

The Value of Autopsy in Neonates in the 21st Century

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Keywords

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Abstract

Background: Autopsy rates in neonatal intensive care unit (NICU) patients who died are declining worldwide. Postmortem magnetic resonance imaging (MRI) is suggested as adjunct to or substitute for autopsy. **Objective:** The aim of this paper was to determine the additional diagnostic value of autopsy in NICU patients and whether autopsy findings were potentially detectable using postmortem MRI. **Methods:** From 2008 to 2015, 298 infants died during admission to our NICU. Permission for unrestricted, nonforensic autopsy was obtained in 100 (33.6%) of these 298 infants. Retrospectively, autopsy reports and medical records of NICU patients were compared. Additional autopsy findings were graded according to the Goldman system, grading the clinical relevance of additional findings. In addition, the potential detectability of these additional findings on postmortem MRI was assessed. **Results:** Additional findings obtained by autopsy were found in 48% of the cases, divided into major (Goldman I/II, 24%) and minor (Goldman III/IV, 24%) additional findings.

Major additional findings were significantly more often found in patients with a lower gestational age, and minor additional findings in patients with a higher postnatal age at death. Of all patients with additional findings determined by autopsy, 56.3% would most likely not have been detected using postmortem MRI. **Conclusions:** Our results emphasize the still very important role of autopsy in the NICU setting and show that conventional autopsy could probably not be completely substituted by postmortem MRI.

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Introduction

Autopsy of newborn infants can provide vital information to clinicians and families about the cause of death and the accuracy of antemortem clinical diagnosis [1]. Since clinical manifestations of conditions in newborn infants are often nonspecific [2], unintentionally delayed, wrong, or missed diagnoses are still inevitable. In the literature, the latter are defined as diagnostic errors [3]. Patients admitted to an intensive care unit appear to be more prone to diagnostic errors [4–6]. The detection of

diagnostic errors is of great importance for clinicians to evaluate the accuracy of diagnostic methods and to improve medical education. For families, outcomes of autopsy can be a meaningful component of the bereavement process and provides information about the risk of recurrence in future children [7].

Autopsy data are most frequently used as the gold standard compared with clinical diagnoses to identify missed diagnoses. Although there are many potential advantages, declining autopsy rates in deceased neonatal intensive care unit (NICU) patients have been recorded in different countries [8–10]. This can be accounted for by clinicians' fear of confronting families; an inability to adequately explain the value of autopsy; or barriers for families, e.g., conflicts with religious or cultural beliefs, delay of the funeral, and fear of disfigurement [11, 12]. In addition, advances in new methods of diagnosis are being made [13]. Particularly the value of postmortem magnetic resonance imaging (MRI) as adjunct to or substitute for autopsy is increasingly being studied [7, 14]. Postmortem MRI was unable to detect focal or microscopic injury, functional changes, and some focal forms of brain injury, due to the lower resolution and nature of MRI. In 25% of the deceased patients, postmortem MRI findings did not agree with the cause of death determined by autopsy [15].

Although adult and pediatric intensive care unit patients seem to have a higher risk of diagnostic errors [5, 6], limited information is available on diagnostic errors in NICU patients in particular [2, 4]. Even less is known about the clinical relevance of additional findings, missed due to the use of postmortem MRI instead of autopsy. At present, postmortem MRI is not a standard procedure in our unit. The goals of this study were twofold: first, to determine the additional diagnostic value of autopsy in neonates admitted to a NICU, and second, to determine whether autopsy findings were potentially detectable using postmortem MRI.

