CSF 5-MTHF levels in Indian neonates with Pyridoxine dependent seizures, Nonketotic hyperglycinemia (NKH), Aicardi Gautiers syndrome and Mitochondrial encephalopathy

Shinde DH[1], JalanAB[1], Joshi MM[1], BorugaleM A[1], Mahakal JM[1], Sonalkar ND[1], Jalan RA[1], Kudalkar KV[1], Pawaskar MS[1], Damle SV[2]

1. NIRMAN, Department of Biochemical Genetics: C-116, Om Rachna Society, Sector - 17, Vashi, Navi Mumbai- 400705, India.

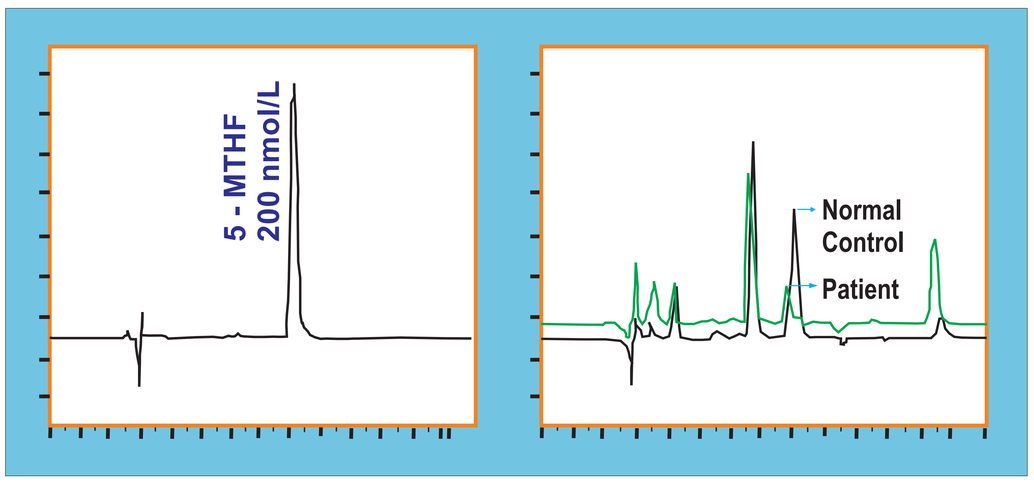
2. KishinchandChellaram College, Department of Life Sciences, Churchgate, Mumbai, India.

Introduction : 5 - MTHF in cerebral spinal fluid (CSF) is considered an important metabolite. Folates are essential for foetal development. Many diverse metabolic pathways can lead to depletion of CSF - 5 MTHF, whose supplementation may help.

Objective : To study children with neuro - metabolic disorders, from India, for CSF - 5MTHF levels and compare it with clinical - biochemical spectrum.

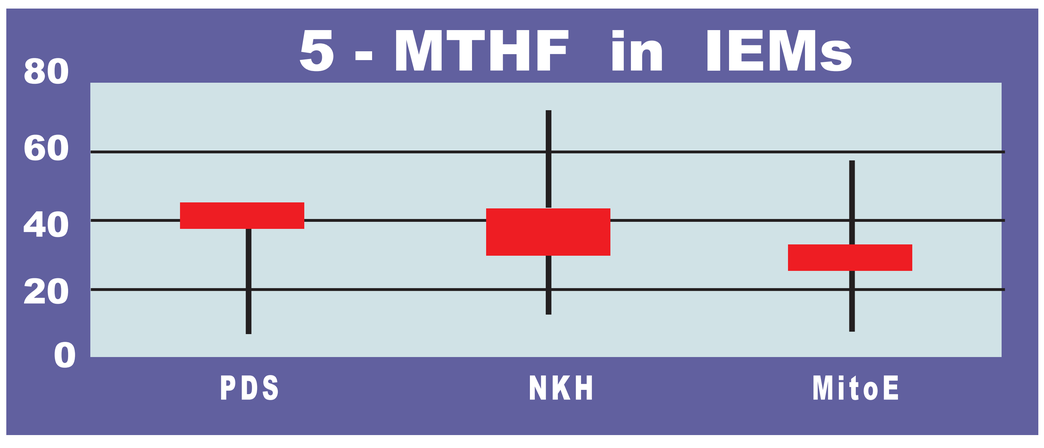
Materials & Methods : We analysed four groups of neurological disorders - Pyridoxine dependent seizures (PDS), Glycine Encephalopathy (NKH), Aicardi Gautiérs Syndrome (AGS) and mitochondrial encephalopathy (MitoE). CSF - 5MTHF, CSF - Pterins, CSF - Pipecolic acid, Plasma and CSF Glycine, Urine Organic acids (GC-MS), Carnitine - Acyl / Carnitines (MS-MS) were analysed.

CSF 5 - MTHF and Pterins are detected on U-HPLC by reverse phase chromatography with fluorescent detector, as previously described by Blau et al[1]. The separation was carried out in C 18 column and analysed with EZChrom Elite software, Agilent.



