Acute Necrotizing Encephalopathy (ANE)

Mutations were noted in 75% of cases and not in 25% with recurrent or familial disease, so the authors suggest calling these familial or recurrent cases as ANE1.

There are isolated non-familial cases of ANE without mutations in RANBP2.

Similarities with ANE1 were

- preceding infection
- seizures,
- coma
- ↑ CSF protein
- MRI.

However, these patients had elevated LFT.

Novel Leukoencephalopathies with Calcifications

RNASET2 gene defect

Aicardi Goutieres syndrome

Cerebroretinal microangiopathy with calcifications and cysts (CRMCC).

Recessive developmental delay, small stature, microcephaly and brain calcifications with locus on chromosome 2
Cockayne Syndrome


CMV Infection


RNASET2-deficient cystic leukoencephalopathy resembles congenital cytomegalovirus brain infection.

Autosomal recessive disorder

Loss-of-function mutations in the gene encoding the RNASET2 glycoprotein lead to cystic leukoencephalopathy.

Indistinguishable clinical and neuroradiological phenotype from congenital cytomegalovirus infection

Congenital CMV and RNASET2 deficiency may interfere with brain development and inactivation through angiogenesis or RNA metabolism.

The RNASET2 gene encodes the glycoprotein RNASET2, the only human member of the RNase T2 family of RNases.

Hermela M et al

Nat Genet. 2008; 41:773-8
CMV Like cystic Leukoencephalopathy

Human RNASET2 protein enters the secretory pathway and is secreted.

CMV seems to be involved in chronic vascular disease.
A role in angiogenesis is also described for RNASET2.

After CMV infection, activation of human RNase L by oligoadenylate synthetases is a known antiviral response to degrade viral and cellular ss RNAs, which the virus tries to block as an evasion strategy.

During brain development, both an inborn failure of RNASET2 activity or the prevention of Rnase L activation by CMV would result in raised levels of ssRNA, stimulating a comparable immune response.

Aicardi-Goutieres Syndrome

Autosomal Recessive inheritance

Early onset encephalopathy, s/s, thrombocytopenia, organomegaly, fever, chilblains

CSF:
- T WBC (>5)
- T interferon-alpha (>10pg/ml)
- Teterins (neopterin),
  Respond to folic acid if low in CSF MTHF

Calcifications:
- basal ganglia & in tissues and perivascular cuffs with microinfarcts/microangiopathy

Gene defects:
- 127 pedigrees: TREX1 (32), H2A (5), H2B (50), H2C (18), Unknown (22)

TREX1
- AGS1: 3p21(Cree encephalitis) exonuclease excises nucleoside monophosphates from 3'-5'DNA, caspase independent apoptosis

RNase H2:
- cleaves RNA from RNA:DNA or DNA:DNA duplexes

AGS 2 (13q14-21, RNase H2B, AGS 3 (11q13.2 RNAs H2C)

AGS 4 (19p13.13 RNAs H2A)
- T supported AGS 5.

Mutations:
- TREX1 and H2 complexes impair enzymatic activity involved in proof reading & processing of DNA & RNA.
- Tclearance of anomalous DNA/RNA triggers immune response


Aicardi-Goutieres Syndrome

TREX1 gene defect: homozygous c.341 g>a R114H.
A mutation common in patients of European origin
Labrune disease
Cerebroretinal microangiopathy with calcifications and cysts (CRMCC).

Labrune P. Neurology. 1996; 46: 1297

Recessive developmental delay, small stature, microcephaly and brain calcifications with locus on chromosome 2

Anna Rajab et al

Thin Anterior Corpus Callosum, and Leukoencephalopathy-SPG11
Spastic Paraplegia with Thin Corpus Callosum SPG 11
Autosomal recessive hereditary spastic paraplegia (ARHSP) + TCC
Spasticity: Begins from infancy-puberty.
Central: Insidiously progressive dementia, dysarthria, dysphagia.
Systemic: Gradual to rapid progression of spasticity, axonopathy: motor & sensory
Neuroimaging: MRI-thin rostral CC, hyperintense WM-periventricular, frontal & occipital, cortical atrophy frontal & thalamic.
PET scans:↓ glucose in cortex and thalamus
Gene defect: 15q21.1
KIAA1840 (FLJ21439), (40 exons), missense, deletions, insertions, spastacin - dioxygenase superfamily, 4 transmembrane domains, localizes to cytosolic, perinuclear and nuclear regions, membranes, cytoskeleton, not seen in newborn rat brain