Methods

Study Design and Population

A retrospective cohort study of autopsy findings and corresponding medical records of NICU patients was conducted at the Wilhelmina Children's Hospital of the University Medical Center Utrecht, The Netherlands. From 2008 to 2015, 4,785 patients were admitted to the NICU of whom 298 patients died. We included all NICU patients who underwent autopsy at the department of pathology of our institute ($n = 117$, 39.3%). Patients who did not die at the NICU ($n = 3$) and patients who underwent limited ($n = 13$) or forensic ($n = 1$) autopsies were excluded, leaving a total of 100

Table 1. Patient characteristics of the study cohort

Sex, <i>n</i>	
Male/female	51/49
Median gestational age at birth (IQR), weeks	37.3 (8.0)
Median birth weight (IQR), g	2,675 (2,011)
Median postnatal age at death (IQR), days	4 (8)
Median Apgar score (IQR)	
1 min	4 (6)
5 min	6 (5)
Type of pregnancy, <i>n</i>	
Singleton	84
Twin	14
Triplet	2
Mechanical ventilation, <i>n</i>	96
Sepsis, <i>n</i>	18
Seizures, <i>n</i>	50
Inotropes, <i>n</i>	65
Congenital malformations diagnosed before death, <i>n</i>	38

eligible patients for this study. Patient characteristics of the study cohort are listed in Table 1.

Parental informed consent for autopsy was obtained in all cases. The Ethical Committee of the University Medical Center, Utrecht, The Netherlands, waived the need for informed consent for this study according to Dutch legislation reporting anonymized data.

Evaluation of Reports

Clinical diagnoses and causes of death were obtained from the electronic medical records and discharge letters of the patients. Autopsy diagnoses were obtained from the completed autopsy reports. Autopsies were performed by an experienced pathologist (P.G.J.N.) specialized in perinatal and pediatric pathology using a standardized procedure according to Khong and Malcomson [16]. The latter includes external examination and open dissection with macroscopic and histological examination of all organs. External examination also included photography of the whole body from a frontal and lateral view, and of external abnormalities if present. Additionally, a whole-body radiograph was performed in most cases to detect skeletal deformities. The weight of each organ was assessed against the means for gestational age, and tissue samples of each organ were collected for histological examination. The brain was removed and fixed in formalin prior to histological examination [16].

The causes of death were classified according to the main causes of newborn deaths: perinatal asphyxia, congenital/genetic disorder, prematurity, infection, or 'other'. Both clinical and autopsy diagnoses were classified in 2 ways: by organ system (respiratory, circulatory, nervous system, gastrointestinal, urinary, or "other") and by type of condition (infection, congenital malformation, or acquired injury). Discrepancies between clinical and autopsy diagnoses were assessed by an experienced neonatologist (F.G.) and a pathologist (P.G.J.N.) and classified using a classification system by Goldman et al. [1]. This system divides additional findings determined by autopsy into major (class I and II) and

minor (class III and IV) additional findings. Major additional findings contain either principal underlying diseases or primary causes of death. Minor additional findings contain related diagnoses, contributing causes, antecedent conditions, or other important conditions. The Goldman criteria are listed in the online supplementary Table (for all online suppl. material, see www.karger.com/doi/10.1159/000493003) [1]. The most relevant additional finding was used to classify each patient.

To determine whether the additional findings were potentially detectable using postmortem MRI, the most relevant finding of each patient was reviewed by a pediatric radiologist experienced in postmortem MRI (M.H.L.) and scored as yes, doubtful, or no.

Statistical Analysis

Statistical analysis was performed to investigate the association between different patient characteristics and the occurrence of missed diagnoses (agreement, minor, or major) using SPSS Statistics 22.0 (SPSS Inc., Chicago, IL, USA). Gestational age, birth weight, sex, Apgar score (after 1 and 5 min), postnatal age at death, and type of pregnancy (singleton/twin/triplet) were analyzed. Continuous variables were analyzed using the Kruskal-Wallis analysis. Significance was set at 0.05. A significant Kruskal-Wallis test was followed by the Bonferroni post hoc method. Binary variables were analyzed using the χ^2 test.