Results : Out of 7 patients with PDS (elevated CSF-pipecolic acid and good response to Pyridoxine) 5 had low 5 - MTHF level, (44.79 ± 37.62) (NR = 64 - 182 nmol/l). 2 of 3 patients of NKH (Glycine Encephalopathy with elevated CSF & Plasma Glycine and normal Urine-GC - MS) had low 5 - MTHF, (42.71 ± 29.58). One patient with AGS (elevated CSF - INFα, elevated Neopterin and Classical CT - Scan) had 5 - MTHF of 42.77nmol/L and 5 with MitoE also had low 5 - MTHF (32.39 ± 24.93)

	No. Of patients	Mean 5-MTHF (64 - 182 nmol/l)	SD	Range
PDS	7	44.79	37.62	7.17 - 37.62
AGS	1	42.77	-	-
MitoE	4	32.39	24.93	7.46 - 57.32



Discussion : CSF 5 - MTHF levels seem to be affected in many children with various neuro - metabolic disorders. Supplementation with Folinic acid may be offered, which is economical, safe and effective[2]. In our cohort one child with Aicardi Gautiérs Syndrome and one child with NKH have shown good clinical response to supplementation.

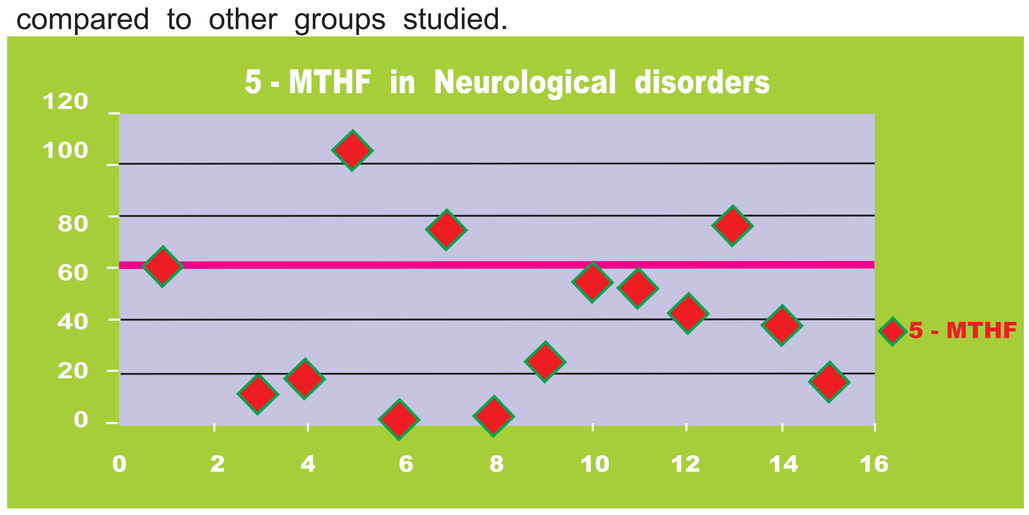
In our cohort of 15 patients with different neurological disorders, 12 of the patients shows reduced 5 - MTHF. The reason for the reduction of cerebral folate concentration in patients with inherited metabolic disorder is not clear and is still a matter of investigation[3]

One explanation for the high clinical impact of folate deficiency might be the fact that folate is a cofactor in processes contributing to preserve the genome, to regulate gene expression, to amino acid metabolism, myel information and neurotransmitter synthesis. Therefore, screening for low CSF 5 - methyltetrahydrofolate (5MTHF) levels has been recommended for various neurological disorders of unknown origin[4].

Pterins like neopterin, biopterin are seen elevated in conditions like Aicardi-Gautiérs[5] which is mostly seen due to inflammation, although our investigation shows elevated neopterin but elevated biopterin levels were not seen. This may be due to fluorescent detector used which is not as sensitive as electrochemical detector used by others. The correlation between concentration of CSF 5 - MTHF and Pterins is seen in many cases but the reason for the correlation is not completely understood[6]. Further investigations, such as correlating the concentrations of these two, may help in better understanding of the disorder.

Two other patients with AGS, investigated after this analysis, also showed same pattern of reduced 5 - MTHF and increased Neopterin. Long term substitution with folinic acid (2-4 mg/kg/day) resulted in substantial clinical recovery with normalization of CSF folate and pterins in one patient and clinical improvement in another[5].

Some patients in our cohort also showed normal levels of 5 - MTHF and pterins. In our study we found lowest mean levels of 5 - MTHF in MitoE, whereas PDS shows better values of 5 - MTHF as compared to other groups studied.



Patients with various neurological disorders shows very low 5 - MTHF levels in CSF than normal ranges (64 to 182 nmol/L)

Conclusion : Neurological disorders like Aicardi - Gautiers Syndrome, Neuro degenerative disorders, metabolic disorders like Mitochondriopathy, Non – Ketotic hyper glycinemia, Pyridoxine dependent seizures, etc. show folate metabolism defects. Deficiency of cerebral folate in these disroders may contribute to some of the neurological symptoms. Supplementation with folinic acid has been effective in two of our patients - one with AGS and one with NKH. Thus, monitoring levels of CSF 5 - MTHF and supplementation with folinic acid may improve the clinical outcome.

References :

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