Does Aicardi- Goutières syndrome present with High Neopterin and Biopterin?

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Abbreviations : **AGS :** Aicardi-Goutières syndrome, **INFα:** Interferon α, **GTPCH I:**Guanosine Triphosphate Cyclohydrolase I, **PTPS :** 6-puruvol-tetrahydropterin synthase, **BH_4:** Tetrahydrobiopterin, **GFRP :** GTPCH I feedback regulatory protein, **DHPR :** Dihydropterin reductase

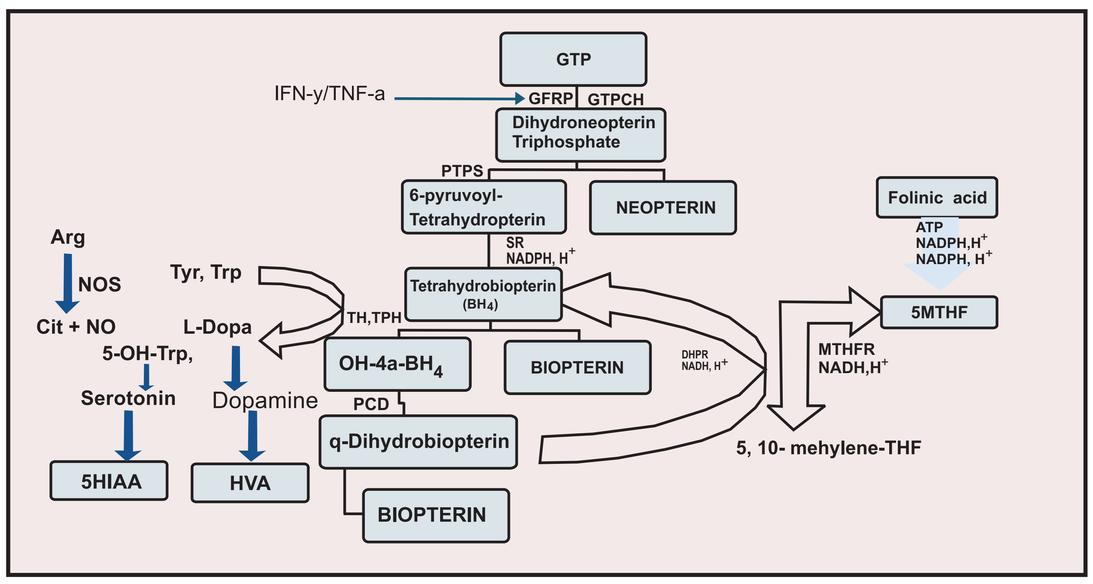
Introduction : Aicardi - Goutières syndrome (OMIM no. 225750) is a heterogeneous, autosomal recessive, progressive encephalopathy, presenting in early infancy. It is a disorder that mainly affects the brain, the immune system and the skin. Recent studies showed increased production of Neopterin and Biopterin in CSF of AGS patients and its variant as a response to inflammation[1].

Background : Clinical features of AGS include microcephaly, developmental delay, spastic quadriplegia, extra pyramidal dyskinesia, visual disturbance and refractory seizures[2]. Chronic pleocytosis and elevated levels of interferon alpha (IFN-α) in CSF are of diagnostic importance.

BH_4 is synthesised from GTP by the enzyme GTPCH I, PTPS and SR. During the hydroxylation of tyrosine to L-dopa by tyrosine hydroxylase (TH) and tryptophan to 5-hydroxytryptophan (5-OH-Trp), BH_4 is oxidized to OH-4a-BH_4 and subsequently regenerated by the enzymes pterins - 4a - carbinolamine dehydratase (PCD) and DHPR.

Biosynthesis of BH_4 is regulated by the GTPCH feed-back regulatory protein (GFRP) or by cytokines such as interferon gamma (IFNγ) and tumor necrosis factor alpha (TNFα). Thus, depending on types of cell and stimulus only Neopterin or both Neopterin and biopterin can be seen elevated in accordance to inflammatory response.