Results

During the time interval of this study, 289 NICU patients died (6.0%), and 117 autopsies were performed, of which 100 autopsies were included. The clinical data of the patients are described in Table 1. The leading cause of death of the patients in the study cohort was perinatal asphyxia (45 patients), followed by congenital/genetic disorders (27 patients), complications of prematurity, such as severe respiratory insufficiency or necrotizing enterocolitis (13 patients), infection (11 patients), and other (4 patients). Additional findings determined by autopsy were obtained in 48 patients, half of which were major findings (24 patients). Of these 24 major findings, 2 were classified as class I errors. In 1 patient, an infection with cytomegalovirus was determined in the kidneys, which had not been diagnosed during admission. In another patient, meconium peritonitis with candida infection based on a perforation of the terminal ileum was found at autopsy. This had not been diagnosed on antemortem abdominal radiology. Class II findings were found in the residual 22/24 patients with major findings. Minor additional findings were obtained in 24 patients, containing 10 cases of class III and 14 cases of class IV findings. The remaining 52 patients had complete agreement between clinical and autopsy findings. The numbers of additional findings (class I–IV) per organ system and per type of condition are provided in

Table 2. Number of additional findings (class I–IV), according to Goldman et al. [1], per organ system

Organ system	Class I	Class II	Class III	Class IV	Total
Respiratory	0	2	2	3	7
Circulatory	0	9	1	7	17
Central nervous	0	5	4	2	11
Gastrointestinal	1	1	0	0	2
Urinary	1	2	0	1	4
Other	0	3	3	1	7

Tables 2 and 3. Additional findings were most frequently found in the circulatory system (35%), followed by the central nervous system (23%). A common class II finding in the circulatory system was hypoplasia of the ductus venosus (6/9 patients). An example of a class II finding in the central nervous system was a bleeding in the cerebellum, brain stem, and spinal cord, which was not diagnosed using cranial ultrasound. Besides additional findings, congenital malformations were noted in 52% of the cases.

Furthermore, 24 out of the 48 patients with additional findings had more than 1 finding, of whom 14 patients had 2 and 10 patients had 3 additional findings in total.

Patient Characteristics and the Occurrence of Additional Findings

The occurrence of major additional findings is significantly more common at a lower gestational age (agreement 36.8 ± 4.8 weeks, minor 34.4 ± 5.4 weeks, major 34.2 ± 4.9 weeks, $p < 0.05$). Furthermore, minor additional findings were seen in infants with a higher postnatal age at death (agreement 7.3 ± 1.7 days, minor 18.4 ± 5.6 , major 10.6 ± 4.3 days, $p < 0.05$). Clinical data, such as birth weight, sex, Apgar score (after 1 and 5 min), and type of pregnancy (singleton/twin/triplet), did not have a significant effect on the occurrence of additional findings.

Potential Detection of Additional Findings Using Postmortem MRI

Of all additional findings, 27/48 (56.3%) would not have been detected using postmortem MRI. Whether or not additional findings determined by autopsy would have been detected using postmortem MRI is summarized in Table 4. Abnormalities that were unlikely to be detectable by MRI include hypoplasia of the ductus venosus, pneumonia, candida and cytomegalovirus infections, atrial septal defect, and papillary muscle infarction.

Table 3. Number of additional findings (class I–IV), according to Goldman et al. [1], per type of condition

Type of condition	Class I	Class II	Class III	Class IV	Total
Infection	1	4	1	3	9
Congenital malformation	0	13	4	8	25
Acquired injury	1	5	5	3	14

Table 4. Potential detection of additional findings (Goldman class I–IV [1]) using postmortem MRI

	Detectable using postmortem MRI?		
	yes	doubtful	no
Goldman class			
I	0	1	1
II	8	0	14
III	5	1	4
IV	5	1	8
Total	18	3	27

Discussion

In this retrospective cohort study, unrestricted, nonforensic autopsy was performed in 33.6% of the infants who died during their admission to our NICU. Reports in other NICUs range from 20.3 to 82% [2, 4]. Additional findings determined by autopsy (class I–IV) were encountered in 48% of the cases, consisting of major (24%) and minor (24%) additional findings, also referred to as diagnostic errors. Major findings included class I (2/24) and class II findings (22/24). Minor findings included class III (10/24) and class IV findings (14/24). Congenital malformations were found to be the most frequent type of condition causing the additional finding. This coincides with the fact that congenital/genetic disorders were the second most common cause of death in our study cohort. The higher postnatal age at death in patients with minor additional findings demonstrates that these findings were apparently difficult to detect clinically.

