Invited Review

The Future of Pediatric and Perinatal Post-mortem Imaging

Abstract

The field and applications of post-mortem imaging are exponentially growing. Its potential to identify the cause of death in trauma and ballistic cases is now properly documented, as well as its use in drug mules identification. In pediatric and perinatal practice, large significant series are less available, except for MRI and central nervous system analysis where scientific evidence is now robust. In this review, after a short historical review and analysis of current problems and challenges, we will try to depict the way we see the future of this sub-specialty of post-mortem cross sectional, including in the scope all specific situations: terminations of pregnancy, intrauterine death, sudden unexpected infant death, and identification issues.
Introduction
It is widely acknowledged that the provision of perinatal and paediatric pathology services is a sign of an enlightened society. Yet there has been a general fall in autopsy rates throughout the world over the last decade (1). Perinatal pathology requires highly specialised diagnostic skills, and though based on morphological examination at autopsy, it is probably less confined than general histopathology to morphology in reaching clinicopathological correlations. There is a greater need to integrate the results from other laboratory disciplines with the obstetric and neonatal history. Perinatal and paediatric pathologists may require access to other perinatal and paediatric clinical specialists to plan the autopsy or interpret the findings, and towards this purpose, imaging is taking a growing importance.

Conventional plain film skeletal radiography is the most widely used post-mortem radiology technique, and together with an external and internal clinical examination, photography, placental assessment and supporting laboratory investigations, forms an essential diagnostic adjunct to formal paediatric autopsy examinations.

As antenatal diagnostic ultrasound continues to improve, the yield of routine radiography in apparently anatomically normal fetuses and stillbirths may be lower. Although the cost of performing an individual radiograph may also be relatively low, when used as a form of routine screening investigation this may not be cost-effective, especially in busy units performing several hundred investigations per year (2). As cross-sectional imaging studies have become a routine part of diagnostic clinical practice, these new imaging modalities are slowly being adopted into post-mortem investigations.

Considerations common to the whole field of post-mortem imaging
Forensic medicine adopted the use of radiology shortly after the discovery of X-rays with the investigation of a ballistics case in Canada in 1895 (3). The first use in a homicide investigation followed shortly in England in 1896 (4). Since then radiology has established itself in both clinical and autopsy forensic practice. The first use of computed tomography (CT) in clinical forensic practice was reported in 1977 when its use in the investigation of cranial ballistic injury was reported (5). This was shortly
followed in 1983 with the first reported autopsy use for the investigation of diving related deaths (6). The most significant change came in 1994 when it was reported for the first time from Israel that CT could be used not only as an adjunct, but as an alternative to conventional autopsy (7). Then, in 1996 a group from the UK proposed a similar use of magnetic resonance for perinatal autopsies (8). After this there was a slow but steady drip feed of papers into the literature until this accelerated with the work of the Virtopsy® group after 2003. The technology was changing with the development of enhanced detectors and software. Today post-mortem CT (PMCT) and MR (PMMR) (9) has become almost routine in many countries across the world in adult and pediatric practice, with scanners now incorporated into mortuaries, local and national provision of post-mortem imaging services, agreed international nomenclature, an international Society, and a dedicated international post-mortem imaging journal.

Post-mortem cross sectional imaging allows, without any material destruction, the analysis of the whole corpse. In the case of pediatric examinations, due to the size of the subject volumetric reconstructions are possible after a single helical acquisition with PMCT and / or PMMR, which allow:

- Areas to be virtually dissected without invasive procedures and documented in a more jury-friendly format than conventional autopsy photographs. This is particularly useful for anatomical areas which are difficult to dissect (i.e. facial bones and pelvis) and for cases of severe trauma, where photographs of the victim could be traumatic for members of the public.

- The preservation of digital data obtained, taking into account necessary constraints in terms of confidentiality in digital archiving of medical imaging services systems and national medico-legal/police digital image data storage requirements.

- So called « virtual exhumation » i.e. revisiting / reviewing a historical case

- Multidisciplinary interpretation of images be it local or remote to the place of acquisition. The post-processing possibilities that are now available are vast and
multi-planar reconstructions (MPR), curved MPRs, maximum intensity projection (MIP) or volume rendered (VR) images can be produced rapidly at the request of the forensic pathologists, for a demonstration as tailored as possible.

