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Post-mortem whole body computed tomography of opioid (heroin and methadone) fatalities: frequent findings and comparison to autopsy

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Abstract
Objective To investigate frequent findings in cases of fatal opioid intoxication in whole-body post-mortem computed tomography (PMCT).
Methods PMCT of 55 cases in which heroin and/or methadone had been found responsible for death were retrospectively evaluated (study group), and were compared with PMCT images of an age- and sex-matched control group. Imaging results were compared with conventional autopsy.
Results The most common findings in the study group were: pulmonary oedema (95 %), aspiration (66 %), distended urinary bladder (42 %), cerebral oedema (49 %), pulmonary emphysema (38 %) and fatty liver disease (36 %). These PMCT findings occurred significantly more often in the study group than in the control group ($p<0.05$). The combination of lung oedema, brain oedema and distended urinary bladder was seen in 26 % of the cases in the study group but never in the control group (0 %). This triad, as indicator of opioid-related deaths, had a specificity of 100 %, as confirmed by autopsy and toxicological analysis.
Conclusions Frequent findings in cases of fatal opioid intoxication were demonstrated. The triad of brain oedema, lung oedema and a distended urinary bladder on PMCT was highly specific for drug-associated cases of death.
Key Points
- *Frequent findings in cases of fatal opioid intoxication were investigated.*
- *Lung oedema, brain oedema and full urinary bladder represent a highly specific constellation.*
- *This combination of findings in post-mortem CT should raise suspicion of intoxication.*

Keywords Forensic pathology · Post-mortem diagnosis · Heroin · Opioid · Computed tomography

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Introduction

Intoxication with opioids such as heroin or methadone represents an important public health problem and continues to be a frequent cause of death [1, 2]. In many Western countries, the consumption of heroin as a main substance has decreased over time [3]. However, the use of methadone for treating opiate dependency has increased in the past years [4].

Cause of death in drug or drug overdose deaths can be suspected on the basis of circumstances: a body found with drug utensils or next to empty bags or containers would raise suspicion; death in drug addict supportive housing would usually make an overdose a likely option. In addition, when

a deceased has a history of many years of drug-related charges, one is more likely to consider an overdose. Particular findings on the body, such as needle marks or scarred subcutaneous veins at external inspection, already indicate a possible overdose. Autopsy findings suggestive of opiate poisoning are oedematous and congested internal organs, particularly in conjunction with a distended bladder, as well as signs of prior addiction such as sequels of endocarditis or liver tissue damage [5].

Heroin intake resulting in blood levels of its main metabolite morphine of over 0.05 mg/l can have a fatal outcome in opioid-naive users, with addicts tolerating 10 times higher blood levels. The parent compound heroin (diacetylmorphine) is often not detectable in blood, due to its short elimination half-life. However, the detection of its first metabolite monoacetylmorphine allows differentiation between heroin and morphine intake. Methadone is often involved in fatal intoxications as well, especially during methadone maintenance treatment. Blood levels of methadone in excess of 0.2 mg/l can have a fatal outcome for the naïve consumer; addicts with a higher tolerance show much higher concentrations after lethal intoxication [6, 7].

Computed tomography (CT) represents the most promising imaging modality in post-mortem investigations, having the potential to reduce autopsy workloads and related biohazard exposures—also when investigating cases that turn out to be related to drug abuse and other intoxications [8–10].

While CT does not prove drug poisoning, documenting absence of fractures and haemorrhages in bodies found or detected in public settings (which can be seen as typical for drug-related deaths), falls into the particular strength of post mortem CT. One has to also consider that the forensic pathologist could be exposed to other diseases the body might contain—including tuberculosis [11] or syphilis [12]. A recent study demonstrated the benefit and value of post-mortem imaging to reduce the risk of infections for forensic pathologists involved in high risk autopsies of patients with HIV or hepatitis [13].

Imaging of the pathological changes associated with illegal drug consumption in the living has been repeatedly investigated [14–19]. However, only a few studies covering single cases of drug abuse and fatal intoxication have been published so far [20]. The high percentage of drug abuse cases among conventional medico-legal autopsies demonstrates the need for evidence-based scientific research in the field of post-mortem imaging.

Therefore, the purpose of our study was to investigate and analyse frequent findings in whole-body post-mortem computed tomography (PMCT) in cases of fatal opioid intoxication, and to compare these findings with an age- and sex-matched control group and conventional autopsy.

Materials and methods

This was a retrospective study. The study was approved by both our institutional review board and the public prosecution department. Due to the post-mortem nature of this study, informed consent was not applicable.

