Title:

Ligamentum arteriosum calcification on paediatric post-mortem computed tomography

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Ligamentum Arteriosum Calcification on Paediatric Post-Mortem Computed Tomography

Background:

Ligamentum arteriosum calcification is a normal finding in some children, although the frequency and significance at post-mortem imaging is unknown.

Objectives:

To estimate the frequency of ligamentum arteriosum calcification in children at post-mortem imaging, and association with patient demographics.

Methods:

A single centre retrospective review of paediatric post-mortem computed tomography (CT) and chest radiographic imaging was performed over a 6 year period (January 2012 to December 2018). The presence of calcification on imaging was assessed by 2 independent reviewers. Descriptive statistical analysis of ligamentum arteriosum calcification frequency and association with age and gender were calculated.

Results:

220 children underwent whole body post-mortem CT and 182 underwent radiographic imaging. The frequency was higher on post-mortem CT than plain radiographs (67/220, 30.5% vs 3/182, 1.5%), and highest in children within cohorts aged 1-7 years old (53.6 - 66.7%), with gradual reduction in frequency after this, and none in children aged above 12 years old. There was no gender predilection.

Conclusion:

In the post-mortem setting, ligamentum arteriosum calcification is a common finding in children < 8 years of age. It can be better identified on post-mortem CT than chest radiographs. Radiologists new to reporting post-mortem paediatric CT studies should recognise this as a common normal finding to avoid unnecessary further unnecessary investigations at autopsy.

Keywords: Post-mortem, Computed Tomorgraphy, Children, Paediatric, Imaging

Declarations:

Funding information:

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Conflicts of interest:

None of the authors have conflicts to declare

Ethics approval:

Ethical approval was granted for this single centre, prospective cohort study (IRAS ID:13195; REC reference: 13/LO/1494 and CE2015/81).

Consent to participate and publication:

Where the paediatric post-mortem CT was conducted for the investigation of a non-suspicious death, then all parents/guardians signed a consent form for use of imaging for research/ audit/ educational purposes.

Availability of data and material:

All relevant clinical information is already provided within the manuscript. Additional information is available from the corresponding author upon reasonable request.

Code availability:

Not applicable

Authors' contributions:

ND and SCS performed the data collection, analysis and primary write up of the manuscript. ND, AA and MC performed the literature review, JCH, HB and LP provided histological expertise, and OJA conceived the idea of the research project. All authors have had an input in reviewing and editing the final draft of this manuscript.

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Introduction

The ductus arteriosus plays an important role in the foetal circulation, connecting the pulmonary artery to the aorta and allowing blood to flow from right to the left, bypassing the lungs *in utero*. After birth, the ductus arteriosus involutes and occasionally calcifies, forming the ligamentum arteriosum [1, 2]. On computed tomography imaging (CT), ligamentum arteriosum calcification has been identified in adults, and described as punctate or curvilinear in morphology, coursing from the proximal descending aorta to the superior aspect of the pulmonary artery [1].

In adults, ligamentum arteriosum calcification is considered a benign process, and differentiated from calcified anatomic structures in the mediastinum (e.g. calcified pulmonary arteries in patients with longstanding pulmonary hypertension, coarctation of the aorta, ductus arteriosus aneurysm or pericardium), and other pathologies (e.g. granulomatous infections, neoplasms - neuroblastoma, teratoma, treated lymphoma) by the precise anatomical location, lack of associated soft tissue mass and a lack of other evidence of mediastinal or congenital heart disease (including indirect signs of patent ductus arteriosus) [1, 3].

Whilst ligamentum arteriosum calcification is a recognised phenomenon amongst experienced paediatric radiologists, there are only 6 reports in the medical literature to date with dissimilar frequency findings [3 - 8]. Four of these studies included a paediatric cohort with frequencies ranging between 13.2% to 60.9% on CT and 0.1% to 3.6% on XR [3 – 6]. Of these paediatric reports, 2 were conducted 2 decades ago and only 1 study utilised a post-mortem cohort where motion artefact is non-existent and therefore frequency is likely to be more comparable with histopathologic studies [3 – 5]. Given the growing demand for paediatric imaging nationwide, and lack of specialist services for reporting, the onus on general radiologists to report routine paediatric imaging (and in particular post-mortem CT imaging) may increase [9]. Therefore, the ability to recognise normal anatomical variation from pathological processes will be vital in order to avoid unnecessary additional tests and inappropriate diagnoses.