- A "transferability" of data, which facilitates the remote interpretation of data from multiple forensic practitioners, simultaneously, to obtain expert advices in specific areas, if required.

- Accurate measurements (with a spatial resolution of up to 0.6 mm) and a near-perfect localization of foreign bodies.

In adults, PMCT is extremely powerful in looking for gaseous effusions (10), traumatic bone lesions and identification problems (11). However, it also has several limitations, e.g. its contrast resolution is limited for soft tissues and fluid effusions.

PMMR finds its place in research of neurological lesions (12, 13), as well as the spinal cord, especially in the cervical region (14). Contrast resolution of MRI is valuable in characterizing fluid effusions, especially blood-containing ones (15) and solid organ injuries. The disadvantages are artefacts caused by metallic foreign bodies, theoretical risk of secondary displacement of ferromagnetic foreign bodies, and the reduced availability of machines.

Besides, in pediatric practice PMMR has been used to estimate organ volumes. For large organs (brain, liver, lungs), measurements are satisfactory with a tendency to overestimation. For small organs (spleen, adrenal), the measurements are less accurate, especially for paired organs (16). PMMR can also be used to help the pathologist to drawing targeted abnormal areas which are then correlated with microscopic images.

Considerations specific to perinatal pathology

Foetopathology is a field at the heart of some critical issues in terms of public health. Indeed it is meant to determine the causes of death in the perinatal period (in utero
fetal death), to understand the causes of spontaneous miscarriages, and in the context of termination of pregnancy for medical reasons, to best advise couples for any subsequent pregnancies. It can also be considered as an audit of growing practices of screening and prenatal diagnosis (both in terms of imagery and molecular genetics).

According to the 2012 French Society of Perinatal Pathology (SOFFOET) survey (17), 9732 autopsies are undertaken each year in France of which 2,675 autopsies are performed in the aftermath of a termination of pregnancy (TOP), 3050 following a stillbirth, 3622 for spontaneous miscarriage in the first trimester (FTM) as well as 385 neonatal autopsies. In addition to this 18,600 placental examinations are undertaken. TOP is undertaken for chromosomal abnormalities (12.5 %) and malformative syndromes (15.2%), congenital heart diseases (8.7%), renal abnormalities (8.7%), brain disorders (23.8%) and fetomaternal anomalies (28%), mostly infections.

This survey highlights practical difficulties. Recent changes in the law require practitioners increasingly growing obligations in terms of time and quality of the return of the body. The average delay for giving the full autopsy report is more than 1 month in 30% of cases and more than 2 months in 60 % of cases. In addition, the age of practitioners is such that 40% of them will retire within 10 years, 80% of them have no successor, and that 70% of centres have no young practitioner in training.

This situation worldwide has led to the introduction of "less invasive" autopsy protocols combining external examination, modern cross-sectional imaging techniques, organ sampling and / or targeted biopsies. The key idea is definitely not to create competition between these different procedures, but to optimize and tailor their use depending on what each can conveniently bring.

In Perinatology, PMMR has already achieved a strong evidence base in the literature. In a recent article in the Lancet, Thayyil et al. (18) analysed 400 cases, of which 277 (69%) were fetuses and 123 (31%) were children. Cause of death or major pathological lesion detected by minimally invasive autopsy was concordant with conventional autopsy in 357. The dedicated radiologist or pathologist review of the minimally invasive autopsy showed that in 165 (41%) cases a full autopsy might not have been needed; in these
cases, concordance between autopsy and minimally invasive autopsy was 99.4%. They conclude that minimally invasive autopsy has accuracy similar to that of conventional autopsy for detection of cause of death or major pathological abnormality after death in fetuses, newborns, and infants, but was less accurate in older children. They propose that, if undertaken jointly by pathologists and radiologists, minimally invasive autopsy could be an acceptable alternative to conventional autopsy in selected cases (19).

