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AMERICAN EPILEPSY SOCIETY

# Epilepsy Associated with Neurocutaneous Disorders

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## Neurofibromatosis Type 1:

DIAGNOSTIC CRITERIA AND FEATURES

- Diagnostic criteria adopted in 1988 – NIH Consensus Statement [1] = 2 of the following

| | |
|---|---|
| • 1st degree affected relative<br>• ≥6 café-au-lait patches (>0.5 cm in children and >1.5 cm in adults)<br>• Axillary or groin freckling<br>• ≥2 Lisch nodules (iris hamartomas) | • Optic pathway glioma<br>• ≥2 neurofibromas of any subtype or 1 plexiform neurofibroma<br>• A distinctive bony dysplasia (sphenoid wing, thinning of a long bone cortex ± pseudoarthrosis) |

- Neuropathologic manifestations are related to cells derived from neural crest which during development cover the anterior neural plate and influence growth of the telencephalon, thalamus, optic tectum, facial skeleton, peripheral nervous system, and melanocytes.

GENETICS

- Incidence of 1/2,500 – 3,000, segmental incidence 1/36,000-40,000
- Chromosome 17q11.2 close to the centromere which codes for neurofibromin.
- Gene is 300 kb and contains 4 alternative exons coding for several distinct proteins suggestive of complex transcriptional regulation.
- 30-50% of cases are thought to be sporadic.
- Inheritance is autosomal dominant with complete penetrance.

- High baseline mutation rate in this gene (10x most other genes) with ~500 mutations reported. In general, repeated mutations only found in a few percent of families.
- There is some clustering of missense mutations 2 out of 3 of the protein's domains.
- Variable mutation types but most result in truncated protein.
- Deletions of the gene account for 4-5% of NF1. Recombination either during maternal meiosis or post-zygotic recombination which can lead to mosaic phenotypes (either generalized or segmental but typically more mild).
- Deletions of the gene + contiguous regions can occur and typically result in a more severe phenotype with associated facial dysmorphisms and ID. These patients may also have more dermal neurofibromas and are at higher risk for malignant peripheral nerve sheath tumors.
- Phenotypic overlap with other Ras-opathies (Noonan, LEOPARD, Costello, etc) which are caused by mutations in the related cascade and are potential disease modifying genes for NF1.
- Gene function - neurofibromin
    1. Tumor suppressor gene that acts as a negative regulator of the Ras signal transduction pathway by hydrolysis of Ras-GTP to -GDP. Mutations decrease Ras-inactivation and result in cell proliferation.
    2. Expressed in cerebral cortex during embryonal development and is involved in neuronal differentiation which may explain some of the learning and memory phenotype.
    3. There is some evidence that it may also modulate the mTOR pathway.
- Tumor formation is thought to be the result of a "second hit" in somatic cells leading to more frequent unregulated growth. First proposed by Knudson in relation to retinoblastoma (1971).

EPILEPSY

- Seizures have been reported to occur in approximately 4–7% of individuals with NF1. In a large retrospective series, at least one unprovoked seizure occurred in 9.5% (50/536) and epilepsy in 6.5% (35/536). [2]
    1. Most common seizure type reported is focal onset; however, there were also syndromes more consistent with JME and CAE in addition to 2 cases of spasms (1 progressed to myoclonic epilepsy).
    2. In contrast to older studies which showed good response to anticonvulsants, only 34% were controlled with ≤1 AED with a majority

(60%) meeting criteria for intractable epilepsy or undergoing epilepsy surgery.

- Retrospective analysis of 198 patients –
  1. 7% had epilepsy, predominately focal, and 9/14 patients had structural lesions (tumor, MCD, MTS).
  2. 2 patients had infantile spasms progressing to focal seizures. [3]
  3. Seizure control was attained for 8/14 – 6 with medical management and 2 with surgical resection.
  4. 4 patients with intractable epilepsy also had mental retardation with IQ <45 and 3 of these patients had MCD (polymicrogyria and pachygyria).
- Radiographically, seizures are often related to tumor occurrence and location but not the presence or location of unidentified bright objects. [4]
- Surgical treatment of epilepsy in NF1 [5]
  1. 12 patients identified in a survey of 23 European epilepsy centers with at least 1 year of follow-up. This accounted for 0.5% of surgeries in the 8 centers that identified patients.
  2. 11/12 patients were lesional on MRI with a unilateral temporal distribution in 8 (in contrast to prior series which contained a majority of extratemporal cases).
  3. Single stage procedure was performed in 7 cases and surgery ranged from lesionectomy to multilobar resection based on results of non-invasive pre-surgical evaluation and intracranial monitoring.
  4. 8/12 patients were seizure free and 1 had worthwhile improvement.
  5. There was a mixture of pathology including PMG, FCD, hippocampal sclerosis, white matter angiopathy, DNET, and astrocytoma.

