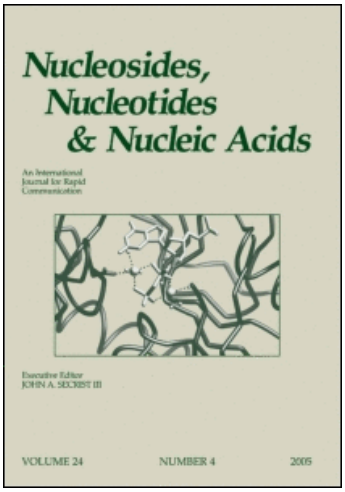

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L. D. Fairbanks[a]; J. C. Harris[b]; J. A. Duley[c]; H. A. Simmonds[a]
[a] Purine Research Unit, Guy's Hospital, London, UK [b] Johns Hopkins University Medical School, Baltimore, USA [c] University of Queensland, Australia

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Nucleotide Degradation Products in Cerebrospinal Fluid (CSF) in Inherited and Acquired Pathologies

L. D. Fairbanks,[1,*] J. C. Harris,[2] J. A. Duley,[3] and H. A. Simmonds[1]

[1]Purine Research Unit, Guy's Hospital, London, UK
[2]Johns Hopkins University Medical School, Baltimore, USA
[3]University of Queensland, Australia

ABSTRACT

CSF purines were grossly elevated compared with controls only in adenylosuccinate lyase (ADSL) deficiency and TB meningitis. The former representing low permeability, the latter severe damage to the normal blood/brain barrier. By contrast, the similarity to controls, with no difference between Lesch–Nyhan disease (LND) or LND variants, would exclude hypoxia as a factor in the severe neurological deficits in LND. Similar findings in purine nucleoside phosphorylase (PNP) deficiency (although nucleosides replace the normal bases) likewise exclude hypoxia in the aetiology of the albeit milder neurological deficits.

Key Words: CSF purines; Lesch–Nyhan disease; Adenylosuccinase deficiency; Purine nucleoside; Phosphorylase deficiency; TB meningitis.

INTRODUCTION

We aimed to determine whether differences in purines or pyrimidines in CSF could aid understanding of the pathophysiology of the neurobehavioural abnormalities underlying LND, or in the other disorders studied.

*Correspondence: L. D. Fairbanks, Purine Research Unit, Guy's Hospital, London, UK.

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PATIENTS AND METHODS

Metabolites were measured by RPLC in the following patients: 8 classic LND (severe neurological deficits), 5 partials (milder deficits/LND variants)—1 of each not on allopurinol (allop); 2 deficient in ADSL, 1 in PNP, 6 with suspect tuberculous meningitis (TBM). Controls were 21 patients referred with no known basis for their neurological disorder.

RESULTS

Twelve purine components of human plasma were found in CSF. The notable findings (Table 1) are:

Hypoxanthine (Hyp) alone is elevated in LND or variants not on allop compared to controls, uric acid in all is only slightly higher than controls (and much lower than plasma in LND). Hyp and xanthine (Xan) are elevated by allop, uric acid reduced, with *no difference between classic LND and partial variants*. Oxipurinol found in all on allop, but again lower than in plasma.

No purine bases in PNP deficiency—inosine (Ino) replacing Hyp, guanosine (Guo) replacing Xan.

Table 1. CSF purine and pyrimidine metabolites (μmol/l).

Defect	C	?TB	TB	ADSL	ADSL	PNP	LND	HPRTH	PRT/LND
Age (yr)	6–32	35	77	4 wks	26	5	21	22	19
n	21	5	1	1	1	1	7	4	2
Sex	9f, 12m	1f, 4m	f	f	f	m	m	m	1m, 1f
Purine metabolites								Allop	Allop
Uric acid	9–14	42	506	22	27	11	13	22	39
Hyp	52.4	121	3.5	3.2	nil	63	57	31	
Xan	2.3–3.6	1.8	46	3	3	nil	15	19	3.5
Ino	0.7	0.7	24	0	3.1	19.6	1.1	1.8	1.5
Guo	0	0	0	0	0	12	0	0	0
SAICAr	< 0.01	< 0.01	< 01	921	314	0	0.8	0.8	0.75
SAdo	0.9–1.5	1.6	2.8	477	401	0	0.9	0.9	0.85
Pyrimidine metabolites									
Uridine	3.6–4.3	3	11	7.2	2.4	1.6	8.7	8.2	9.5
Psu	2.0–2.3	3.4	25	3	4	3.8	2.6	3.8	3.5
Other									
Oxipurinol								40	19
Allopurinol								1.6	0.8
Creatinine	33–44	56	450[a]	30	45	25	50	49	42

C = neurological control.
TB = tuberculous meningitis.
[a]Renal failure.

Very elevated concentrations of SAICAr (succinylaminoimidazolecarboxamide riboside) and SAdo (succinyladenosine) only in ADSL deficiency, but Hyp, Xan, uric acid in the control CSF range.

Elevated uric acid, Xan, Hyp, Ino levels in the single TB meningitis case, *similar to normal plasma*.

DISCUSSION

The lack of difference in CSF concentrations of Hyp, Xan and uric acid between classic LND and LND variants (on or off allop), excludes the proposed involvement of Hyp through ATP breakdown due to hypoxia in the aetiology of the severe neurological deficits in classic LND.[1,2] The much lower Xan and uric acid, identical to controls, also confirms the absence of xanthine dehydrogenase in human brain. The lower Xan has two possible explanations: GTP turnover is lower than ATP,[1] or GTP concentrations are already very low.

The fact that in PNP deficiency Ino is half mean plasma concentrations is consistent with a similar lack of involvement of ATP breakdown in the neurological deficits in PNP.

The gross elevation of SAICAr and SAdo in CSF and urine in ADSL deficiency, not plasma, and Sado/SAICAr ratio < 2, accords with: 1) the Type 1 disorder with severe neurological deficits; 2) low permeability of succinylpurines and slow exit through the blood–brain barrier, combined with a high urinary clearance.[3] Low amounts of SAICAr and SAdo only in LND, suggest increased activity of this synthetic route in brain in LND.

Elevated uric acid, Hyp, Xan, Ino and creatinine in TB meningitis, at concentrations similar to plasma, confirm severe damage to the normal blood–brain barrier.[4]

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