

Leukodystrophies with Intracranial Calcifications

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The leukodystrophies are a heterogeneous group of diseases, which primarily affect white matter. An integrated description of the clinical, neuroimaging and pathophysiological features is crucial for categorizing these disorders. A group of leukoencephalopathies are associated with calcifications. In this article, we review these disorders briefly.

Aicardi-Goutieres Syndrome: Aicardi-Goutieres syndrome (AGS) is a genetically heterogeneous autosomal recessive group of encephalopathies with 5 subtypes. Classic AGS is characterized by cerebral atrophy, white matter abnormalities, intracranial calcifications, chronic CSF lymphocytosis, and elevated CSF alpha-interferon. Broadly speaking, 2 clinical presentations have been delineated: an early onset neonatal form, highly reminiscent of congenital infection seen particularly with TREX1 mutations, and a later-onset presentation, sometimes occurring after several months of normal development and occasionally associated with remarkably preserved neurologic function. Severe neurologic dysfunction becomes clinically apparent in infancy, and manifests as progressive microcephaly, spasticity, dystonic posturing, profound psychomotor retardation, and often death in early childhood. Outside the nervous system, thrombocytopenia, hepatosplenomegaly, and elevated hepatic transaminases along with intermittent fever may also erroneously suggest an infective process. It is important to exclude of pre-/perinatal infections, in particular the TORCH complex. Genetic screening for mutations in the four genes known to cause AGS allows definitive confirmation of the diagnosis in the majority (83%).

Cockayne 's syndrome: Cockayne syndrome is an autosomal recessive disease due to a DNA repair defect. Patients show psychomotor developmental delay, dwarfism, progeroid appearance, microcephaly, deafness, pigmentary retinal degeneration, optic atrophy, and photosensitivity. Abnormal peripheral nerve conduction is due to a demyelinating polyneuropathy. Neuroimaging shows brain atrophy of variable degree, namely in brainstem and cerebellum; abnormally high signal intensity on T2-weighted images throughout the hemispherical white matter; late involvement of the subcortical fibers; abnormal hyperintensity on T1-weighted images in the basal ganglia corresponding to calcification.

Cystic leukoencephalopathy without megalencephaly (RNASET 2-deficient cystic leukoencephalopathy): It is caused by homozygous or compound heterozygous mutation in the RNASET2 gene on chromosome 6q27. Neurologic deficits were noted within the first months of life, and included severe intellectual impairment, motor retardation, and spasticity. Brain MRI showed extensive cysts within the anterior temporal lobes, ventricular enlargement, and white matter disease. The signal intensities of the cysts were identical to those of cerebrospinal fluid. CT scans showed intracranial calcifications in some subjects.

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Cerebrotendinous xanthomatosis: Also called cerebral cholesterosis, is an autosomal recessive form of xanthomatosis. It is characterized by progressive cerebellar ataxia beginning after puberty and by juvenile cataracts, juvenile or infantile onset chronic diarrhea, childhood neurological deficit, and tendinous or tuberous xanthomas. The initial clinical manifestation may be neonatal cholestasis or chronic diarrhea from infancy. In 75% of cases, cataract is the first finding, often appearing in childhood. Pyramidal signs and/or cerebellar ataxia are present in the 20s or 30s. Patients may experience extrapyramidal manifestations (dystonia and atypical parkinsonism), and peripheral neuropathy. MRI shows bilateral hyperintensity of the dentate nuclei and cerebral and cerebellar white matter.

Leukoencephalopathy with calcifications and cysts: Triad of leukoencephalopathy, cerebral calcifications and cysts (LCC) is a recently reported rare disease named 'Labrune syndrome'. The clinical presentation is insidious and variable. Typically, initial symptoms are of raised intracranial pressure, later followed by focal neurologic deficits resulting in spasticity, dystonia, seizures, and cognitive decline. Cerebroretinal microangiopathy with calcifications and cysts, an autosomal recessive disorder caused by mutation in the CTC1 gene that shows phenotypic similarities to Labrune syndrome. CRMCC includes the neurologic findings of intracranial calcifications, leukodystrophy, and brain cysts, but also includes retinal vascular abnormalities and other systemic manifestations, such as osteopenia with poor bone healing, a high risk of gastrointestinal bleeding, hair, skin, and nail changes, and anemia and thrombocytopenia. Although Coats plus syndrome and Labrune syndrome were initially thought to be manifestations of the same disorder, namely CRMCC, molecular evidence has excluded mutations in the CTC1 gene in patients with Labrune syndrome, suggesting that the 2 disorders are not allelic.

Naku-Hakola's disease: Affected patients had onset in the third decade of pain and swelling following strain of the wrist or ankle; fractures occurred after minor accidents. Radiographs showed cystic rarefactions in the epiphyseal regions of bones. The cysts contained jelly-like material and microscopically showed membranous and lamellar structures between fatty and collagenous

connective tissue. In the fourth decade, patients developed neuropsychiatric symptoms, including memory impairment, euphoria, loss of social inhibitions, and impotency or frigidity. Neurologic examination showed exaggerated deep tendon reflexes, pathologic reflexes, and dysplasia. Patients usually die between ages 35 and 45, and the later features of the disorder resemble those of Alzheimer disease.

Globoid Cell Leukodystrophy (Krabbe Disease): The manifestations of Krabbe disease are due to accumulation of galactocerebrosides and galactosylsphingosine, which in turn leads to loss of oligodendrocytes. Infantile Krabbe disease presents in the first 6 months of life as hyperirritability, increased muscular tone, fever, and developmental arrest. As the disease progresses, there is further cognitive decline, myoclonus, opisthotonus, nystagmus, and optic atrophy. Patients diagnosed in infancy rarely survive beyond 2 years. In an estimated 10% of cases, symptoms begin after the patient has begun to walk; these are considered "late-onset." Central motor signs include spasticity, ataxia, and weakness. Of late-onset patients, 20% have abnormal peripheral nerve conduction studies with uniform slowing of conduction velocities.

Demyelination of the deep WM, progressively involving the subcortical white matter. Calcifications within the thalami, basal ganglia, and corona radiata shown by CT scan.

Keywords: Leukodystrophy; Calcification; Bbrain white matter; Children