TARGETED TREATMENT

- Farnesyl transferase inhibitor (cancer agent which acts on Ras pathway) – impaired learning and attention reversible with this agent in mouse models. [6]
- Both simvastatin and lovastatin have been used in human clinical trials to address cognitive impairment with mixed results.

## Tuberous Sclerosis Complex (TSC):

DIAGNOSTIC CRITERIA AND FEATURES

- International TSC Consensus Group – [7]
  *Definite* = 2 major criteria OR 1 major + 2 minor

*Probable* = 1 major and 1 minor
*Possible* = 1 major OR ≥2 minor

- Percentages below approximate the number of TSC patients with these findings:

| MAJOR | MINOR |
|---|---|
| • Skin manifestations<br>  ○ Facial angiofibromas<br>  ○ Ungual fibroma<br>  ○ > 3 hypomelanotic macules (90%)<br>  ○ Shagreen patch (20-30%)<br>• Brain and eye lesions<br>  ○ Cortical tubers (>80%)<br>  ○ Subependymal nodules (95%)<br>  ○ SEGA (6-10%, peak 8-18y)<br>  ○ Multiple retinal harmartomas (87%)<br>• Tumors in other organs<br>  ○ Renal angiomyolipoma (40-80%)<br>  ○ Cardiac rhabdomyoma (50%)<br>  ○ Lymphangioleiomyomatosis (1%) | • Dental enamel pits<br>• Rectal polyps<br>• Bone cysts<br>• White matter migrational abnormalities<br>• Gingival fibromas<br>• Non-renal hamartomas<br>• Retinal achromatic patches<br>• Confetti skin lesions<br>• Multiple renal cysts |

GENETICS

- Autosomal dominant with high penetrance.
- 2/3 of mutations are de novo.
- 2 genetic causes:

1. TSC1
   a. Encodes hamartin.
   b. Most mutations are small changes leading to a truncated protein.
   c. Complex splicing pattern and alternative transcripts.
   d. Accounts for 13-30% of TSC cases.
   e. Typically a milder phenotype and more often found in familial cases.
2. TSC2

a. Encodes tuberin.
b. Majority of TSC patients which has been confirmed in multiple studies.
c. Missense, nonsense, frameshift, and large deletions have been reported.
d. 15% of patients without an identifiable mutation
e. Associated with earlier onset epilepsy, higher risk for infantile spasms, and poorer outcomes with respect to seizure control and neurodevelopmental outcomes

- Gene products bind to each other in vivo and negatively regulate the mTOR pathway. Regulate progression from G1-S phase of the cell cycle in addition to other functions.
- Segmental cases with mosaicism have been reported

EPILEPSY

- 80% of TSC patients will have seizure onset within the first 3 years with 66% in the first year. 12% of patients experience their first seizure in adulthood.
- Poor prognostic factors for the development of refractory epilepsy [8, 9]
  1. Seizure onset within first 3 years
  2. Frequent seizures of multiple types
  3. Incomplete response to anticonvulsants
  4. Multifocal EEG abnormalities
  5. High tuber burden or cystic lesions
- Infantile spasms - [10]
  1. Develop in 30% of TSC patients and TSC is the most common single cause of infantile spasms (25% of cases)
  2. Spasms often present earlier and are preceded by or coexist with focal seizures
  3. Vigabatrin (VGB) is the drug of choice for treatment and 96% of TSC patients with IS respond to this agent
  4. IS increase the risk for ID, ASD, and intractable epilepsy; however, more favorable outcomes have been reported, especially with early and appropriate treatment
- Epilepsy in children and adults –
  1. Approximately 30% of patients are refractory to medication and they more often have a history of IS or LGS with an early age at diagnosis
  2. 93% of adults have focal onset seizures; however, >50% have multiple seizure types

3. No particular agent has been shown to be preferred.
4. VGB can be used for the ongoing treatment of focal seizures with an appropriate discussion of risks.

