The signs and symptoms manifest within first 3 years of life. Occur in 12% cases with neurocutaneous melanosis. The signs are hydrocephalus, macrocephaly, increasing head circumference, bulging fontenelle, seizures and developmental delay.

Associated Findings with Giant Congenital Melanocytic Naevus

Local Changes – Loss of subcutanesous fat and limb hypoplosia. **Malignancies –** Malignant melanoma, liposarcoma, rhabdomyosarcoma, primitiveneuroectodermal tumours, mixed malignant neoplasm. **Malformations –** Vascular malformations, supernumerary nipples, ear deformities, preauricular appendages, cryptorchidism, club Foot.

Large congential naevi are reported more frequently with neuro fibromatosis type I[69]. Patients with 'satellite' melanocytic naevi are at a greater risk for the development of manifestations than patients without satellite lesions.

STURGE – WEBER SYNDROME (SWS)

Synonyms : Encephalotrigeminal angiomatosis.

Definition : SWS is a rare, sporadic, neurocutaneous disorder consisting of facial capillary vascular malformations or port wine stain in a trigeminal nerve distribution in association with ipsilateral neurologic and ocular abnormalities.

Incidence : 1 in 50000; equal sex incidence

Cutaneous Findings

Erythematous, blanching, segmental homogenous patch that is restricted to the midline (although can be bilateral) is noted on the face shortly after birth. This evolves into characteristic port wine stain, with or without nodular lesions.

Distribution : One half of forehead, ipsilateral eyebrow, upper eye lid, nasal sidewall (opthalminc branch of trigeminal nerve) must be affected to diagnose SWS. Port wine stain can be bilateral also. However, port wine stains over maxillary and mandibular branches of V nerve are not at risk of SWS. 52% have additional port wine stain else where.

Neurologic Manifestations

Seizures, developmental delay, contralateral hemiplegia, mental retardation, homonymous hemianopia and sporadic hemiplegic migraine. Seizures (80%) present as infantile spasms, generalized tonic clonic or focal seizures. Classically seizures are difficult to control with medications.

Ocular manifestations.

Occurs ipsilateral to the port wine stain; Glaucoma occurs in 50%, cases. It starts before 1 year of age. Retinal vascular anomalies in the posterior pole are seen – "Tomato catsup" fundus. Visual field impairment and buphthalmos also occur. Choroidal angiomas push the retina forward producing a refractive abnormality termed hyperopia.

Etiology: Defect occur during embryogenesis (5-8th week) of the mesoectodermal tissue.

Unusual Associations of SWS. Phakomatosis pigmentovascularis, Klippel – Trenauny – weber syndrome[70] and naevus of ota[71].

ELEJALDE SYNDROME

Neuroectodermal melanolysosomal disease[72]. Autosomal recessive by inheritance. It should be distinguished from Chediak Higashi syndrome and Griscelli syndrome[73].

Characteristic Features are:

- Bronze skin, silvery hair, severe CNS dysfunction, mental retardation, severe hypotonia and seizures
- Hair shaft examination shows coarse irregular pigment clumps within hair shaft.

OCULOCUTANEOUS ALBINISM

It is an autosomal recessive disorder characterized by partial or complete failure to produce melanin in the skin and the eyes. Melanocytes are present in normal distribution but fail to synthesize melanin adequately. There are 11 subtypes. Among these tyrosinase negative, tyrosinase positive and yellow mutant types are significant.

Cutaneous features : Absence of pigment in the skin and hair[74]. They are prone to develop actinic keratosis, squamous cell carcinoma, melanoma in the sun exposed skin at an early age.

Ocular features : Nystagmus, photophobia, strabismus, reduced visual acuity

ADAMS OLIVER SYNDROME

It is an autosomal dominant disorder characterized by congenital midline scalp defects and asymmetrical distal limb reduction anomalies.

Skin lesions are solitary or multiple bald scars, near the vertex. Dilated scalp veins[76] are frequently associated. Intellect is normal. Hypoplastic or absent distal phalanges are the most common limb anomalies[77]. Lower limb more commonly affected. Congenital heart disease affects about 8% of cases. Persistent cutis marmorata[78] reported in 12% of cases.