Our objective in this study was to provide the reporting radiologist a better understanding of paediatric ligamentum arteriosum calcification frequency and appearances in order to aid post-mortem image interpretation.

Materials & Methods

This study was performed as part of an ethically approved larger study investigating minimally invasive autopsy techniques and novel methods of post mortem imaging (CE13/LO/1494 and CE2015/81).

We conducted a retrospective review of all whole body paediatric post-mortem computed tomography (CT) of patients <16 years old at our institution over a 6 year period (1 Jan 2012 - 1 Dec 2018). All study results, including demographic details for each patient (e.g. gender, age at death, mode of death/delivery, days from death to post-mortem CT and/or radiography) were recorded on a predefined study template.

Imaging Protocols

Post-mortem CT

All post-mortem CTs were performed as part of a routine paediatric autopsy for coronial or forensic purposes according to standard practice and Royal College of Pathologist guidelines [10]. (10) Whole-body unenhanced nonventilated post-mortem CT was performed on either a 64-multidetector CT system before December 2014 (Somatom Definition, Siemens Healthcare) or a 384-multidetector CT dual-source system after January 2015 (Somatom Force, Siemens Healthcare) [12]. Volumetric whole-body post-mortem CT was performed from the vertex to the toes at 120 kV with a variable tube current–exposure time product, a pitch of 1, and 0.625-mm collimation. Images were reconstructed with a soft-tissue and bone algorithm (kernel) to provide 5- and 1.25-mm slices and were viewed on standard soft-tissue, lung, and bone window settings on our local institutional PACS software (Centricity, GE Healthcare) [12]. Multiplanar reconstructions and 3D volume-rendering techniques were available for each radiologist to perform on individual workstations for further image examination if required.

Post-mortem Radiography

Where a post-mortem skeletal survey was performed prior to the post-mortem CT this was acquired on a Ysio digital radiography imaging system with wireless detector (Siemens, Erlangen, Germany) at 3–6 mAs and at 64 kVp, and done as per Royal College of Radiologists guidelines [13].

Data Collection

Post-mortem CT imaging and any contemporaneous post-mortem chest radiography (XR) was reviewed by a radiology trainee (ND: 4 years general radiology experience, 2 years of post-mortem imaging experience) solely for the purposes of identification of ligamentum arteriosum calcification. This trainee was not involved in formal clinical post-mortem CT or XR reporting, and therefore had no knowledge of the final outcome of the patient or clinical history.

Where calcification was present, this was labelled as either 'coarse' or 'subtle/punctate' in morphology (see Figures 1 - 3). Multiplanar reconstruction techniques were used when reviewing the post-mortem CT images, using both mediastinal/soft tissue and bone window settings to accurately determine location and presence of ligamentum arteriosum calcification. Digital XR images were reviewed when available in patients who had underwent post-mortem CT.

Prior to the full imaging review by the radiology trainee, in order to ensure repeatability and correct classification of ligamentum arteriosum calcification, a second reader (SS: 10 years radiology experience; 4 years of paediatric post-mortem imaging experience) was randomly allocated a subset of 30 examinations from the data cohort. Where discrepancy between readers was found, resolution was determined by consensus review.

Data Analysis

Descriptive statistics (using percentages) were used to calculate the ligamentum arteriosum calcification frequency, and estimated 95% confidence intervals.

Results

Study Cohort

Over the 6 year study period, 222 post-mortem computed tomography (CT) examinations were included and 182 of these patients (82.7%) additionally had post-mortem skeletal survey radiographs (XR) for review. Two (2/222; 0.9%) were excluded due to duplicate entries on the radiology information system (RIS). The final study sample size therefore included 220 patients, of which 113 (51.4%) were male. The age range of the cohort spanned from 0 days (fetuses) to 16 years old. The average age of the patients was 828 days (2.3 years) with 116/220 (52.7%) of the cohort aged <1 year.