- Pathophysiology of epilepsy – (hypotheses, mechanisms not well defined)
  1. Disruption of mTOR regulation of neurotransmitter receptor and ion channel expression, neuronal structure, and synaptic plasticity. [11]
  2. Unclear if tuber itself is the generator of seizures or if there is abnormal connectivity with the surrounding tissue and a broader network. Studies of surgical specimens suggest that severely dysplastic cells are not hyperexcitable. [12]
- Epilepsy surgery in TSC - [13]
  1. Identification of the epileptic tuber can be challenging with several non-invasive options available – tryptophan PET [14] and specialized MRI characteristics such as ADC coefficient and tractography [15, 16]
  2. As with other dysplastic lesions, best outcomes are obtained when resection is complete and data is concordant without evidence of generalized abnormalities or significant ID
  3. Surgical approaches have consisted of single stage resection of the lesion and/or surround and intracranial monitoring.
  4. Meta-analysis of 177 patients found a seizure freedom rate of 57% and >90% improvement in another 18% [17]

TARGETED TREATMENT

- Everolimus – initial studies of this drug were done to assess SEGA response with seizures as a secondary endpoint and showed conflicting results. A prospective open-label study showed a ≥50% reduction in seizure frequency for 12/20 patients. [18] Recently, a larger placebo-controlled trial for adjunctive therapy in adults (EXIST-3) showed similar benefits in both a low and high dose arm (combined responder rate of 68%). [19]
- Sirolimus – prevented development of seizures and treated established epilepsy in conditional TSC1 knockout mice in addition to normalizing brain histology; however, rapid return of seizures when agent was withdrawn [11]
- Early monitoring and treatment – Prospective trial in 45 patients with serial EEG monitoring in infancy showed a lower number with developmental impairment and epilepsy (with milder features of the latter when present). Infants in the treatment arm were given VGB after the onset of epileptiform

EEG abnormalities but before the presence of seizures. [20] This data has provided the background for the EPISTOP trial which is being conducted in 16 sites throughout Europe.

## Sturge-Weber Syndrome (SWS):

DIAGNOSIS AND FEATURES:

- 1/20,000 – 50,000 births, with facial capillary malformations occurring in 3/1,000
- Two or three of the following symptoms:
  1. Port-wine stain in the ophthalmic division of the trigeminal nerve
  2. Vascular malformation in the brain
  3. Abnormal blood vessels in the eye causing glaucoma
- 10% of patients have brain involvement without the birthmark

GENETICS

- Activating, somatic mutation of GNAQ resulting in mosaicism. A single point mutation (c.548G→A) identified in 23/26 patients. Familial inheritance has not been documented
- Gene function = Gαq
  1. Subunit of a heterotrimeric GTP binding protein that interacts with transmembrane G-protein coupled receptors including several that regulate vascular development and function
  2. Mutation impairs the ability of the protein to return to the deactivated state and interact with the receptor resulting in constitutive over-activation of downstream pathways which regulate gene expression for cell proliferation and differentiation

EPILEPSY

- Case series of 55 patients and review of the literature - [21]
  1. Seizures occurred in 47/55 (86%) which is similar to ranges for other large series (62-89%). Some degree of motor impairment was present in all patients ranging from clumsiness with hyperreflexia to hemiplegia. Intellectual disability is reported in approximately 50% of patients and is more often present with bilateral disease and early onset or poorly responsive seizures.