Another recent article (20) demonstrated the feasibility of visualizing fetal cardiac structures on 3-tesla post-mortem MRI. With sufficient resolution, normal cardiac structures could be discriminated and measured as early as 14 weeks of gestation. Other authors (21) conclude that only by using a 9.4T MRI fetal cardiac structures could be visualized irrespective of GA, but herein they showed that the main cardiac structures can be identified on 3T MRI in fetuses beyond 14 weeks. Moreover, this technique allows examination of the fetal heart in situ, where connections with other structures are maintained and can easily be assessed (22).

To date there is no published data comparing perinatal PMCT to conventional post-mortem X-Ray. However the unpublished experience of the Marseille authors of this review article concerning 40 cases, identifies that PMCT proves superior to post-mortem X-ray examination except for the analysis of limb extremities, i.e. the fingers and toes.

In many perinatal autopsies the histological examination identifies normal developmental structures showing no abnormality. In cases of termination for fetal abnormality, histological abnormalities may only be expected in a small number of organs, usually suspected in advance on prenatal imaging. The only published experience of post-mortem percutaneous organ biopsy in children used ultrasound guidance to obtain biopsies of organs in 19 children (23). Again, in the case of the Marseille authors of this review article they have developed a dedicated protocol including:

- post-mortem ultrasound: the high frequency linear probes used in pediatrics are quite adequate for the post-mortem study. The technique has no specificity but the interpretation of needs
learning and pathological correlations. The group has thus begun to describe aspects of normal organs. For example, the brain is less well differentiated, and in normal kidneys, hypoechoic pyramids are always circled by a thin very hyperechoic rim. For referred malformations suspected in utero, this technique seems very promising.

- PMCT and PMCT angiography (PMCTA): the group has now published the technique (24) having completed more than 20 cases of post-mortem injection by the unthrombosed umbilical vein (figure 1). At this stage of the project the method proves feasible, reliable and reproducible, with respect to certain technical precautions during catheterization and/or injection. Cases of prenatally suspected congenital heart disease have already been confirmed (which is the major drawback of all other post-mortem imaging techniques), with the performance offered by the spatial resolution of the CT-scanner.

**Considerations specific to pediatric pathology - SUDI**

Sudden unexpected death in infancy (SUDI) is the commonest presentation of post-neonatal infant death. “SUDI” is a term used to refer to all cases of sudden and unexpected death in infancy (25). In a proportion of SUDI cases, a post-mortem examination will reveal the cause of death (26). However a large number of SUDI cases still remain unexplained. The search for and identification of the cause of death are highly desirable, especially in order to exclude non-accidental trauma that may require provision of preventive care services (27).

Recommendations exist in France (28) and in other countries (29, 30) to provide guidelines for investigation of infant deaths. In France these investigations are conducted in SUDI referral centres. Radiographic skeletal surveys and cross-sectional brain imaging form part of the recommended imaging investigations. A systematic conventional autopsy, with macroscopic and histological investigation, is also advocated and systematically offered to parents.
However there has been little focus on post-mortem imaging specifically for paediatric populations, and only one study (31) has focused on PMCT for detecting causes of sudden death in infants and children (15 patients, and an autopsy was conducted on 2).

Usual pediatric practice utilizes the so-called "babygram", that is to say a single whole-body X-Ray AP view. However, it is crucial in the context of suspected abuse to implement an X-Ray protocol at least as extensive as that achieved in the living, namely: skull AP and lateral views, full spine (by segments) AP and lateral views, 4 limbs (by segments) AP views, chest and abdomen AP views (a so-called «skeletal survey»). Metaphyses must be thoroughly analysed and additional focused views should be made for any clinical or radiological doubt (32).

Nevertheless, X-Rays, even targeted, are about twice less sensitive than CT to detect rib fractures, as suggested by a small preliminary study (33). But conventional radiography is more sensitive for the diagnosis of fractures of the extremities (phalanges i.e. lesions with high specificity of abuse) than CT reconstructions (34).

A single helical acquisition can be performed, from vertex to toes. No contrast is injected. The acquisition is in supine position with the arms along the body, in the closest possible to the anatomical reference position. Acquisition parameters vary according to body size: 80 to 120 kV voltage, intensity from 60 to 300 mAs, field of view 240-400 mm, pitch of 0.4 to 0.6, acquisition thickness 0.6 mm. Reconstructions are performed with different filters to allow analysis of brain, bone structures, lung and solid organs.

