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BIOGENIC AMINE STATUS IN ACUTE FULMINANT HEPATOCELLULAR FAILURE IN CHILDREN

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Summary : This study involved pediatric cases with Acute fulminant hepatocellular failure (AFHF) put on conventional therapy at the Hospital for children, Madras. In these cases, the biogenic amine status was studied at the time of admission, during therapy and at the time of recovery in responders. The CSF 5-HT, 5-hydroxyindoleacetic acid (5-HIAA) and Homovanillic acid (HVA), blood 5-HT and 5-HIAA, and urinary 5-HIAA followed almost a similar pattern of changes during the course of AFHF : increase at precoma, further increase at coma, return towards control at recovery. In striking contrast, urinary 3-methoxy-4-hydroxyphenyl glycol (MHPG) and 3-methoxy-4-hydroxymandelic acid (VMA) registered a decrease at precoma, a further fall at coma and a value closer to control at recovery. The results suggest the usefulness of assay of these parameters in monitoring cases of AFHF during therapy and in offering prognosis for these cases.

Key words : fulminant hepatocellar failure children biogenic amine metabolites 5-HT, 5-HIAA and HVA in CSF 5-HT and 5-HIAA in blood 5-HIAA, VMA and MHPG in urine

INTRODUCTION

Acute fulminant hepatocellular failure (AFHF) constitutes one of the major medical emergencies in pediatric practice with a high mortality rate. It is distinctly ushered in by an acute and rapid onset of progressive mental disturbance, advancing fast to stupor or coma. Signs of encephalopathy usually appear within a few days of the onset and the whole illness may span for less than a week (1) . An imbalance of central neuroamines was suggested to be one of the causes of hepatic coma (2). In patients with stupor or coma from fulminant hepatic failure, high levels of CSF Homovanillic acid (HVA) and 5-hydroxyindoleacetic acid (5-HIAA) were reported (3, 4). However, the reports concerning changes in the levels of CSF neuroamines and metabolites during conventional therapy of AFHF in children are meager. Hence, it was decided to study the biogenic amine status in pediatric cases at the time of admission, during conventional therapy and at the time of recovery in responders. The main objective of this work was to find out if the study of the amine profile would be helpful to monitor the course of AFHF during therapy and to offer prognosis in these cases.

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MATERIALS AND METHODS

Eighty children that had no previous liver disease and manifesting characteristic diagnostic features of AFHF (5), within preceding 8 weeks and admitted at the Institute of child health and Hospital for children, Madras were included in this study. Control CSF samples were obtained from 12 pediatric cases of leukemia with secondary complications wherein lumbar puncture is done for drug administration.

In children admitted in precoma stage manifesting early signs of encephalopathy, conventional therapy (6)—elimination of dietary protein, i.v. infusion of hypertonic glucose with electrolytes, vitamins—K, B-complex and C, prophylactic antibiotics (neomycin orally), large doses of steroids, sedatives, purgatives and enema—was at once instituted. In these cases. CSF and blood samples were collected at the time of admission and thereafter, every 48 hr.; 24 hr. urine samples were also collected. The sample collection was continued until recovery or death of the patient as the case may be.

