Leucoencephalopathies associated with Inborn Errors of Metabolism

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Introduction: - The term 'Leukoencephalopathies' means disorders that selectively or predominantly involve the white matter of the brain (1). The discovery of a leukoencephalopathy is often a diagnostic challenge. The first step in the diagnostic approach is to search for acquired, potentially treatable cause. These causes are numerous and include inflammatory, infectious, metabolic, neoplastic, paraneoplastic, toxic (e.g. Methotraxate) or vascular diseases. (2) Metabolic investigations leading to treatable disease should be implemented in order of priority and include homocysteine, amino acids and organic acids analysis. (1).

Objective: - Aim of this study was to understand the spectrum of Leucoencephalopathies (LEP) associated with IEM presenting as neuro-regression in Paediatric age group in Indian subcontinent. Since there is no newborn screening in India, we are likely to miss some of the treatable IEMs (e.g. MMA, homocysteinuria etc.). Also because of higher incidence and degree of consanguineous marriages in certain parts of India, certain metabolic disorders like Krabbe's dis and MLD are likely to be higher.

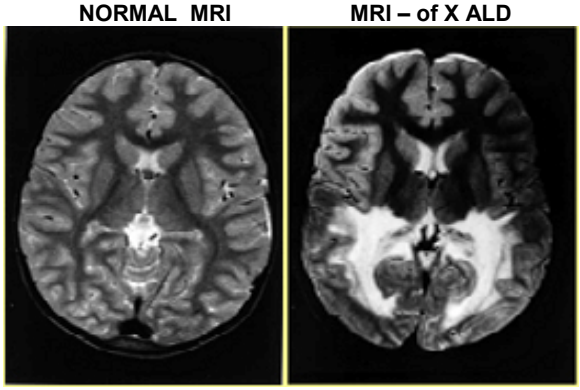
Subjects and method: - 31 cases from 2003 – 2008 were analyzed for presentation with Neuro-regression and LEP. Since all these cases were referred by Paediatricians or Neurologist, basic causes like infection and neoplasm were already ruled out. A detailed metabolic workup was undertaken including following studies. Molecular studies were not routinely employed because of cost and unavailability but one or two cases were subjected to gene sequencing.

1. Aminoacids & Hcy in Plasma and Urine
2. Carnitine / Acyl carnitine Profile by TMS
3. GC-MS of Urine for Organic acids
4. VLCFA analysis – For Peroxisomal disorders
5. Aryl Sulphatase A – For MLD
6. Galactosyl Cerebrosidase – For Krabbes
7. NAA estimation on Plasma and Urine for Canavan's Dis.

Results: -

Disorders	*N = 31*
Glutaric Aciduria Type I	***9***
X – Linked Adrenoleukodystrophy	**7**
Metachromatic Leukodystrophy	**5**
Krabbe's Disease	**3**
Canavan's Disease	**3**
MMA	**2**
Mitochodriopathies	**2**

NORMAL MRI **MRI – of X ALD**



Discussion: Disorders known to be associated with LEP.

1. Adrenoleukodystrophy (ALD) - X Linked / neonatal
2. Alexanders Disease
3. CADASIL (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts Leukoencephalopathy)
4. Canavan Disease (Spongy Degeneration)
5. Cerebrotendinous Xanthomatosis (CTX)
6. Cobalamin C Dis. (Cb1C) / MMA
7. Globoid Cell (Krabbes) Leukodystrophy
8. Glutaric Aciduria Type I (GA)
9. Metachromatic Leukodystrophy (MLD)
10. Methylene Tetra hydro Folate Reductase (MTHFR)
11. Ovarioleukodystrophy
12. Pelizaeous – Merzbacher Disease
13. Peroxisome Biogenesis Defect (PBG)
14. Respiratory Chain Defect (RCD)
15. Van der Knaap Syndrome

The protocol followed at our institute is already mentioned in the methods but it may be modified according to clinical features.

Episodes of Confusion, Coma, Strokes	MMA, MELAS, HMG CoA Lyase Def., Fabry's Dis.
Cutaneous Signs	ALD (Melanoderma), Fabry's Dis, CTX, Sjogren Larsson Syn.
With Visceral Signs	CTX, ALD, MNGIE
With Macrocephaly	GA Type I, 2 OH GA, Canavan's Dis
With Cataracts	CTX, PBD, RCD
With Retinitis Pigmentosa	Cb1C, RCD, PBG
With Polyneuropathy	Krabbe's Dis, MLD, Cb1C, MTHFR Def., PBG

Striking MRI features:-

GA - I	Periventricular LEP, Involvement of U Fibers, Typical Bat wing sign
X - ALD	Bilateral Periventricular LEP, Parieto-occipital predominance, Corpus Callosum and Pyramidal Tract Involvement, Gadolinium enhancement
MLD	Bilateral Periventricular LEP, Sparing of U fibers, Pyramidal tract involvement, Frontal predominance, Cerebral atrophy
Krabbe's	High signal of Pyramidal tracts, involvement of splenium of corpus callosum and optic radiation
Canavan	Diffuse, symmetrical white matter changes are observed in the subcortical areas and in the cerebral cortex; involvement of the cerebellum and brainstem is less marked. MRS shows elevated NAA peak.
MMA	Bilateral basal Ganglia lesion (Pallidum), delayed myelination, immature gyral pattern, thinning of corpus callosum, Cerebellar volume loss (3)

References:-

1. F. Sedel, A Tourbah, B Fontaine – Leucocencephalopathies associated with Inborn Errors of Metabolism in Adults, J. Inherit Metab Dis (2008) 31: 295-307
2. Filley CM, Kleinschmid – DeMasters BK (2001) Toxic leukoencephalopathy. N Engl J Med 345:432
3. I. Harting, A Seitz – Looking beyond the Basal Ganglia : Spectrum of MRI changes in Methyl Malonic Acidemia, J. Inherit Metab Dis (2008) 31: 368-378

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