Sample source

Data for this study were collected retrospectively from cases examined during a 2-year period (2010-2012). During this study period, all cases referred to our institution underwent full body PMCT and subsequent medico-legal autopsy. Only a few cases did not undergo medico-legal autopsy and were therefore excluded from the sample source. Toxicology was performed in all drug-associated cases. Conventional autopsy served as the "gold standard". All cases examined in this study were supposed to be dead when they were initially found (determined by forensic investigations). None of the cases was hospitalised. No major medical treatments were performed. No urinary catheter was placed in any of the cases.

Study group

The study group contained 55 deceased adult humans (16 women and 39 men; mean age 37.9 years, range 18–63 years) who had died from fatal opioid intoxication such as heroin and/or methadone (Table 1). Cases with advanced post-mortem decomposition [21] or medically prescribed opioids were not included. Interpretations of blood and urine levels regarding heroin, methadone and its metabolites were performed by forensic toxicologists. Cause of death was issued by forensic pathologists after the circumstances, autopsy findings and toxicology results were reviewed. Of the cases included in this study, 19 deaths (35 %) were attributed to opiate (such as heroin) intoxication and 27 (49 %) to methadone intoxication. In nine of the 55 cases (16 %), both substances were detected during toxicological analysis.

Control group

The control group was matched to the study group with respect to age and sex, and included 55 decedents (16 women, 39 men; mean age 37.9 years, range 20-64 years) who also underwent whole-body PMCT prior to autopsy. Decedents who were tested positive for heroin (and its metabolites), methadone, or any other illegal drug, were excluded from this group (*see* Table 1).

CT imaging and medico-legal autopsy

Whole-body PMCT was performed in all cases prior to autopsy [22], within 48 h after death as determined by forensic

Table 1 Demographics of the study and the control group

Variable	Study group	Control group	*p* value
Total (*n*)	55	55	1
Gender	16 women, 39 men	16 women, 39 men	1
Mean age	37.9 years	37.9 years	0.984
Age range	18–63 years	20–64 years	n.a.
Cause of death (*n*)	Opioid intoxication (e.g. heroin or morphine) (19)	Cardiovascular failure (31) Trauma with loss of blood (9)	n.a
	Methadone intoxication (27)	Metabolic disease (5)	
	Combined intoxication (opioids and methadone) (9)	Respiratory disease (3)	
		Asphyxia (3)	
		Infection (2)	
		Other/unknown (2)	

investigations. A second-generation 128-section CT machine (Somatom Definition Flash; Siemens Healthcare, Forchheim, Germany) with the following parameters was used: tube voltage of 120 kVp, variable mAs values (reference, 400 mAs) using automated attenuation-based tube current modulation (CareDose4D, Siemens), 128×0.6 mm slice collimation, rotation 0.5 s, pitch 0.6. Data were reconstructed with a soft and sharp tissue convolution kernel (B30f and B70f, respectively) with a slice thickness of 1.0 mm and an increment of 0.6 mm. All head CTs were performed with a minimal field of view (FOV); they were viewed in 1-mm slice thickness reconstructions.

All autopsies were performed within 24 h after CT imaging by board-certified forensic pathologists in our institution (seven specialists with 7-30 years of experience), assisted by forensic pathology residents and mortuary technicians using standard forensic autopsy procedures [23, 24].

The final reports, which were used as the "gold standard" for fatal heroin and methadone intoxication, contained all evidence (post-mortem imaging, autopsy and toxicology), as well as the interpretation of manner of death and cause of death.

Image analysis

Whole-body PMCT datasets including axial and multiplanar reformations were evaluated using standard workstation equipment (Somaris/7 syngo 2011A software on a Leonardo workstation, Siemens) and radiology image software (Sectra Workstation IDS7 Version 14.3.5.136; Sectra, Linköping, Sweden). Window settings were manually altered. Evaluations were performed by a radiologist and a forensic pathologist (with 2 and 5 years of experience in post-mortem imaging) by consensus. Readers were blinded to the autopsy results and to previous post-mortem imaging reports.