2. Onset prior to age one in 75%. In another series of adults 12% had onset of epilepsy in the 3rd decade. Patients with more severe epilepsy typically had earlier age of onset.
3. 3 patients (7%) presented with infantile spasms but most had focal motor seizures contralateral to the facial nevus. Later development of secondarily generalized convulsions and occasionally myoclonic seizures has been reported.
4. Characteristic findings can occur without facial nevus in 5-14%. 7/17 patients with bilateral facial findings had bilateral cortical abnormalities which were typically more pronounced in 1 hemisphere (6/7). Color and location of the nevus flammeus did not predict severity of disease.
5. EEG shows asymmetry with attenuation and spike discharges in the affected hemisphere that is apparent in infancy and can progress as atrophy worsens. However, in adults without significant atrophy, the asymmetry can be difficult to appreciate.
6. SPECT and PET demonstrate decreased perfusion and glucose metabolism in the affected hemisphere in addition to abnormal volumetrics, most prominent posteriorly.
7. MRI with gadolinium can facilitate identification of subtle abnormalities in the cerebral hemispheres as well as extension into the cerebellum and eyes.

- Hemispherectomy with 81% seizure freedom rate [22] in an international cohort of 32 patients. In the large case series discussed above, only 33% were able to achieve seizure control with medication.
- Focal resection and lesionectomy 60-80% seizure freedom [23]
- Pathophysiology:
  1. Intracranial angiomatosis of the pia mater leading to chronic ischemia and atrophy of the underlying brain. There may also be adjacent migrational abnormalities such as polymicrogyria and heterotopia.
  2. Microscopic features include neuronal loss and gliosis which may extend beyond the angioma. The abnormal vessels are typically thin-walled veins of variable size which may extend into the brain parenchyma. Parietal and occipital lobes are more frequently affected.
  3. Retrospective review of surgical specimens from 6 patients showed dysmorphic neurons with hypertrophic cell bodies (similar to FCDIIA) but without associated migrational derangement. Patients with early seizure onset (n=4) showed polymicrogyria as well. [24]

4. Surgical specimens from 4 patients also subject to more detailed analysis and patch-clamp recording [25]. Pathologic findings included delayed maturation with limited dendritic branching and preserved growth cones. Electrophysiology showed a depolarized resting membrane potential with spontaneous firing and these findings are consistent with those seen in ischemia models.
5. Study of 5 subdural electrode recordings in patients undergoing epilepsy surgery showed origination of the seizure was the cortex under leptomeningeal angioma with slow spread to adjacent brain areas and had similar features to the PLEDS seen in ischemic penumbra as they progressed. [26]

TARGETED TREATMENT

- Specimens from SWS patients had elevated expression of phosphorylated S6 (downstream of AKT in the m-TOR pathway) which could indicate sensitivity of the lesion to rapamycin. Currently there is a study for sirolimus on cognitive impairment and epilepsy in SWS. Other inhibitors within this pathway are also being considered as potential targets for clinical trials.
- Aspirin – Doses of 3–5 mg/kg/day have been used to decrease stroke-like episodes with some potential effects on seizures although data is limited and some complications have been reported.
- Treatment of infants with PHB prior to the development of seizures has been reported in this condition (in addition to TSC) without improvement in motor deficits but some gains with regard to epilepsy incidence and IQ. [27]
- Biomarker development - urine angiogenesis factors, GNAQ mutation status and hyperphosphorylation in downstream proteins, evidence of vascular remodeling on neuroimaging – and in vivo models to facilitate an understanding of disease progression for clinical trials and pathogenesis for the development of targeted treatment is being researched.

## Hypomelanosis of Ito:

DIAGNOSIS AND FEATURES:

- Characterized by hypopigmented whorls and streaks that follow Blaschko's lines and can occur in a variety of distributions (isolated, diffuse, unilateral). These lines represent the streams of growth of cutaneous cells derived from a limited number of precursors and different clones early in embryogenesis.

The hypopigmentation is the result of a decrease in the number of melanocytes and melanosomes with poor melanin production.

- Neurologic manifestations (70% of patients). Structural brain malformations (listed below) in addition to intellectual disability (57-70%) and autism (8-10%). Macrocephaly occurs in 16% of patients.

| | |
|---|---|
| • Hemimegalencephaly<br>• Pachygyria<br>• Megalencephaly with letptomeningeal neuroglial heterotopias | • Focal cortical dysplasia<br>• Hamartomas<br>• Hypoplastic corpus callosum<br>• Hemiatrophy or porencephaly |