AIM OF THE STUDY

1. To study the incidence of Neurocutaneous disorders in the outpatients attending the Department of Dermatology in Government General Hospital, Chennai, from July 2006 to September 2008.
2. To determine the age and sexwise distribution of Neurocutaneous disorders.
3. To study the clinical morphology and distribution of lesions.
4. To correlate the morphological lesions with the histopathological freatures.
5. To evaluate incidence of associated systemic abnormalities.
6. To determine the involvement in other family members.

MATERIALS AND METHODS

The study was conducted at the Department of Dermatology Government General Hospital, Chennai for a period of 24 months, from July 2006 to September 2008. Patients were selected among those attending the outpatient department with signs and symptoms pertaining to neurocutaneous syndromes.

Preliminary informations like age, sex, educational qualification, present and past illness, family history along with consanguity were elicited. A detailed systemic examination was done, particularly central nervous system.

Dermatological examination consisted of thorough screening of patients to detect the cutaneous markers for neurocutaneous disorders. Ophthalmic examination, Ear and dental examinations were also carried out in relevant cases.

Apart from the routine investigations like hemogram, renal and liver function tests, X-rays, ECG, Echo, EEG, CT scan and MRI were done in appropriate cases. Skin biopsies were carried out in willing patients who included 23 patients with neurofibromatosis, 5 cases of tuberous sclerosis, one case of naevus comedonicus, xeroderma pigmentosum and Adams Oliver syndrome, Giant congenital melanocytic naevus each.

Whenever systemic abnormalities were detected / suspected the patients were referred to appropriate speciality departments like the department of cardiology, ophthalmology, orthopedics and neurology for further investigations and management. All the patients were followed to detect the onset of other neurological and systemic manifestations.

The data thus obtained was compiled tabulated and statistically summarized.

OBSERVATION AND RESULTS

INCIDENCE:

Out of the total 30056 new patients attending skin OP at GGH during the period between July 2006 to September 2008, the number of patients with neurocutaneous disorders were 109. Incidence of neurocutaneous disorders was 0.3%. Out of 109, the following diseases were found to occur in the order of frequency.

1.	Neurofibromatosis	-	75	68.8%
2.	Tuberous sclerosis complex	-	20	18.3%
3.	Xeroderma pigmentosum	-	3	2.7%
4.	Giant congenital melanocytic naevus	-	2	1.8%
5.	Epidermal naevus syndrome	-	2	1.8%
6.	Waardenburg syndrome	-	2	1.8%
7.	Sturge weber syndrome	-	1	0.9%
8.	Naevus Comedonicus	-	1	0.9%
9.	Elejalde syndrome	-	1	0.9%
10.	Oculo Cutaneous albinism.	-	1	0.9%
11	Adams Oliver Syndrome		-	1 0.9%

NEUROFIBROMATOSIS (NF)

Of the 75 case of NF, 68(90.6%) cases were of type-1, 4 cases (53.3%) were of type-V and 2 cases (2.6%) were type VI, and 1 case of type-II (1.3%). Age and sex

distribution : The age group of patients with neurofibroma ranged from 6 to 60 years with the mean age 33 years.

TABLE-1

The Age And Sex Distribution Among Patients With Nf (N=75)

Age	No. of Cases	M	F
0 – 10 yrs	3	2	1
11 – 20 yrs	23	14	12
21 – 30 yrs	22	9	10
31 – 40 yrs	14	9	5
41 – 50 yrs	7	6	1
51 – 60 yrs	6	2	4
Total	**75**	**42**	**33**

Highest age incidence was between 11 – 20 years.

Family History : There was history of consanguinity in 14 cases (18.6%)

The neurofibromatosis were encountered among the family members in 19 cases (25.3%). Fathers were affected in 9 cases, Mother in 3 cases, Brother in 4 cases, Sister in 2 cases and daughter in 3 cases. More than one family member in 2 cases.