Radiological criteria

The following findings were evaluated on CT: (1) Cerebral oedema, defined as brain swelling with effacement of cerebral sulci and loss of grey-white matter distinction [25–27]. (2) Pulmonary oedema, defined as interstitial or alveolar fluid accumulation in the lung with ground-glass opacities, parenchymal consolidation and interlobular septal thickening with a subjective graduation in mild, moderate and severe [28]. (3) The lungs were screened for centroacinar or paraseptal emphysematous changes of the distal airspaces [28]. (4) Cardiomegaly, determined by the cardio-thoracic ratio in axial slices defined by the technique of Miller et al. [29, 30] and compared with normal heart value tables by Zeek [31]. (5) The coronary arteries and (6) the cardiac valves were evaluated for the presence of calcifications. (7) The upper and lower airways were assessed for fluid levels or for fluid due to aspiration [5, 32, 33]. (8) The liver was evaluated for steatosis, defined as parenchymal liver attenuation ≤40 Hounsfield units (HU) [34–36]. (9) Maximal transverse diameter of the urinary bladder to distinguish between distended or non-distended urinary bladder, as described by Rohner et al. [8], with a cut-off value of 8.5 cm.

Pathological/macroscopic criteria

Medico-legal autopsy reports were reviewed for the same findings as CT images, based on measurements and descriptions obtained and performed by the forensic pathologists. Brain and lung weight, as well as the urinary bladder volume were also extracted.

Statistical analysis

Continuous variables were expressed as means ± standard deviations or medians and ranges. Categorical variables are provided as frequencies and percentages. The Kolmogorov-Smirnov test was used to determine normality of continuous

variables. Pearson's chi-squared tests were used to evaluate the relationship between findings in PMCT and drug-death cases. Sensitivity and specificity for determining whether particular findings were drug related were assessed for both individual and combined findings.

Mann-Whitney *U* tests were used to compare values of continuous variables with non-normal distribution (bladder volume) while Student's *t*-tests were used to compare values of normally distributed (lung/brain) variables in the study group compared with the control group.

Statistical analyses were performed using commercially available software (release 20.0; IBM SPSS, Chicago, IL, USA). A p value of <0.05 was used to denote statistical significance for all tests.

Results

PMCT findings

The most frequent PMCT findings in the study group were pulmonary oedema (95 %), aspiration (66 %), cardiomegaly (64 %) and a distended urinary bladder (42 %) (Table 2).

A significant relationship between CT findings and drug abuse was found for cerebral oedema ($p<0.05$), pulmonary oedema ($p<0.01$), pulmonary emphysema ($p<0.05$), aspiration ($p<0.05$), fatty liver disease ($p<0.05$) and distended urinary bladder ($p<0.0001$).

Frequencies (n) of cardiomegaly (35 vs 28; $p=0.177$), coronary artery calcification (16 vs 20; $p=0.416$), and cardiac valve calcification (7 vs 9; $p=0.589$) did not differ significantly between the study group and the control group (Table 2).

Almost half of the drug-death subjects (49 %) showed signs of brain oedema on CT. This compared with only 27 % in the control group. Medium or severe pulmonary oedema was detected in the study group in 34 of the 55 cases (62 %), whereas only 20 (36 %) of the control group cases showed this condition ($p<0.05$). The frequency of mild pulmonary oedema was not significantly different in both groups (study group 18 cases; control group 22 cases; $p=0.428$).

Sensitivity and specificity of most individual CT findings regarding the diagnosis of drug abuse was only moderate, except for pulmonary oedema (sensitivity 95 %) and distended urinary bladder (specificity 95 %) (Table 2, Fig. 1).

The combination of cerebral oedema, pulmonary oedema and urinary bladder distension was found in 14 (26 %) in the study group but never in the control group (0 %). The sensitivity and specificity of this triad of imaging findings in the study group was 26 % and 100 %, respectively.

Autopsy findings

Average lung weight at autopsy was 1,730 g (690–3,150 g) in the study group and 1,478 g (420–3,360 g) in the control group ($p<0.05$). Mean heart weight in autopsy was 386 g in the study group and 387 g in the control group ($p=0.957$). Mean weight of the brain at autopsy was 1,414 g in the study group and 1,427 g in the control group ($p=0.678$). The urine volume according to autopsy was significantly higher in the study group (median 150 ml; range 0–1,000 ml) compared with the control group (median 20 ml; range 0–300 ml) ($p<0.001$).

Discussion

This study describes findings in post-mortem CT that are associated with fatal opioid (e.g. heroin and/or methadone) intoxication in the medico-legal investigation of death.