A systematic review of 6 studies by Custer et al. [4] reporting diagnostic errors in the NICU according to Goldman et al. [1] showed major errors in 19.2% (class I, 3.7%; class II, 15.5%). However, not all included studies reported class III and IV errors. Class III errors were reported in 5 studies and were identified in 434/1,168 cases (37.2%), class IV errors were reported in 3 studies and identified in 97/621 cases (15.6%). To compare the outcome of this study with our study, the 95% confidence intervals (CI)

of our results was calculated according to a method described by Newcombe [17]. Class I findings were found in 2% (95% CI: 0.55, 7), class II findings in 22% (95% CI: 15, 31.1), class III findings in 10% (95% CI: 5.5, 17.4), and class IV findings in 14% (95% CI: 8.5, 22.1). This shows that our findings are in the same range as those of the study by Custer et al. [4]; however, less class III findings were found. This could be explained by the fact that some included studies by Custer et al. [4] reported multiple errors per patient, which results in a slightly higher percentage of error.

The findings of our study are relevant, since even small congenital malformations may lead to the diagnosis of a syndrome and improved genetic diagnostics and pre-pregnancy counselling, even in the era of whole-exome sequencing. Recently, it has been suggested that appropriate postmortem MRI of neonates who died could replace autopsy, but it has been emphasized in both papers that histological information is lost [7, 14]. The fact that in our cohort >55% of the additional findings determined by autopsy would likely not have been detected using postmortem MRI further underscores the still very important role of autopsy in the NICU setting.

There are some limitations of this study that need to be addressed. First, there might be a bias in the selection of cases for autopsy. Of all deceased patients, 33.6% underwent unrestricted, nonforensic autopsy. Parents of infants with uncertain antemortem diagnoses are potentially more likely to grant permission for autopsy, which could cause a selection bias. Therefore, the number of additional findings in the present study might be higher than the number of findings in all deceased NICU patients [18, 19]. However, minor Goldman findings were present even after a more prolonged NICU stay, suggesting that these additional findings could have been found in deceased patients without permission for autopsy as well. Secondly, no postmortem MRI was performed, so only an assessment of potentially missed autopsy findings could be made. The assessment of the potentially missed findings was made, however, by a pediatric radiologist (M.H.L.) with vast experience in postmortem MRI.

Future Directions

Since autopsy rates are declining worldwide, partly due to parents who withhold consent for autopsies, and because postmortem MRI alone cannot provide a histological diagnosis, a new minimally invasive autopsy method is recently being studied [14, 20, 21]. The latter generally involves postmortem MRI with ancillary tests, e.g., external examination of the body, placental histopathological examination, blood sampling and tissue sampling by percutaneous or endoscopic biopsy, which may be supported by image guidance, directed to any abnormal lesion identified with the MRI [20, 22]. A study by the MARIAS collaborative group [14] found that the cause of death or major pathological lesion detected by minimally invasive autopsy, without histological tissue sampling by percutaneous biopsy, was concordant with conventional autopsy in 81.0% of all neonates aged 1 month or younger. This new approach implies minimal cosmetic consequences compared to conventional autopsy and might thus be acceptable in selected cases in which

parents decline a conventional autopsy. Further studies are needed before this technique can be implemented on a larger scale.

In conclusion, our study emphasizes the still very important role of autopsy in infants who died during admission to the NICU and shows that conventional autopsy could not be completely substituted by postmortem MRI at present. Clinicians should be aware of the importance of autopsy and the limits of postmortem MRI when informing parents.

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Disclosure Statement

The authors declare that there are no conflicts of interest to disclose.

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