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Postmortem serotonin levels in cerebrospinal and pericardial fluids with regard to the cause of death in medicolegal autopsy

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ABSTRACT

Serotonin (5-hydroxytryptamine, 5-HT) is a neurotransmitter in the central nervous system (CNS) and a smooth muscle regulator in the cardiovascular and gastrointestinal systems. The present study investigated postmortem 5-HT levels in cerebrospinal fluid (CSF) and pericardial fluid (PCF) with regard to the cause of death in serial medicolegal autopsy cases within 48 h postmortem ($n = 351$, >20 years of age). CSF and PCF 5-HT slightly increased during the postmortem period ($r = 0.298$ and 0.253, respectively, $p < 0.001$), showing no gender-related difference. The CSF level decreased depending on the subject age ($r = 0.497$, $p < 0.001$); however, the CSF and PCF levels showed similar findings with regard to the cause of death: these levels were significantly higher for sedative-hypnotic drug intoxication and hyperthermia (heat stroke), but lower for blunt head injury and hypothermia (cold exposure); the cutoff value was estimated as 25.5 ng/ml and 5.0 ng/ml, respectively. For other cause of death groups, some cases showed a higher level. These findings suggest elevations in CSF and PCF 5-HT levels due to systemic toxic or hyperthermic neuronal dysfunction, and systemic stress responses to trauma without CNS involvement.

1. Introduction

Serotonin (5-hydroxytryptamine, 5-HT) is a neurotransmitter in the central nervous system (CNS), a regulator of smooth muscle function in the cardiovascular and gastrointestinal systems, and also of platelet function. 5-HT is found in specific regions of the CNS, and the principal cell bodies of 5-HT neurons are located in the raphe nuclei of the brainstem [1–3]. It is believed that an excess of 5-HT brings about CNS stimulation, while a deficiency produces a depressant effect [4–6]. Dysfunction of the CNS serotonergic system has been discussed in depth with regard to affective disorders, alcohol and drug abuse and posttraumatic stress disorders [7–10]. Serum 5-HT is mainly derived from enterochromaffin cells of the gastrointestinal tract and platelets [11–13], but the serum level does not affect CNS function because 5-HT itself does not pass through the blood–brain barrier to any significant degree [14], suggesting that 5-HT in CSF is mainly derived from the brain. In contrast, blood 5-HT together with other plasma components may gradually permeate the pericardial fluid (PCF) [15], although the PCF level may not be significantly affected within about half an hour [16,17]; however, PCF 5-HT may partly derive from the heart [18–20]. Thus, a comparison of postmortem 5-HT levels between CSF and PCF may be useful to investigate CNS and cardiac functions immediately before death.

The present study investigated postmortem 5-HT levels in CSF and PCF with regard to the cause of death to examine the topographical characteristics of postmortem 5-HT profiles in relation to the CNS and cardiac function in the fatal process.

2. Materials and methods

2.1. Autopsy materials

Serial medicolegal autopsy cases having a postmortem time within 48 h ($n = 351$) over a period of 6 years (2005–2010) at our institute were examined. Case profiles are shown in Table 1. For all groups, clearly accountable cases were collected. PCF and CSF were drawn using sterile syringes after opening the pericardial and cranial cavities, respectively, at autopsy. PCF and CSF samples were immediately centrifuged and stored at −20 °C until use.

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Table 1
Case profiles (n = 351).

Cause of death	Case number	Male/female	Age (median, years)	Survival time (median, h)	Post-mortem interval (median, h)
Blunt injury[a]					
Head	32	27/5	44–96 (65.0)	<0.5–2880 (36.0)	5–35 (20)
Non-head	34	28/6	23–86 (58.5)	<0.5–940 (2.5)	9–37 (18)
Sharp instrument injury[b]	11	8/3	34–75 (47.0)	<0.5–5 (1)	11–38 (14)
Mechanical asphyxia					
Hanging	14	11/3	27–74 (60.5)	<0.5	12–46 (23)
Strangulation	9	2/7	33–87 (61.0)	<0.5	9–32 (23)
Others	12	8/4	32–85 (67.0)	<0.5	16–38 (18.5)
Drowning[c]	29	19/10	34–94 (69.0)	<0.5	10–47 (20)
Fire fatality					
COHb <60%	34	22/12	22–89 (67.5)	<0.5	7–46 (16)
COHb >60%	42	29/13	21–90 (67.0)	<0.5	8–31 (15)
Hyperthermia	9	6/3	39–92 (64.0)	1–168 (4)	11–34 (28)
Hypothermia	18	14/4	26–87 (66.0)	4–24 (4)	8–37 (22.5)
Intoxication					
Methamphetamine	10	9/1	30–60 (38.5)	1–36 (6)	6–42 (18)
Sedative-hypnotic drugs	17	8/9	20–62 (37.0)	<0.5–36 (4)	6–38.0 (28)
Acute cardiac death[d]	54	46/8	33–94 (65.0)	<0.5	5–44 (21)
Pneumonia	17	15/2	41–81 (67.0)	72–840 (120)	9–41 (19)
Cerebrovascular disease[e]	9	6/3	23–77 (65.5)	<0.5–4.0 (0.5)	10–38 (29)
Total cases	351	258/93	20–96 (64.0)	<0.5–2880 (0.5)	5–47 (19)