Eleven patients (4.5%) succumbed within 24 hours of delivery (i.e. age = 0 days), ranging from 25 to 40 weeks gestational age (average 34.1 weeks). The mode of demise for these children included complications of prematurity (2/11), early neonate death of unknown cause within 24 hours of delivery (6/11), strangulation (1/11) and unascertained due to lack of documentation (2/11).

Post-mortem CT was acquired on average 5 days from recorded date of death, ranging from approximately 0 to 28 days. XRs were taken on average 4 days after death, ranging from approximately 0 to 21 days.

Frequency of ligamentum arteriosum calcification

There was 100% agreement between the two readers regarding presence of ligamentum arteriosum calcification on post-mortem radiography, with 93.3% agreement (28/30) regarding ligamentum arteriosum calcification on post-mortem CT, reaching 100% agreement after consensus review. Where both readers agreed on presence of calcification, there was 100% agreement on the type of coarse or punctate calcification identified.

Ligamentum arteriosum calcification frequency on post-mortem CT was 67/2020 (30.5%) compared to 3/182 (1.6%) on radiography. Where this was present on post-mortem CT, it was coarse in 36/67 (53.7%) of patients and punctate and subtle in 31/67 (46.2%). There were no patients in which ligamentum arteriosum calcification was seen on radiography but not on post-mortem CT. On post-mortem CT, approximately half of all patients with ligamentum arteriosum calcification were male (33/67 (49.3%)) without any gender predilection identified. At post mortem radiography, all 3 patients with ligamentum arteriosum calcification were male, aged < 1 year old.

The average age of patients with ligamentum arteriosum calcification was 664 days (2 years), with a range of 41 days to 11 years old. Ligamentum arteriosum calcification was not seen in foetal or neonatal cohorts. The earliest observation of ligamentum arteriosum calcification was seen in a 41 day old infant.

The highest ligamentum arteriosum calcification frequency was found in the 6 to 7 year old age group, at 66.7% (95% CI: 12.5% – 98.2%) (2/3) without any ligamentum arteriosum calcification seen in patients aged >12 years old (See Figure 4, Table 1). Examples of ligamentum arteriosum calcification on post-mortem CT and post-mortem radiography are showed in Figures 1 – 3 ,and histopathological appearances in Figure 5.

Discussion

Our study demonstrated an overall childhood ligamentum arteriosum calcification frequency of 30.5% (95% CI: 24.5% – 37.1%) on post-mortem computed tomography (CT), much higher than on equivalent post-mortem radiography (1.6%). The highest frequency was in 6 to 7 year olds followed by a gradual decline with age and no ligamentum arteriosum calcification in children aged > 12 years old. The clinical implications are that radiologists who report post-mortem CT in children should be particularly aware of ligamentum arteriosum calcification in the infant population, even if this is not initially identified on post-mortem radiography. Where ligamentum arteriosum calcification is seen in a child aged >12 year old then an alternative explanation should be sought, particularly if there are additional pathological findings in the chest.

The ligamentum arteriosum calcification frequency derived from our study on post-mortem CTs are similar to those of Hong et al. [6] quoting a frequency of 37.8% on non-contrast CT in live children and 3.6% on paediatric radiography. Differences to other studies may be due in part to differences in CT equipment and sensitivity of the readers. In our study, we employed a CT slice thickness of 0.7mm, whereas thicker slices may have missed subtle calcifications leading to lower rates reported e.g. 13.2% on CT in live children using 5 – 10 mm slices [3]. Hong et al. [6] utilised 3 – 5mm slices, whereas Proisy et al. [5] used 2mm slices. Our thin slice post-mortem CT study is arguably the more sensitive assessment of ligamentum arteriosum literature compared to the available papers on ligamentum arteriosum frequency in a paediatric cohort, which have been summarised in Table 2 for ease of reference. This therefore means we were able to detect some fine punctate calcification that would not have been detected utilising thicker collimation sections. However it is unclear whether there were specific population differences in studies with a higher frequency [5].