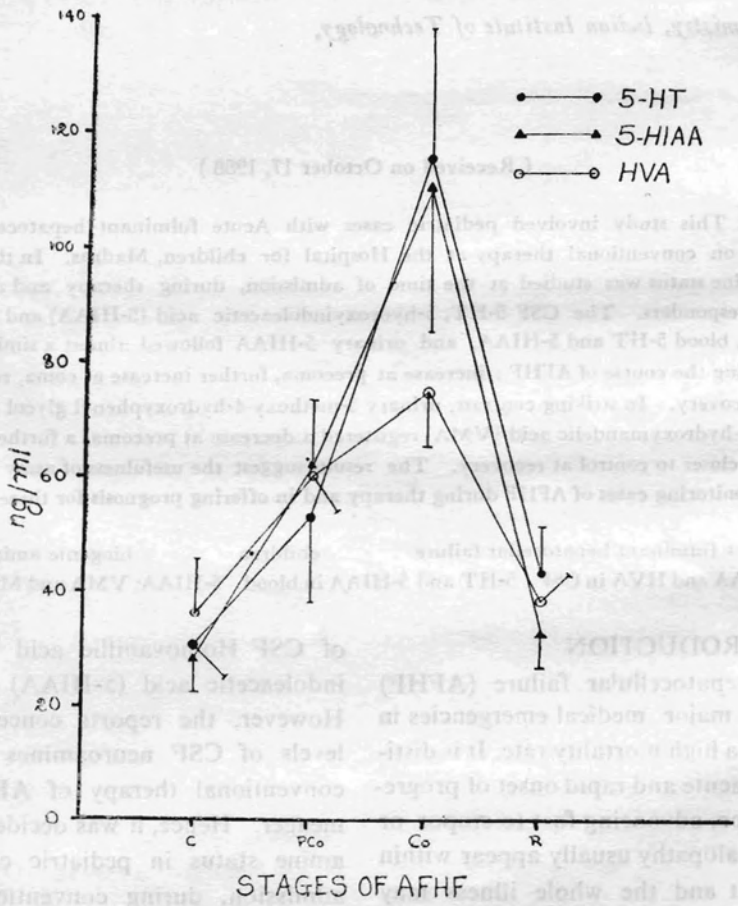

Fig. 1 : 5-HT, 5-HIAA and HVA levels in CSF at different stages of AFHF in children. C - Control (n=12); PCo - Precoma (n=30); Co - Coma (n=30); R - Recovery (n=8). The values shown are Mean±S.D. of 'n' number of trials.

5 - HT - C Vs. PCo, Co and R - P<0.01; Co Vs PCo and R - P<0.01.

5 - HIAA - C Vs. PCo and Co - P<0.01: C VS. R - N.S.; Co Vs. PCo and R - P<0.01.

HVA - C Vs. PCo and Co - P<0.01; C Vs. R - N.S.; Co Vs. PCo and R - P<0.01.

Throughout this study, CSF and blood samples were collected between 11 am and 12 noon to eliminate diurnal variations. The blood stained CSF samples were discarded. CSF and blood samples were collected in test tubes containing ascorbic acid 1 mg/ml, and a mixture of 3 mg ascorbic acid and 15 mg EDTA per ml respectively and kept frozen until analysis. To facilitate collection of 24 hr. urine samples, an indwelling catheter was fixed *in situ*. The collections were made in polythene containers containing 10 ml of 6N HCl, which were kept stored under refrigeration until analysis.

The following parameters were assayed in CSF, blood and urine samples utilizing the standard fluorimetric assay procedures :

CSF : 5-HT and 5-HIAA by the method of Curzon and Green (7); HVA by the method of Ashcroft et al. (8); 3—methoxy—4—hydroxyphenyl glycol (MHPG) by the method of Sapira (9).

Blood : 5—HT and 5—HIAA (7).

Urine : 5—HIAA by the method of Korf and Valkenburg-sikkema (10); 3—methoxy—4—hydroxy-mandelic acid (VMA) and MHPG (9).