Figure 1 : Pterins pathway



Objective : To study Pterins – Neopterin, Biopterin levels in CSF of AGS patients diagnosed clinically and radiologically.

Materials & Methods : We have studied 6 patients, all males. All of them had microcephaly, seizures and calcifications of basal ganglia. Diagnosis was supported by elevated INF-α in CSF. CSF INF-α was more than that of serum. Collected CSF samples were stored at -20° before analysis. Pterins were analysed by reverse phase ultra high pressure liquid chromatography (UHPLC). Samples were oxidised with MnO_2 in acidic medium and pterins were detected by fluorescence at 350/450 nm.

Results : All patients had elevated Neopterin levels, Mean 5,002 nmol/L [130.82 – 17,723.63 (NR 9 – 129)] and normal Biopterin levels Mean 11.87 nmol/L [0.36 – 29.63 (NR 10 – 30)]. 4 out of 6 patients had low 5 MTHF (CSF-folates) [50.62 ± 22.39 (NR 63 – 129 nmol/l)]

Sr. No.	Sample	INF-a-CSF(<1.0 pg/ml)	INF-a--Serum(<1.0 pg/ml)	Neopterin (9-20 nmol/1)	Biopterin (10-30 nmol/1)	5-MIHF (63-129 nmol/1)
1	ZS	41.262	2.427	166.27	0.36	42.78
2	SS	48.26	66.25	130.82	3.59	79.101
3	NS	9.2	1.95	9795.15	13.13	51.12
4	AC	33.28	5.09	17723.63	29.63	70.63
5	LH	14.57	3.85	1891.13	1.87	61.69
6	RS	6.45	5.51	309.07	2.65	35.74