1) *General examination* : Short stature in one case. Other cases were normal.
2) *Systemic examination :* Bony abnormalities noted in 6 patients(8%) in the form of kyphoscoliosis, facial asymmetry and local gigangitism, each comprising of 2 cases respectively (2.6%).
3) *Central nervous system examination :* 4 patients affected with seizures, 3 with learning difficulties, 2 cases with delayed milestones and MR respectively.
4) *Ophthalmic examination : 61(81.3%) patients were found to have lisch nodules in*

the eye, all of them bilaterally.

TABLE-2

Systemic manifestations observed in patients with neurofibromatosis.

S.No.	Systemic Manifestations	No. of Patients %
1.	Bony abnormalities	
	• Kyphoscoliosis	6 (8%)
	• Facial asymmetry	2 (2.6%)
	• Local gigantism	2 (2.6%)
2.	CNS Manifestations	
	• Delayed milestones	2 (2.6%)
	• Learning difficulty	3 (4%)
	• Mental retardation	2 (2.6%)
	• Seizures	4 (5.3%)
3.	Ophthalmic Manifestations	
	• Lisch nodules	61 (81.3%)

Dermatological examination: Mollusca fibrosa was observed in 65 patients (86.6%). Plexiform neurofibromatosis was observed in 9 patients (12%).

Pigmentary changes in the form of CALM occurred in 73 patients (97.3%) out of which 69 patients had more than 6 in number (94.5%) of them, 34 cases (46.5%) presenting after puberty showed bigger macules, more than 15mm. Freckling was noted in 86.6% of the case which was observed in the following pattern.

- Palmar, Axillary and inguinal freckling – in 30 cases (45.9%)

- Palmar, Axillary, inguinal and plantar freckling– in 6 cases (9.4%).
- Palmar and Axillary freckling in 12 cases (18.4%)
- Palmar freckling only in 10 cases (15.3%)
- Axillary and inguinal freckling in 4 cases (6.1%)
- Axillary freckling only in 3 cases (4.6%)

One female patient showed extensive facial freckling, one patient had a giant congenital melanocytic naevus over the trunk.

Localized hypertrichosis was observed in 3 cases (4%). Other skin lesions observed were prurigo nodularis, Hansens disease, and epidermal naevus 2 cases respectively (2.6%) syringoma, macroglossia, psoriasis, one case respectively (1.3%). A case of sarcoma was seen. A case of pregnant female showed increased in size and number of lesions.

Investigation : Electroencephalogram (EEG) was normal in all cases. ECG was normal in all cases expect one case with MS which showed Bifid'P' waves. 13 affordable patients underwent CT head and neck examination which were normal 12 patients. One patient with NF-II showed features suggestive of ependymoma, meningioma, Acoustic schwannoma which was confirmed with MRI.

Histopathological Examination showed unencapsulated tumour composing of pale eosin stained collagen with spindle shaped cells and eal shaped nuclei. Few sections showed sebaceous gland and eccrine gland structures within the tumour mass.

Extravasated RBC's were also seen in some of the cases. One case showed tumour mass in close approximation with the epidermis.

TUBEROUS SCLEROSIS (TSC)

The total number of cases diagnosed to have tuberous sclerosis was 20 (18.3%) of whom 8 were males and 12 females. **Age Distribution (Table -3).** The age of these patients ranged from 4 to 42 years – the mean age being 22 years.

TABLE – 3

The age and sex distribution in tuberous sclerosis complex (n=20)

Age	No. of Case	M	F
0 – 10 yrs	3	1	2
11 – 20 yrs	8	3	5
21 – 30 yrs	5	3	2
31 – 40 yrs	2	1	1
41 – 50 yrs	2	-	2
TOTAL	**20**	**8**	**12**

Clinical Presentation

The patients presented with seizures 14 cases, (70%) angiofibromas 20 cases (100%), 2 were mentally retarded (10%).

H/o delayed mile stones was observed in 2 cases along with learning disabilities in 9 (45%) patients.

Family History: A positive family history was observed in 6 patients. The members affected in these 6 patients were mother 3, daughter in 2 and grandmother in one.

General Examination: Was normal in all except one patient who had moderate hypertension (150/100 mmHg) on three consecutive reading on 3 days.

Systemic examination : CNS – 2 patients were mentally retarded while IQ was found to be low in 5 cases (25%). Other systems were normal.