[a] Traffic accident (n = 10), falls (n = 19), blows (n = 18), and others (n = 19).
[b] Chest (n = 4) and others (n = 7).
[c] Fresh water drowning.
[d] Acute myocardial infarction (n = 30), ischemic heart disease without infarction (n = 21) and hemopericardium (n = 3).
[e] Spontaneous cerebral hemorrhage (n = 5), cerebral infarction (n = 1), and subarachnoid hemorrhage (n = 3). COHb, carboxyhemoglobin.

Clearly blood-contaminated CSF samples were excluded except for cases of head injury and cerebrovascular disease, and blood-contaminated PCF samples were also not used. The case history, pathological and toxicological data were collected from autopsy documents. Cases of hypo- and hyperthermia during drug abuse and bathing, respectively, were excluded [21]. The postmortem interval was defined as the time from estimated time of death to autopsy. Survival time was the period from the onset of a fatal insult to death.

2.2. Analytical procedure

5-HT in CSF and PCF was measured using high performance liquid chromatography [22,23]. Blood % carboxyhemoglobin (COHb) saturation was analyzed on a CO-oximeter system (Ciba Corning 270, New York, or Radiometer OSM 3 and/or ABL 80 FLEX system, Copenhagen) [24,25]. Blood cyanide and alcohol levels were determined by head-space gas chromatography/mass spectrometry [26]. Drug analyses were performed by gas chromatography/mass spectrometry.

2.3. Statistical analysis

Fisher's exact test was used to compare two parameters, including 5-HT levels, gender and age of subjects, survival time and postmortem interval. The Scheffe test was used for multiple comparisons among groups, and comparisons between groups were performed by the non-parametric Mann–Whitney U test. These analyses were performed using Microsoft Excel and Statview (version 5.0; SAS Institute Inc., Cary). A p value of less than 0.05 was considered significant. In Fig. 1a and b, the results of data analysis are shown as box-plots, for which 50% of the data are summarized in the box. The line in each box represents the median, and the lines outside of each box represent the 90% confidence interval. The sensitivity and specificity in distinguishing two groups using cutoff 5-HT values were estimated by receiver-operating characteristics (ROC) analysis [27,28]. The area under the curves was calculated and analyzed by the one-tailed test. The optimal compromise between sensitivity and specificity was determined graphically.

3. Results

3.1. Influence of critical medical care, postmortem interval, age and gender of the subjects

The medians (range) and means ± SD of the 5-HT level (ng/ml) were 23.6 (1.6–125.6) and 26.4 ± 16.4 for CSF, and 5.6 (1.0–125.2) and 9.1 ± 11.8 for PCF, respectively. For all cases, a mild correlation was detected between CSF and PCF 5-HT (r = 0.321, p < 0.001). There was no difference in 5-HT levels of CSF or PCF between subjects with and without critical medical care at hospital. No gender-related difference was detected. The CSF level decreased with subject age (r = 0.497, p < 0.001), but such a finding was not significant for PCF (r = 0.185). A tendency toward a postmortem increase in 5-HT was seen for CSF (r = 0.298, p < 0.001) and PCF (r = 0.253, p < 0.001).

3.2. Relationship to the cause of death

3.2.1. Cerebrospinal fluid

CSF 5-HT level was higher for sedative-hypnotic drug intoxication and hyperthermia (heat stroke), lower for blunt head injury and hypothermia (cold exposure), and intermediate for other causes of death; although acute cardiac deaths showed a lower level, there was no difference compared with other intermediate groups (Fig. 1a). Cerebrovascular disease also showed a tendency toward a lower level (insignificant). In injury cases, survival time dependency was insignificant. There was no significant difference among subgroups of mechanical asphyxiation (hanging, strangulation and others), or between fire fatalities with lower (<60%) and higher (>60%) blood COHb levels. The difference among the manner of death (homicide, suicide or accident) was not significant for injury and drowning cases.