Figure 2 : Pterins Standard

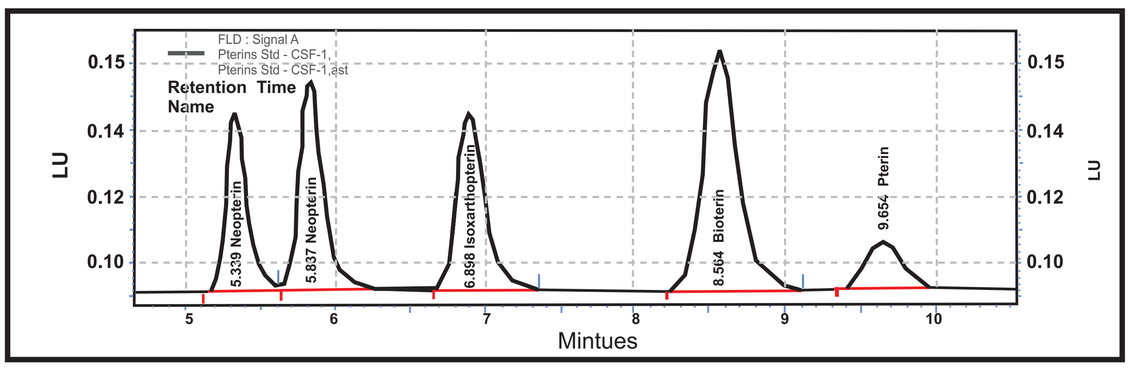


Figure 3 : AGS patient sample with High Neopterin and normal Biopterin

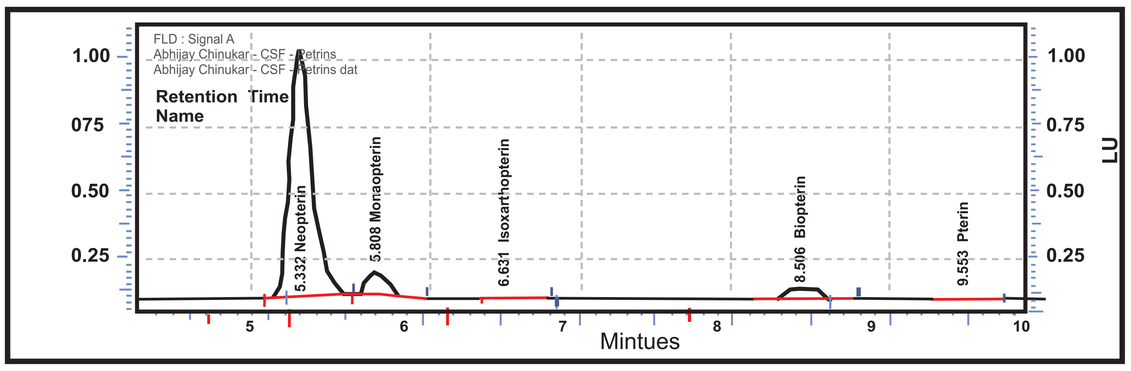
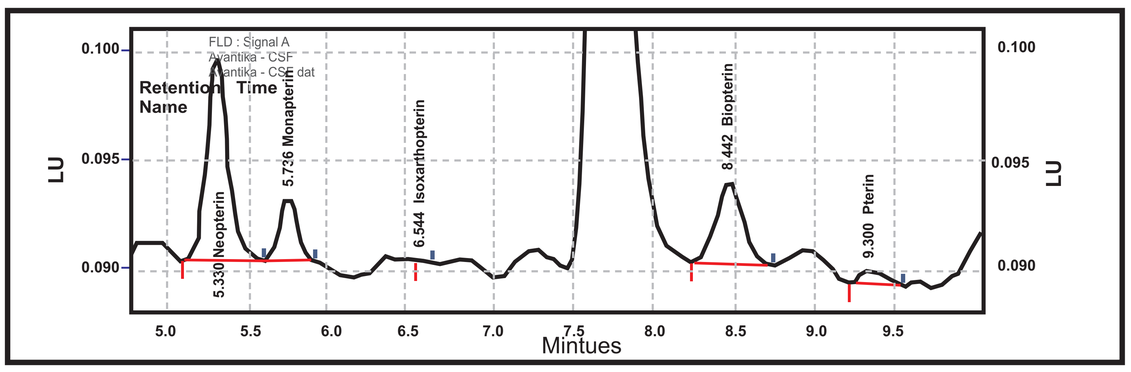


Figure 4 : Normal patient sample with Normal Neopterin and Biopterin



Discussion : AGS is a progressive encephalopathy with onset in the first year of life[4]. All of our 6 patients had onset within 1st year of life. Clinically AGS is suspected on the basis of microcephaly, severe psychomotor delay, spasticity and extra pyramidal signs, associated with typical calcification on CT scan of brain. Discussion on other differential diagnosis is beyond the scope of this poster. We studied CSF Pterins and 5 MTHF and found only elevated Neopterin and normal Biopterin. However previous work on pterins levels in CSF of AGS by Nenad Blau et al, have shown elevated levels of both Neopterin and Biopterin, as an inflammatory response[3].

Nenad Blau et al have reported 3 patients (2 of AGS variant and 1 with classical AGS) with low 5 - MTHF, who were treated beneficially with folinic acid (Leucovorin)[3]. In our series 4 out of 6 patients had low CSF-folate. All these children were treated with Folinic acid supplementation with some benefits. However long term follow- ups are necessary to understand the real effect of Folinic acid supplementation. Unfortunately we could not perform follow-up CSF studies, even though these were recommended to all.

Conclusion : CSF neopterin and biopterin have been reported to be elevated in AGS due to various reasons, but in our cohort of 6 patients, Neopterin was found high in all the patients but Biopterin was normal. Also 4 patients had low folate levels. A possibility of Folinic acid substitution exists in AGS patients with low folates. Thus, investigation of CSF metabolites like pterins and 5-MTHF may be used as important tools in diagnosis and management.

Conflict of interest : None

References :

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