Ophthalmic examination : was normal.

Skeletal examination : Showed bone cyst in one case.

Dermotological examination: showed the following features.

Angio fibroma was observed in all 20 cases (100%) over the face. Ash leaf macule in 17 cases (85%). Of them 11 patients had a number of macules <3 and 6 patients had >3 Shagreen patch occurred in 15 cases (75%) out of which 11 was in the lumbosacral, 2 in the upper back and 1 each in the thigh and gluteal region respectively. Molluscum pendulum was seen in 7 cases (35%) , forehead plaque in 4 cases (20%), Koenen's tumour in 6 cases (30%), CALM in 2 (10%), confetti in 2 (10%), gingival fibroma 1 (5%) and enamel pits in 12 (60%) cases.

Investigation : Skiagram of skull was normal. CT Brain, showed sub-ependymal nodules in 5 patients, cortical tubers in 2 pts, astrocytoma in 1 and cyst in the parietal region in one patient was observed.

Among the 10 CT investigated patients, 3 affordable patients underwent MRI which showed findings consistent with CT.

- USG abdomen was done in all patient out which 2 showed renal angiomylipomas . ECG was normal in all cases.

- Histopathology of angiofibroma showed few blood vessels in the mid dermis. Pale stained collagen in the upper dermis, fenestrated and deeply eosin strained collagen in the mid & deeper dermis. Histopathology of shagreen patch showed vertically oriented collagen in the mid & deeper dermis.

XERODERMA PIGMENTOSUM (XP)

Out of the 109 cases who presented with neurocutaneous disorders, three cases (2.7%) had xeroderma pigmentosum among which one was female (21 years) and 2 were males (17 & 32 years).

Clinical Presentation

Extensive freckling over the face, chest and arms which started around an average age of 6 years. All had photophobia. The female patient had conjuctival congestion, pigmentation and loss of vision. One patient had cheilitis.

Family History : The female patient had family history of XP, in her elder sister and a positive history of consanguity in her parents.

General examination : 2 patients were moderately built. One female patient was with short stature.

Systemic examination: revealed no abnormality including CNS assessment.

Ophthalmic examination: showed conjunctival pigmentation and congestion, optic atrophy and loss of vision in the female patient.

Dermatological examination: revealed extensive freckles and lentigenes, hyper and

hypo pigmentation over face, upper chest and arms mainly in the exposed surfaces. Mild xerosis was evident, but no telangiectasia could be made out. There was a fungating tumour over the cheek in one patient, which was biopsied and proved to be squamous cell carcinoma. The same patient showed mutilation of the nose which was found to be BCC.

Investigation : Histopathological section of a hyperpigmented macule revealed heavily pigmented basal layer. Pigment deposits were also noted in the upper dermis. Patchy inflammatory cells in the upper dermis. Dilated blood vessels with RBC in the upper dermis, pale stained collagen in upper dermis and fenestrated in mid & lower dermis.

CT – Head & Neck of the female patient revealed bilateral maxillary and ethmoidal sinusitis, intraventricular obstructive hydrocephalus and diffuse cortical atrophy.

STURGE – WEBER SYNDROME

1 patient (0.9%) was identified to have components of Sturge – Weber syndrome.

Family History : There was neither family history nor history of consanguinity.

Age & Sex incidence : One adolescent female patient was observed.

Clinical Features : She presented with portwine stain and epilepsy

General and Systemic examination : Were normal

Ocular examination: Conjuctival congestion, prominent blood vessels over the upper and lower eyelids were seen.

Dermatological examination : Extensive portwine stain involving the forehead, upper and lower eye lids, conjunctiva, cheeks and chin was seen in both the patients.

Investigation : EEG showed focal epileptiform spikes in one patient.

NAEVUS COMEDONICUS

1 female patient aged 23 (0.9%) presented with naevus comedonicus syndrome.

Clinical Presentation : the patient presented with clusters of closely set comedone like, firm, slightly elevated papules with a central horny plug, which are unilaterally distributed in left side of the back.

General, Systemic and Ocular examination : Were normal.

Investigation : Were normal.

Histopathology showed deep and wide invagination of epidermis filled with keratin and concentric lamellae of collagen.