Progressive Cavitating Leukoencephalopathy
5.5 yr Male


Progressive Cavitating Leukoencephalopathy

Leukoencephalopathy with brainstem and spinal cord involvement, and lactate,

MRS in Leukoencephalopathy with brainstem and spinal cord involvement and lactic acidosis

Neonatal porencephaly and adult stroke related to mutations in collagen IV A1


Deficiency of hyccin, a newly identified membrane protein, causes hypomyelination and congenital cataract

Federico Zara et al. Nature Genetics 2006 - 38, 1111 - 1113
Cerebellar and Brainstem Leukodystrophy with Basal Ganglia Involvement

NI pre, peri, and postnatal history

NI growth and development until 12 years.
School grades A’s and B’s

12 years: Insidious onset of gait disturbance, slurred speech, behavior problems including large ingestion of Tylenol,
School grades dropped to D’s and F’s

Neurological exam: No nystagmus, rigidity, dystonia, ataxia,
TDTR’s, bil. Babinski’s

NI Evaluations: SCA, DRPLA, lysosomal disorders, AFP, NPC, Mito DNA, Mm & skin bx, cobalamine deficiency, Fragile X CDG, Cholestanol, Immunological, AA, Organic acids, VLCFA, EMG/NCV, EKG

NI CSF: protein sugar cultures, amino acids, immunology,
MBP, OL bands

10/1/96 T2 WI (top) and post-contrast T1 WI (bottom): 14 years

5/10/99 17 years
Similarities in established disorders

Metachromatic Leukodystrophy

Late infantile onset MLD

Different anatomical patterns involved in cerebral X-linked Adrenoleukodystrophy

PATTERN 1
Parieto-occipital lobe or splenium 63%

PATTERN 2
Frontal lobe or genu 17%

X-linked Adrenoleukodystrophy

Krabbe Disease

Zarifi MK. J Child Neurol 2001;16: 522
Wenger DA: Metabolic and Molecular Basis of Inherited Disease: 2001; Ed. 8: Vol 3: Chapter 147: 3669
Atherosclerosis Risk in Community (ARIC) Study
White Matter Lesion scale*

10 point scale (0: normal, 9: maximal involvement)
standardized in more than 2000 controls
healthy normotensive individuals (mean age: 60 years)

0: 15%
1: 53%
2: 24%
3-9: 7.6%

*Stroke 1996, 27:2262-70

MRI in clinically/neurologically normal individuals

MRI in clinically/neurologically normal individuals
PMD-Like disease in MCT8 mutated male subjects. Delayed myelination

monocarboxylate transporter 8 gene (MCT8, or SLC16A2, X-linked).

1) Severe: early-onset hypotonia, nystagmus, dystonic movements, spastic quadriplegia, milder forms exist

2) Abnormal thyroid hormone transporter function is increased free triiodothyronine (T3), low free thyroxine (T4), and normal thyroid-stimulating hormone (TSH) levels in the serum.

3) MCT8 mutations induce a deficiency in T3 cell entry despite high circulating T3 levels. No neurological improvement even with a T4 substitutive therapy confirms the need for T3 in the brain. Based on neuronal Mct8 expression in mice, a defect in T3 hormone in neurons is responsible for the severe mental and motor deficiencies in MCT8-deficient patients.

Leukoencephalopathy in 21-β hydroxylase deficiency:

21-Hydroxylase deficiency is the most common cause of congenital adrenal hyperplasia. Autosomal recessive: due to impaired cortisol synthesis from cholesterol by adrenal cortex. Carrier parents also show signs of leucoencephalopathy. White matter anomalies may be present in carriers of a mutation in the CYP21 gene. Therefore authors suggest performing CYP21 gene analysis in subjects with brain MRI evidence of white matter abnormalities that cannot otherwise be explained.