GENETICS

- 1/8,000-10,000 children with a 2:1 female:male ratio
- 3rd most common neurocutaneous syndrome (behind NF1 and TSC but more common than SWS).
- In one report, represented 1/600-700 patients referred to the pediatric neurology service of a large national children's hospital [28]
- Mosaicism for chromosomal Xp11 mutations (non-identical breakpoints, 60%) although increasing evidence suggests other types of mosaicism may present with similar features.
- Reported alterations include trisomy 18, monosomy, ring chromosomes, and inversions/translocations.
- Blood testing may be normal and diagnosis may require skin fibroblasts from affected and unaffected regions.
- No correlation between extent of skin lesions and severity or presence of neurologic disease

EPILEPSY

- Case series (5 pts) and review of the literature – [29]
  1. Range of frequency of epilepsy (9-64%), potentially related to ascertainment bias based on the clinic in which the child was diagnosed.
  2. The article above diagnosed epilepsy in 5/56 (9%) of an 8 year cohort of patients with HI (none of these patients had radiologic malformations on MRI).
  3. The overall tabulation was epilepsy in 140/415 = 34%.
- Case report of 34 patients with a variety of seizure types – infantile spasms (6), GTC (19), focal (9), and myoclonic (3). [28]

- Treatment responsiveness is reported as variable without any agent identified as particularly effective.
- For those with apparent cortical malformations, surgical treatment may be beneficial; however, this has not reported systematically.

TARGETED TREATMENT
- None reported as a molecular target in the Xp11 region has not been identified in addition to considerable genetic heterogeneity with additional mosaic changes reported

## Menkes Syndrome:

DIAGNOSIS AND FEATURES – No formal diagnostic criteria
- Laboratory testing
    1. Serum copper <70 µg/dl, ceruloplasmin <20 mg/dL
    2. Levels can be normal in milder variants or during the neonatal period, especially in preterm infants
    3. Alternative assays can detect patterned deficiencies of catecholamine metabolites and some of these may act as biomarkers for disease progression

| HAIR | OPHTHALMOLOGIC |
|---|---|
| • Kinky, coarse, twisted (*pili torti*), short and sparse<br>• Abnormal eyebrows and lashes with hypopigmentation<br>• Hair is fragile and fractures easily (*trichorrhexis nodosa*) | • Ptosis<br>• Optic disc pallor<br>• Decreased pupillary light response<br>• Iris hypoplasia and/or hypopigmentation |
| FACIAL FEATURES | CONNECTIVE TISSUE |
| • Sagging cheeks and ears, depressed nasal bridge, high arched palate, delayed tooth eruption | • Hernias, bladder diverticuli<br>• Joint hypermobility<br>• Vascular defects, arterial rupture |
| NEUROLOGIC FEATURES | SKELETAL |
| • Developmental regression<br>• Seizures – myoclonic and epileptic spasms<br>• Axial hypotonia and appendicular hypertonia<br>• Temperature instability<br>• CT/MRI - dysmyelination, atrophy, SDH, strokes, tortuous intracranial vessels | • Congenital fractures<br>• Osteoporosis<br>• Pectus excavatum<br>• Wormian bones |
| | BLEEDING DIATHESIS |

GENETICS

- X-linked recessive inheritance which affects boys with carrier mothers although some cases of affected females with X:translocations, X0/XX mosaicism, or unfavorable lyonization have been reported
- 1/3 of cases are de novo mutations in ATP7A which result in decreased mRNA production
- Identified mutations have been unique without hotspots or prevalent mutation types
- Splicing defects and exon skipping are common and have been associated with a milder form of the disease (occipital horn syndrome a.k.a. X-linked cutis laxa or Ehlers-Danlos Type 9)

- 55% homology with Wilson disease gene with differential tissue expression accounting for the presentations
- Gene function =
    1. Normally transports copper into the secretory pathway of the cell for incorporation into cuproenzymes and subsequent excretion. Localization of the enzyme is regulated by intracellular Cu concentrations and it migrates from the trans-Golgi network to the cell surface.
    2. In Menkes disease, the transport of dietary copper from intestinal cells is impaired leading to low serum levels but there is paradoxical accumulation in other tissues
    3. Specific enzyme deficiencies likely account for the various features:
        a. Cytochrome C-oxidase which affects mitochondrial activity and apoptosis leading to neurologic symptoms.
        b. Decreased lysyl oxidase activity may be responsible for connective tissue fragility and vascular abnormalities.
        c. Tyrosinase is involved in melanin biosynthesis and deficiency results in hypopigmentation.
        d. Copper may also modulate neuronal transmission and regulate NMDA receptor activity [30]