Overall, there were six pathological organ changes that were significantly more frequent in opioid-related deaths than in the control group in this study: cerebral oedema, pulmonary oedema, aspiration of gastric contents into the airways, distended urinary bladder, chronic pulmonary emphysema

Table 2 Frequencies of CT findings, p values and sensitivity/specificity for the diagnosis of fatal drug abuse

Pathological findings in CT	Brain oedema	Pulmonary oedema	Pulmonary emphysema	Aspiration	Cardiomegaly[a]	Coronary artery calcification	Cardiac valve calcification	Fatty liver	Distended bladder >85 mm
n (study group)	27 (49 %)	52 (95 %)	21 (38 %)	36 (66 %)	35 (64 %)	16 (36 %)	7 (13 %)	20 (36 %)	23 (42 %)
n (control group)	15 (27 %)	42 (76 %)	11 (20 %)	25 (46 %)	28 (51 %)	20 (29 %)	9 (16 %)	10 (18 %)	5 (9.1 %)
p value	<0.05 [b]	<0.01 [b]	<0.05 [b]	<0.05 [b]	0.177	0.416	0.589	<0.05 [b]	<0.001 [b]
Sensitivity for drug related death (%)	49	95	38	66	64	29	13	36	42
Specificity for drug related death (%)	73	24	80	55	49	64	84	82	95

p values are given for the comparison of findings in CT between the study group and the control group assessed by Pearson's chi-squared test

[a] Cardiomegaly in autopsy was defined by Zeek et. al. [28]

[b] Significant correlation

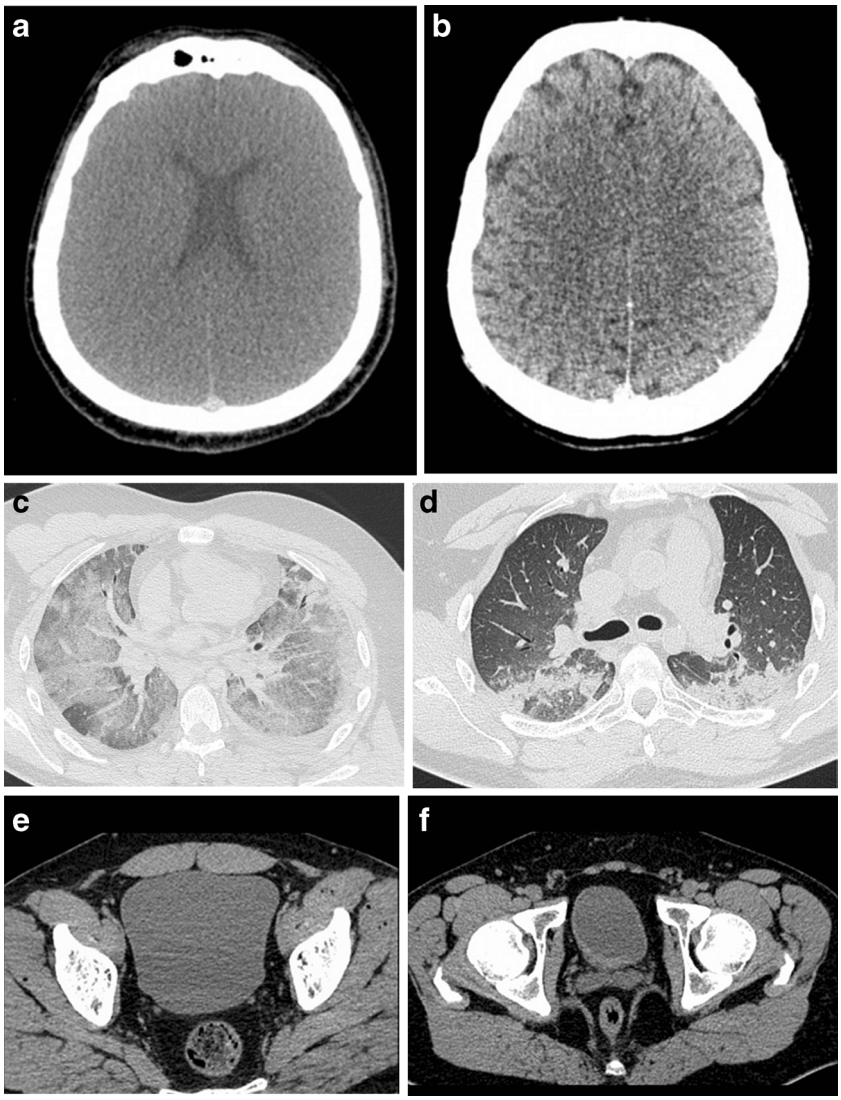

Fig. 1 Characteristic constellation in a high number of drug associated cases: Axial CT images demonstrating brain oedema (**a**), lung oedema (**c**) and distended, full bladder (**e**). Axial images in (**b**), (**d**) and (**f**) show the same structures in the control group without evidence of brain oedema (**b**), only orthostatic inclined post mortem fluid formation in the lung lobes (**d**), and a slightly filled urinary bladder (**f**)

and liver cirrhosis. The first four represent acute changes, while pulmonary emphysema and cirrhosis are pathologies resulting from chronic processes and are more likely a consequence of smoking and alcohol abuse than heroin or methadone abuse. These results match typical autopsy findings in drug abuse as documented in other studies [37].