There is emerging evidence that PMMR may also be useful. The body can be left in its plastic cover, supine, the closer to the anatomical reference position. Despite this acquisition plans are often oblique to obtain standard anatomical planes. For optimal image quality, it is important to use an antenna adapted to the size of the body. On a 1.5 Tesla clinical MR, a chest antenna is usually adequate. Minimal protocol requires T2-weighted sequences in three planes centred on the head and whole body, and T1-weighted sequences in the sagittal plane of the head and coronal for the rest of the body. Balanced steady-state free precession imaging sequences can be contributory because fast, allowing large fields of exploration and forming a composite ponderation tracking. 3D Sequences are of great help, as well as T2 STIR sequences for bone disease and soft
tissue swelling. T2 * sequences may be performed in search of bleeding, but their post-mortem changes are poorly described. Post-mortem MR angiography is described only in adults. The total duration of a post-mortem MRI can be about 45 minutes, which is problematic in the absence of dedicated device.

In a very recent study from Rennes (35), forty-seven cases of SUDI investigated with radiographic skeletal survey, whole-body PMCT and autopsy were enrolled. There were 31 boys and 16 girls. Of these, 44 children (93.6 %) were younger than 2 years. The cause of death was found at autopsy in 18 cases (38.3 %), with 4 confirmed as child abuse, 12 as infectious diseases, 1 as metabolic disease and 1 as bowel volvulus. PMCT results were in accordance with autopsy in all but three of these 18 cases. Death remains unexplained in 29 cases (61.7 %) and was correlated with no abnormal findings on PMCT in 27 cases. Major discrepancies between PMCT and autopsy findings concerned pulmonary analysis. The authors consistently conclude that whole-body PMCT may detect relevant findings that can help to explain SUDI and is essential for detecting non-accidental injuries. They found broad concordance between autopsy and PMCT, except in a few cases of pneumonia. It is a non-invasive technique acceptable to relatives.

**PMCT and Developing Human Identification**

Establishing the biological and personal identity of human remains is of fundamental importance in a forensic investigation (36). Legally, religiously, and culturally it is **recognized** that all human beings have the right to remain anonymous, even in death (37). Preliminary determination of age-at-death, racial affiliation or ancestry, living stature and biological sex is the first step towards arriving at a positive identification. These four basic parameters are then supplemented by more *individuating* traits that include: evidence of dental or surgical intervention, body modifications, evidence of trauma, fingerprints and DNA. These features help to narrow the wide boundaries established by the basic biological criteria to arrive at a physical identity that will, with reasonable certainty, confirm the provenance of the human remains. When dealing with juvenile remains age-at-death is the only biological demographic that can be reliably determined and is therefore the most vital criteria for identification purposes (38). Sex,
stature, and race/ethnicity cannot be estimated with any degree of reliability from the skeleton until post puberty.

The specific use of imaging methods for identifying human remains is widely recognised and well documented (39). The comparison of ante and post-mortem radiographs is one of the most accurate techniques to establish identity. Culbert and Law (1927) made the first recorded identification of human remains in 1927, by comparing ante-mortem and post-mortem radiographs of the frontal sinus (40). In the UK, clinical images are normally retained for at least 8 years (or in pediatrics, until the patient turns 25 years old) and for 3 years after death. However, with the advent of electronic image storage (Picture Archiving and Communication Systems, PACS) this is becoming longer. In general, they are fairly accessible for investigative purposes and are therefore an excellent source of data. Forensic radiology is particularly important for the investigation process and identification of victims following a mass fatality incident such as a road traffic accident, terrorist attack or natural disaster. In these situations, the remains are often skeletonised, mutilated, decomposed, fragmented or otherwise disfigured. Subsequently, identification by means of the skeleton and the highly resilient dentition assumes a greater importance, and the true benefit of medical imaging is realised.

The current standard approach, as used in previous incidents such as the terrorist bombings in London in July 2005, involves moving fatalities through up to three separate radiology stations: fluoroscopy, to screen remains for potential contaminants or evidence prior to autopsy; standard radiography, principally used for anthropological and pathological examination; and dental radiography. This process requires the procurement and installment of three different imaging modalities in a temporary mortuary environment, sufficient staff to operate them and subsequently a number of health and safety implications.