EPILEPSY

- Review of 3 case series found epilepsy in 27/29 patients (93%)
- Epilepsy is often the presenting feature. Case series of 12 patients acquired over 20 years identified several stages of progression. [31]
    1. Focal clonic status epilepticus triggered by fever in 10/12 patients with a mean age of onset 3.5 months. Seizures alternated sides in patients, were associated with hemiplegia in some, and were very refractory to treatment with a mean duration of 3 days. EEG showed runs of focal slow spike and wave activity. No patients in this series had subsequent status epilepticus.
    2. Following this initial presentation, there was a quiescent period ranging from 3-10 months (mean 5.9) without seizure activity.
    3. Infantile spasms represented the second stage of epilepsy and occurred at a slightly later age than typical (mean 9.5m) and were present in 11/12 patients (one died at 8m). 2 patients had spasms without the

preceding stage. EEG background was described as modified hypsarrhythmia in 7/11 cases with a typical ictal pattern. Spasms were resistant to multiple anticonvulsants but ACTH was not reported (1 failed steroids, others failed VGB).

4. Six patients died prior to 18m of age so the numbers are more limited for the 3rd stage. 2/6 patients were seizure free. The remaining 4 developed multifocal epilepsy with myoclonic and tonic seizures, often reflex mediated. 2 patients had persistent spasms. EEG showed multifocal spikes and high amplitude slow waves.

- Review of EEG findings in 10 patients [32]
  1. 7/10 EEGs abnormal with 6 severe (slowing, asymmetry, multifocal spikes).
  2. Normal tracing in neonate (9d) and his affected sibling with classic form and another patient who had been seizure free for 6m prior to the study.
  3. Some suggestion that serum Cu level was correlated with the degree of abnormal findings but it was not statistically significant for a binary assessment.
- Review of EEG findings in 8 patients – [33]
  4. All EEGs abnormal with excess slow activity and an absence of age-appropriate rhythmic activity in the occipital or rolandic regions and frequent spikes.
  5. Early features (3-5m) - high amplitude, multifocal sharp waves, circumscribed areas of amplitude attenuation.
  6. Later features - generalized epileptiform discharges and hypsarrhythmia

TARGETED TREATMENT

- Case series of 24 early treated patients – received Cu injections ≤6 weeks of age. [34, 35]
  1. Assessment of plasma neurochemical profiles in infants at risk due to a positive family history or other suggestive clinical findings led to early diagnosis that was subsequently molecularly confirmed.
  2. In this series, only 3/24 (12.5%) developed seizures although 11/24 (46%) had an abnormal EEG, none developed infantile spasms, and the mean age of onset was later at 20 months.
  3. 62% survival was also statistically different with other series reporting a range of 8-38%.

4. Daily subcutaneous injections of 250–500 μg copper per day (Cu histidine) were begun in the absence of neurological symptoms through an intramural NIH research program.
5. 4 patients had nearly normal neurodevelopmental outcome at 3 years of age and did not develop EEG abnormalities during the course of the 3 year follow-up. Mutations identified in these patients did possess residual copper transport activity and this has relevance to the study as others have reported limited penetration of Cu to the brain in patients with severe loss of function mutations.

- Cupric-chloride administered subcutaneously in another case report led to correction of biochemical markers and improvement in non-nervous system manifestations (hair and skin) but did not improve epilepsy, again secondary to a truncating mutation with no residual activity.
- Case report of another patient with a nonsense mutation predicted to result in severe disease due to a truncated and non-functional protein showed some native read through. In combination with literature from other nonsense mediated disorders (CF, muscular dystrophy, Factor VII deficiency), this raises the possibility that agents to promote read through such as aminoglycosides could be used as treatment for Menkes patients with this type of mutation. [36]
- Gene therapy with adeno-associated virus and a small c-DNA for ATP7A combined with copper-chloride injected into the lateral ventricles of mouse model for Menkes was able to partially rescue the phenotype. [37]

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