The higher prevalence of pulmonary oedema in opiate overdose is well known also for overdose survivors [38, 39]. The pathophysiological mechanisms are not known, however. Distension of the urinary bladder in PMCT, which is probably indicative of a relatively long agony as well as opiate-induced sphincter dysfunction, has previously been documented in cases of lethal intoxication [8, 40, 41]. We found a distended bladder in multiple cases of the drug-death individuals but only in a few cases of the control group. Except for the high sensitivity of pulmonary oedema and the high specificity of distended bladder in drug related deaths, individual CT findings showed a low-to-medium sensitivity and specificity in the correct identification of a drug-related death compared with conventional medico-legal autopsy.

The trias of a distended urinary bladder, cerebral oedema and pulmonary oedema on CT appears to be highly specific for cases of fatal opioid intoxication in our collective; however, it is not very sensitive. We frequently found this constellation in the study group, and not at all in the control group. The presence of all three findings on PMCT should, therefore, raise suspicion of lethal intoxication, quite possibly with opioids. Nevertheless it can be assumed that other central depressive drugs might cause similar findings.

The results of this study indicate that even in otherwise morphologically inconclusive deaths, PMCT can help identify and triage cases that might have a particular benefit from immediate (if not overnight) toxicology. This may be particularly advantageous in facilities or situations where PMCT is used as morphological screening tool, where toxicological screening is not performed regularly or when the forensic

scene has not revealed overt evidence for illegal drug consumption. While it may appear obvious in the clinical emergency setting that in clear instances of drug overdose one will expect cerebral and pulmonary oedema, there are undoubtedly cases where circumstantial evidence may be lacking. Then, consideration of opiate overdosing may lead to treatment attempts with naloxone that, depending on their effect, may even be diagnostic.

This study describes typical findings in post-mortem imaging of opioid abusers. The results support the inclusion of forensic radiology in death investigations and suggest that PMCT may be a useful tool for interpreting opioid-related deaths. Although it is not yet a replacement for conventional autopsy, if the approach can be validated in prospective studies, PMCT may help to reduce the number of forensic autopsies [42].

Limitations

A number of limitations of the study deserve comments.

First, the post-mortem interval could have an effect on the investigated findings. This may be due to decomposition or other post-mortem processes [21]. With a maximum time interval of 48 h between death and CT imaging, and a maximum time interval between CT and autopsy, however, the time period was kept as short as practically achievable and was the same in the study group and in the control group. In addition, we cannot demonstrate the extent and the influence of changes to the body associated with a longer or a shorter process of dying as it might apply to our study and control group.

A second limitation relates to the choice of variables to investigate. The selection of findings was based on previously identified findings in opioid abuse cases and on reported changes induced by opioid abuse such as heroin or methadone [14, 37]. Consequently, the variables chosen represent a reasonable starting point but they do not cover the entirety of PMCT data that was captured.

Third, the used control group, which represents cases from our forensic department, does not necessarily reflect the typical type and distribution of cases of other forensic departments. Therefore the calculated sensitivities and specificities could differ when using another control group. In particular, this might apply when post-mortem imaging is performed in non-forensic cases in a pathology department of a hospital, where mainly older deceased patients with a high prevalence of cancer and heart failure are examined. However, the cases in our control group consisted mainly of natural causes of death, probably representing the main work load in forensic departments in the western civilisation.

Fourth, we cannot exclude an influence of resuscitative attempts. However, there were no major medical treatments performed on the deceased, and the number of reanimations by professionals or by laypeople as well as the number of intravenous (i.v.) line placements was similar in both groups (study group: 19 reanimations, 13 i.v. line placements; control group: 24 reanimations, 16 i.v. line placements).

Finally, we cannot exclude the possibility that other coexisting morbidities may be responsible for the findings we associate here with the abuse of the opioids heroin and methadone.

Despite these uncertainties, this study provides preliminary support for the use of PMCT in opioid-related deaths and will hopefully encourage similar research in this area.

In conclusion, our study demonstrates frequent findings of post-mortem whole-body MSCT in cases of fatal opioid intoxication that are in line with clinical experiences in instances of opiate overdose. We found a specific constellation in a high number of cases with a *trias* that contained brain oedema, lung oedema and distended, full bladder.

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