WAARDENBURG SYNDROME

2 patients out of 109 (1.8%) were identified as Waardenburg syndrome which consisted of mother in the age of 25 years and her 2 year old daughter.

presenting Complaints : Hearing loss, graying of hair and ocular discolouration were noted in both mother and child.

Family history : No history of consagunity was noted

General examination : Dystopia canthorum was noted.

Systemic examination : Both patients had defective hearing as bilateral sensoryneural

deafness. No other CNS abnormality was detected.

Ophthalamic examination : showed heterochromia of iris in both cases.

Dermatological examination :

Mother: Unilateral heterochromia of iris, white forelock and congenital vitiliginous patch over the thigh. Daughter: 2 years old girl child had bilateral heterochromia of iris. She had white forelock (poliosis), which was present since birth.

Investigations: Both patients showed changes in the audiogram. Both showed normal EEG, and all other investigatory parameters were normal.

EPIDERMAL NAEVUS SYNDROME

2 female cases (17& 26 yrs) out of 109, presented as epidermal naevus syndrome. They presented with seizures and verrucous asymptomatic lesions over the face and left flank in one and over one half of the body (Left) in the other.

General and Systemic examination: Were normal

Dermatological examination : Multiple closely set hyperpigmented verrucous papules, some coalesced to form plaques arranged in a linear pattern over the one half of the body.

Investigation : EEG showed abnormal bilateral epileptiform spikes however CT was normal.

GIANT CONGENITAL MELANOCYTIC NAEVUS

2 cases (one female child and one adult male) were reported with giant congenital melanocytic naevus. The female child had history of seizures and hypertrichosis over the naevus was noticed.

General examination : was normal

Dermatological examination : The 1 ½ year old female child presented with a huge hyperpigmented patch occupying the trunk, gluteal region, thighs and forearms, few satellite lesions were seen over the face. Hypertrichosis over the patch was seen.

The adult male had similar naevus over the chest and back.

Investigation : EEG showed abnormal bilateral epileptiform spikes.

ELEJALDE SYNDROME

One male child (10 months) presented as Elejalde syndrome. The presenting complaints were pigment dilution of the hair all over the body since birth, delayed mile stones & seizures for the past 2 months. The child was born of 2nd degree consanguinous marriage.

General examination : No head control. Other parameters were normal.

Systemic examination : Cardiovascular system, respiratory system, per abdomen – normal.

CNS : Hypotonia and bilateral extensor plantar were noted

Dermatological examination:

Bronze skin, silvery hair over the scalp, eyebrows, eyelashes & body present.

Investigations : All were within normal limits except hair shaft examination showed coarse & irregular pigment clumps present.

OCULOCUTANEOUS ALBINISM

One female patient out of 109 (0.9%) aged 32 years reported with Oculocutaneous Albinism.

Dermatological Examination : Showed total depigmentation of skin and hair. Face and both forearms showing actinic keratosis like lesions.

Ocular Examination : She had photophobia and nystagmus.

ADAMS OLIVER SYNDROME

1 male child aged 1 year (0.9%) reported with Adams Oliver syndrome.

CVS Examination: Child had ventricular septal defect.

Skeletal Examination : Polydactyly was present.

Dermatological Examination : Revealed two rounded, well circumscribed scalp lesions – aplasia cutis congenita – over the occiput and the parietal bone. Multiple skin tags and hypopigmented verrucous lesions were seen in the midline.

Investigations : MRI brain suggestive of Dandy Walker malformation.

DISCUSSION

NEUROFIBROMATOSIS

Neurocutaneous disorders are genetically determined disorders showing both cutaneous and neurological involvement. The cutaneous markers may be an early diagnostic clue.

In this study, Neurofibromatosis (68.8%), topped the list followed by Tuberous sclerosis complex (18.3%), and other rarer disorders like Xeroderma pigmentosum (2.7%), Giant congenital Melanocytic naevus (1.8%), Sturge Weber syndrome (0.9%), Waardenburg syndrome (1.8%), Epidermal neavus syndrome (1.8%), Naevus comedonicus (0.9%) and Elejalde syndrome (0.9%), Oculocutaneous albinism (0.9%) Adams Oliver syndrome 0.9%.