Cross sectional imaging systems such as PMCT have the potential to replace this three stage protocol with one single imaging modality. Although, despite CT establishing itself as the ‘workhorse’ of clinical medical imaging, it is only recently that PMCT's vast potential for forensic identification has truly been appreciated.
Currently there is no agreed protocol to create a biological profile from PMCT examination of juveniles or adults. The literature presents a number of studies using single osteological or odontological assessments to assist with biological profiling (41-44), but a system compiling all of these assessments into a single protocol had yet to be published or presented. In addition, the majority of these studies have been conducted using an adult cohort, with very few extending to the juvenile age range. This is an issue, as generally, the techniques used to identify juvenile remains vary significantly from those used for adults. For example, juvenile techniques investigate the appearance and fusion of ossification sites, the diaphyseal length of the long bones, and dental development, which are not always applicable to adult remains. However, a recent review by Brough et al. has demonstrated that all the measurements required for current juvenile age estimation methods are reproducible using PMCT and all morphological assessment markers are also discernible (45). The authors illustrated that curved MPR’s could be used to replicate dental orthopantomographs (OPT’s) (Figure 2), MPR’s could be used to produce good quality radiographs in the x-, y-, and z-planes (Figure 3), and three-dimensional volume rendered images could be used to view ossification centers, bones and teeth in detail for a comprehensive full-body assessment (Figure 4). Furthermore, studies of the maximum clavicle length (46) and dental development (47), by the same Leicester based research group, found no significant difference between PMCT measurements compared with dry bone and dental OPT’s, respectively. Interclass correlation analysis for both investigations also illustrated a near perfect agreement between different observers, with varying levels of experience. These results were supported by Lottering et al, who investigated the accuracy of measurements of the juvenile cranium using PMCT. The authors used an ‘off-set plane’ technique of measuring, which involves using defined anatomical reference planes as fixed points from which all other measurements are recorded (48).

It can be concluded from these investigations that PMCT measurements are accurate, produce reliable age estimations and are reproducible with little extra training required. These studies also highlight the necessity to develop more guidelines regarding the correct procedures for the collection, processing and presentation of PMCT acquired anthropological measurements - so that investigations on this subject can be more easily compared to facilitate the progression of research in this area.
this in mind, the Leicester research group have subsequently developed a minimal data set PMCT recording form using an easily reproducible system, for the measurement and assessment of the entire immature human skeleton for biological profiling purposes. This minimum data-set form has been designed to be used by suitably trained assessors, either at the site of image capture or remotely. The results of this investigation are yet to be published, but could potentially provide a template for a worldwide, minimum standard of PMCT anthropological reporting (Figure 4).

CONCLUSION

A new society was recently formed (ISFRI, the International Society of Forensic Radiology and Imaging) that acts as a base for the further international implementation of guidelines and standards in forensic imaging. Future directions in forensic radiology will clearly adopt even more sophisticated and interdisciplinary approaches and will intensify the need for high-quality standards. The field of pediatric and perinatal death pathology will for sure be part of this ongoing (r)evolution, thanks to the involvement of all the specialists concerned: neonatologists, pediatricians, pathologists, geneticists, obstetricians, anthropologists and radiologists
REFERENCES


CAPTIONS FOR ILLUSTRATIONS

Figure 1: 3D-MIP reconstructions in of a perinatal whole-body post-mortem CT angiography a 37 WG male foetus

Figure 2: Digital dental radiography Vs PMCT. a) Orthopantomograph (OPT) image b) Series of PMCT curved MPRs (18 years)

Figure 3: Long bone maximum diaphyseal length measurements; MPRs and 3D reconstructions. a, b) MPR long bone measurements. Parallel planes should be drawn at the most extreme point of the bone; the distance between these points gives the maximum diaphyseal length of the bone. C) 3D reconstruction measurement. End planes cannot be used, as only one length measurement can be made at a time.

Figure 4: Presence of ossification nuclei; PMCT reconstructions of the lower limb. A) PMCT reconstruction; ossification sites can be seen clearly. B) X-ray image; ossification centres are visible, but not as clear as on PMCT. C-F) Lateral, anterior and posterior 3D views; ossification centres are well defined and clearly
Figures

Figure 1