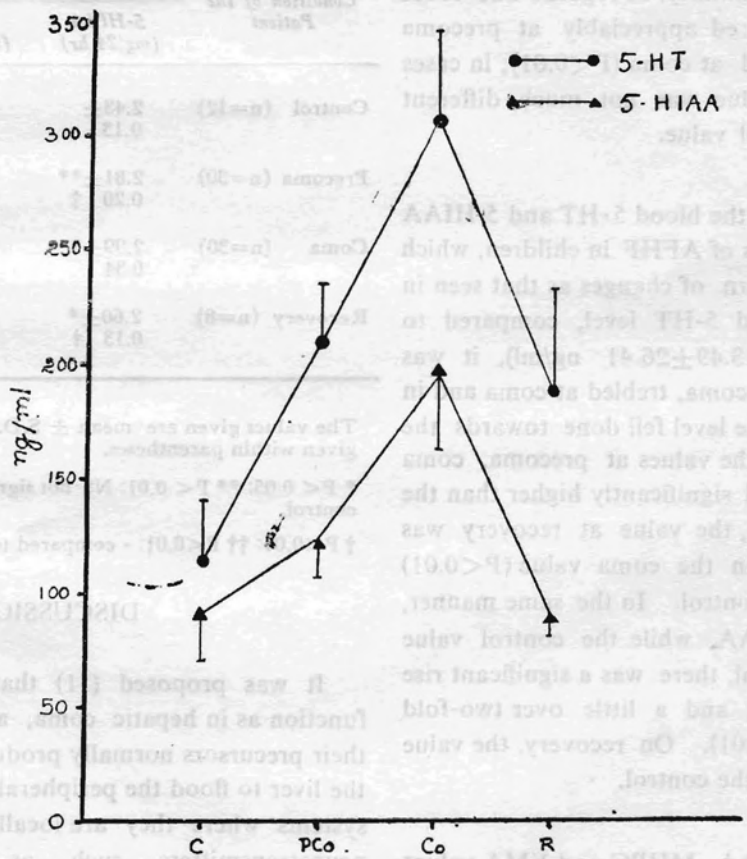

Fig. 2 : 5 - HT and 5 - HIAA levels in blood at different stages of AFHF in children. C-control (n=12); PCo - Precoma (n=30); Co - Coma (n=30); R - Recovery (n=8);
The values shown are Mean±S.D. of 'n' number of trials,
5 - HT - C Vs. PCo, Co and R - P<0.01; Co Vs. PCo. and R - P<0.01.
5 - HIAA - C Vs. PCo and Co - P<0.01; C Vs. R - NS; Co Vs. PCo and R - P<0.01.

RESULTS

The changes in 5-HT, 5-HIAA and HVA levels in CSF at different stages of AFHF are depicted in Fig. 1. The 5-HT and 5-HIAA values were almost doubled ($P<0.01$ for both) at the precoma stage and increased four-fold during coma ($P<0.01$ for both) compared to control values. In those cases that recovered, there was significant decrement in 5-HT and 5-HIAA values compared to coma values and were close to control values. In another comparison, compared to values at coma, 5-HT and 5-HIAA values at precoma and recovery were significantly decreased ($P<0.01$). Similarly, as regards CSF HVA values, the level increased appreciably at precoma ($P<0.01$) and doubled at coma ($P<0.01$); in cases that recovered, the value was not much different compared to the control value.

In Fig. 2 are shown the blood 5-HT and 5-HIAA levels at different stages of AFHF in children, which reveal a similar pattern of changes as that seen in CSF. As regards blood 5-HT level, compared to the control value (113.49±26.41 ng/ml), it was almost doubled at precoma, trebled at coma and in cases that recovered, the level fell done towards the control value. While the values at precoma, coma and recovery were all significantly higher than the control value ($P<0.01$), the value at recovery was significantly lower than the coma value ($P<0.01$) and was closer to the control. In the same manner, in case of blood 5-HIAA, while the control value was 90.28±19.29 ng/ml, there was a significant rise at precoma ($P<0.01$), and a little over two-fold increase at coma ($P<0.01$). On recovery, the value was not different from the control.

The urinary 5-HIAA, MHPG and VMA values at different stages of AFHF are incorporated in Table I. Strikingly, in accordance with the type of changes in 5-HIAA encountered in CSF and blood, in urine too, matched against the control value (2.43±0.13 mg/24 hr.), there was an increase at precoma ($P<0.01$), further increase at coma ($P<0.01$) and a decrement closer to control ($P<0.05$) at recovery. On the other hand, viewed against the control values (1.44±0.10 and 2.56±0.36 mg/24 hr. respectively), in striking contrast, there was a decrement in urinary MHPG and VMA values at precoma ($P<0.01$), a further fall at coma ($P<0.01$) and an increment closer to control on recovery ($P<0.01$) compared to values at coma.

TABLE I : 5-HIAA, MHPG and VMA levels in urine at different stages of AFHF in children.

Condition of the Patient	*Urine*		
	5-HIAA (mg/24 hr)	*MHPG (mg/24 hr)*	*VMA (mg/24 hr)*
Control (n=12)	2.43± 0.13	1.44± 0.10	2.56± 0.36
Precoma (n=30)	2.81±** 0.20 †	1.25±** 0.07 ††	2.00±** 0.17 ††
Coma (n=30)	2.99±** 0.34	1.13±** 0.08	1.83±** 0.20
Recovery (n=8)	2.60±* 0.13 †	1.34±* 0.05 ††	2.30±N.S. 0.21 ††

The values given are mean ± S.D. of 'n' number of trials given within parentheses.