Among the neurofibromatosis, NF1 was by far the most common and accounts for 90.6% in this study which is consistent with the study reported by Husan SM et al[79] which showed a 90% incidence. The most frequent age group affected was 10-20 years. This age group coincides with puberty which time there is increase in number of lesion as noted by Friedmann JM Riccardi et al[80]. There is a male preponderance (56%) in this study as opposed to the studies of Jennifer R. Kam et al[81] which indicates equal sex incidence. The most common clinical sign being CALM (97.3%) followed by mollusca fibrosa (86.6%). In a study by Neil Gold Berg et al[82], the incidence of CALM was 69% CALM were the earliest marker to occur in concurrence with Crow and Schull et all[83, 84].

Plexiform NF occurred in12% of cases in the study in contrast to 30% incidence in the study of Wolkenstein et al. [85]

Regarding pigmentary changes, axillary freckling occurred in 72% of cases which is consistent with 70% of axillary freckling by crowe FW et al[86]. Pruritus was noted in 10.6% as opposed to Riccardi VM et al[87] report of 15 – 20% incidence. Incidence of seizure was 5.3% which was opposed with 10% incidence in study of cramer et al.[88]

Lisch nodules has occurred in 81.3% of cases in contrast to 94– 97% of patients in the literature by Fliieler et al.[89] Kyphoscoliosis was observed in 8% of cases as opposed ot 2% of case in the study of Riccardi VM et al.[87] Learning difficulty was found in 4% case while the study of North Kn et al[9] showed 30 – 70 % incidence.

Incidence of NF type-V is 5.3% in the study by crowe FW et al[5] it was considered to be a rare variant. Incidence of NF type VI is 2.6% in which both cases showed family history. One case of NF-II has been reported in our study (1.3%) as opposed to the 10% incidence as per text.[90]

TUBEROUS SCLEROSIS

Tuberous Sclerosis(18.3%) is the 2nd most common neurocutaneous disorder in this study. The common age group presented was 10 – 20 years with a mean age of 16 years. This is consistent with the study of G. Raghu Rama Rao et al[36] which showed mean age of 15.9 years. According to Rabindrnath Nambi et al[91] there is an equal sex

incidence, but this study showed a female preponderance. Family history was positive in 30% in accordance with the study of H. North rupet et al[92]

The earliest clinical presentation was ash leaf macule which was present at birth as according to study of serguisz Jozwiak et al[31]. Ash leaf macule occurred in 85% as opposed to 80-100% incidence in the study of Jimbow K et al [32].

The commonest cutaneous manifestation was angiofibrona of the face which was seen in 100%. This is consistent with 96% incidence as per the studyof Gomez MR et al[93] . Shagreen patch was observed in 75% as opposed to 50% reported by Harris stith et al[94] . The Commonest site of the patch was lumbosacral region in consistent with the report of Tsao H et al.[33] Molluscum pendulum were seen 35% of the cases as per the previous study.

Forehead plaque was seen in 20% as opposed to 36% incidence in the study of webb et al.[95] Koenens tumour was reported in 30% in contrast to 15% incidence in the study of Joswiak et al[31]. The prevalence of CALM was 10% as against the 30% reported by Tsoa H et al[33]. Seizures were reported in 70% cases as opposed to 53.33% incidence as per Anisya – Vasanth et al[96]. 10% case of mental retardation was seen in our study in contrast to 40% incidence in the study of Raghu Rama Rao et al.[36]

System Involvement :

CNS : Subependymal nodules were seen in 25% of cases as opposed to curatolo p et al[97] study which revealed 50% incidence.

Renal angiomyolipoma was detected in 10% in contrast to 60% reported in literature.

XERODERMA PIGMENTOSUM

2.7% of study patients were involved. Male preponderance was noted, in contrast to equal sex incidence as per the study of Neel JV et al.[98] Photophobia and freckles were the common presentations. One female patient presented with squamous cell carcinoma of the cheek and basal cell carcinoma of the nose. This multiple malignant presentation is in accordance with the study of Mohanty P et al.[99]

STURGE – WEBER SYNDROME

0.9% study patients were identified to have Sturge Weber syndrome with equal sex incidence. According to Tallman B et al,[100] the usual cutaneous finding is a unilateral port wine stain. Only one patient presented with seizures, in contrast to reports by Sujansky E et al[101], where seizures occurred in 75 – 90%. The seizures were intractable to medications as indicated in the literature. EEG of the patient showed focal epileptiform spike discharges, which is very characteristic of Sturge Weber syndrome as per the study of Brennei RP et al[102].

NAEVUS COMEDONICUS

0.9% of cases presented with Naevus comedonicus. The female patient presented with the lesion at the age of 16 yrs, in concurrence with records by Vasiloudes PE et al[103]. The site of comedone nevus in the study, was on the trunk as opposed to the study of Anderson NP et al[104] in which face was the commonest site.

WAARDENEBURG SYNDROME

A rare condition which constituted 1.8% of the study. Both the patients were females. Heterochromia iridis was present in 100% cases as opposed to 86% incidence

in the literature. Incidence of deafness was 100% in contrast to 7-38%[105] reported in literature.

EPIDERMAL NAEVUS SYNDROME

1.8% of the study group had epidermal naevus syndrome. Both patients had seizures and verrucous epidermal naevus, which was consistent with the study of Gurecki PJ et al[106].

GIANT CONGENITAL MELANOCYTIC NAEVUS

It was observed in 1.8% of study group. Back was the commonest location. Hypertrichosis were seen in 100% of the cases. The above 2 finding were consistent with that of the literature[107]. One patient had an associated NF in accordance with the study of Zvulunova et al[69].

ELEJALDE SYNDROME

1 case of Elejalde syndrome was reported in the study (0.9%). The male child had delayed mile stones, seizures, loss of head control, silvery hair and bronze skin. Hair shaft examination showed pigment clumnps. These findings were in accordance with the study of Afifi et al[72].

OCULOCUTANEOUS ALBINISM

Rare condition which constituted 0.9% of the study. The female had diffuse depigmentation of skin, hair and iris. She also had photophobia and nystagmus.

ADAMS OLIVER SYNDROME

0.9% of the study group had Adams Oliver Syndrome. The male child had

polydactyly and ventricular septal defect. He had aplasia cutis congenita scalp and keloid –like skin tags over the chest. MRI showed Dandy Walker malformation with obstructive hydrocephalus.

CONCLUSION

1. In the study of 109 cases of Neurocutaneous syndromes, Neurofibromatosis topped the list followed by Tuberous sclerosis complex.
2. NF – Type –I accounted for the maximum number of Neurofibromatosis.
3. The most common clinical sign in NF was CALM followed by mollusca fibrosa.
4. Axillary, inguinal, palmar and plantar freckling were the notable pigmentary changes in NF.
5. Lisch nodules accounted for 81.3% of the cases in NF.
6. Skeletal abnormalities in the form of kyphoscoliosis, local gigantism and facial asymmetry were reported.
7. One case of sarcoma complicating NF was observed.
8. A case of NF-II with multiple intracranial tumours in MRI was detected.
9. Tuberous sclerosis complex is the second most common neurocutaneous disorder.
10. Angiofibroma was observed in 100% cases followed by ash leaf macules (85%).
11. Few patients had sub-ependymal nodules and cortical tubers.
12. One patient with astrocytoma and one patient with renal angiomyolipoma were observed.
13. Classical features of XP were observed in a patient who also had cutaneous

malignancies – BCC over the nose and SCC over the cheek.

14. Sturge – Weber syndrome with unilateral port wine stain with seizures was reported in our study.
15. One case of unilateral naevus comedonicus was reported.
16. Two cases of Waardenburg syndrome (mother and child) was observed in our study. Both had white forelock, heterochromia iridis and deafness.
17. Two cases of epidermal naevus syndrome with extensive involvement and seizures were noted.
18. Two cases of giant congential melanocytic naevus were reported.
19. A case of Elejalde syndrome with typical clinical manifestations was observed.
20. One case of oculocutaneous albinism was reported.
21. One case of Adams Oliver syndrome with Dandy Walker malformation has been reported.

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