* $P< 0.05$; ** $P< 0.01$; NS-not significant;-compared to the control.

† $P<0.05$; †† $P<0.01$; - compared to the coma value.

DISCUSSION

It was proposed (11) that in impaired hepatic function as in hepatic coma, aromatic amines and their precursors normally produced in the gut, bypass the liver to flood the peripheral and central nervous systems where they are locally converted into false neurotransmitters such as octopamine and β-phenylethanolamine. Eventually accumulation of false neurotransmitters results in the release and replacement of normal endogenous neuroamines, which eventually leads to gross changes in the levels of brain amines.

In the past literature, regarding changes in central 5—HT levels, the reports were conflicting in that some claimed no change in the synthesis of 5—HT (12, 13), while others reported high brain 5—HT and 5—HIAA in rats with acute hepatic necrosis leading to coma (14) and in human patients that died in hepatic Coma (15). Jellinger and Riederer (16) observed a rise in brain and CSF levels of 5—HT, tryptophan and 5—HIAA. In this study, CSF 5—HT and 5—HIAA levels were almost doubled at the precoma and increased four-fold at the coma stages compared to the control (Fig. 1). These data are concordant with the report of Jellinger and Riederer (16). Further, the pattern of CSF HVA changes (Fig. 1) were similar to that of 5—HT and 5—HIAA.

In this present study, the assay of neuroamine metabolites in CSF were undertaken on the assumption that their concentrations were reflective of processess involving the parent amines and their turnover in the CNS (17-19). With regard to CSF 5—HIAA (Fig. 1), the present results are in agreement with the previous reports (3, 4, 13, 20) reporting high values in the spinal fluid of patients with hepatic encephalopathy. High levels of 5—HIAA encountered during precoma and coma may be taken as indicative of increased brain turnover of 5—HT (21).

Likewise, the high CSF HVA could be attributed to an increased brain DA turnover due to increased availability of phenylalanine and tyrosine, but there are several reports indicating no change in synthesis and concentration of brain DA (20, 22) and a slight fall thereof in both experimental and human encephalopathy (16). In view of these reports, it may be suggested that the high CSF HVA might be consequent to defective transport of HVA rather than to abnormal DA metabolism (4).

In those cases that recovered, there was reduction in the levels compared to that at precoma and the value was closer to the control (Fig. 1). Thus, there seems to be a correlation between the different stages of AFHF and the changes in CSF 5—HT and 5—HIAA levls thereat. This finding apprears to be in contradiction to the previous report (23) of lack of consistent changes in lumbar CSF 5—HIAA in patients that recovered from hepatic coma. However, the similar pattern of changes in blood 5—HT and 5—HIAA (Fig. 2) namely an increase at precoma, further increase at coma and return to normal at recovery–further consolidates the occurrence of the pattern of correlation between the changes in these parameters and the different stages of AFHF.

With regard to urinary 5—HIAA, there was an increase at precoma, further increase at coma and later a decrement closer to control, which is similar to the type of 5—HIAA changes encountered in CSF and blood. In contrast to this, there was a decrease in the urinary MHPG and VMA levels at precoma, a further fall at coma and then an increment closer to control on recovery. However. the urinary levels of 5—HIAA and VMA recorded at different stages of AFHF were well within their normal ranges of values. While urinary 5—HIAA and VMA may not be indicative of the status of central 5—HT and NE metabolism respectively, urinary MHPG is accepted to be of value in reflecting NE metabolism in CNS (24). Thus, the urinary MHPG changes recorded during the course of AFHF under conventional therapy may be taken as indicative of an inhibition of central NE metabolism, which is in agreement with the previous reports (25, 26).

Taken together, the data of the present study reveal that there is an augmentation in the metabolism of 5—HT and DA simultaneously with an inhibition in the NE metabolism. The typical patterns of changes discerned in neuroamine metabolite levels in CSF, blood and urine during the course of AFHF suggest the utility of assay of these amine metabolites in monitoring cases of AFHF during its course and therapy and probably

also in predicting the prognosis of the cases based on restoration of these parameters to control levels during therapy.

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