There is only 1 other study apart from ours that has studied a post-mortem paediatric cohort for ligamentum arteriosum calcification frequency [5]. As patients are deceased, the quality of imaging is optimal as the subjects scanned are immobile and there are no radiation safety concerns regarding length of examination exposure. The excellent quality of images would contribute towards better detection of subtle ligamentum arteriosum calcification on CT compared to other studies that utilised live children [4, 6].

On paediatric radiography, Beluffi et al. [3] reported a lower frequency of 0.1%, which is most likely attributable to the use of film-screen radiography as opposed to the more modern digital screen radiography; which was employed by our study and Hong et al [6]. Improvement in radiographic imaging techniques could

therefore have also contributed towards a better detection rate of calcific foci (including ligamentum arteriosum calcification) in our work, although the frequency on plain radiographs remains low.

We have observed a higher frequency of ligamentum arteriosum calcification in patients under 8 years old compared to those > 12 years old. Hong et al. [6] found the highest ligamentum arteriosum calcification frequency in the 6 to 10 year olds age group 48.7% (19/39) and Beluffi et al. [3] found a marked increase in frequency of ligamentum arteriosum calcification within females aged 4 to 6 year old. Whilst it is difficult to explain these slight differences in age of peak frequency, there was a downward trend observed in most studies after the age of 8 years old, which also appears to be supported by studies in adult populations where the ligamentum arteriosum calcification frequency remains low [7, 8]. A comparison of ligamentum arteriosum calcification frequency between paediatric studies [3 – 6] and available adult studies [7, 8] reveals a lower frequency of 11.2% (26/232) and 10.5% (6/57). However Wimpfheimer et al. [7] reported a higher frequency of 48% (193/402). Whilst Hong et al. [6] reported a decreasing ligamentum arteriosum calcification frequency with increasing age (particularly >30 years), Wimpfheimer et al. [7] described a higher frequency of ligamentum arteriosum calcification in adults with atherosclerotic calcification compared to those without (65% vs 21%). However the association between ligamentum arteriosum calcification and atherosclerosis is disputed by Hong et al [6]. We observed the highest frequency of ligamentum arteriosum calcification in the 6 to 7 year old age cohort (66.7%) (95% CI: 12.5% – 98.2%) in our study, however due to the heterogeneity of our patient cohort with a significantly larger proportion of patients in younger age groups (e.g. 0 to 1 year olds, n=118) and having only 3 patients aged 6 to 7 years old, a meaningful comparison is difficult to ascertain between age groups. Nevertheless, correlating our findings with other aforementioned studies, it is likely that ligamentum arteriosum calcification is less prevalent in adolescence and early adulthood.

There was no gender predilection in our study; in keeping with the majority of other studies, although three reported a slight female predominance [2, 4, 7].

We had access to histopathological correlation for 2 patients in our study that were confirmed at autopsy. Our histopathological findings of intimal mural dystrophic calcification correlates with Hong et al.'s [5] speculation of calcification deposition in the myxoid degeneration of the ligamentum arteriosum wall and with Dalith et al. [14], Dohr et al. [15], Child and MacKenzie's [16] observations of calcification within the wall of the ductus arteriosus. Kaushik et al. [17] however alternatively proposed that the 'ductus bump' well-known to the paediatric radiologist as a 'normal mass' is in fact a benign self-limiting ductus arteriosus aneurysm and that

ligamentum arteriosum calcification is caused by thrombus regression within the aneurysm; which was also supported by Slovis and Berdon [18].

There were several limitations to this study, although we are encouraged that our results are similar to a previous study that reviewed live paediatric and adult patients [5]. There was a skewed age distribution in our study cohort with a significantly larger proportion of patients aged 1 year and below likely because post-mortem CT is predominantly performed in our institution for underlying suspicion of non-accidental injury, which is typically in a younger age group. Additionally, there are many different causes of death for the patients included in our study, adding to the heterogeneity of our cohort. None of the causes for death in our study were thought to be related or caused by the presence of ligamentum arteriosum calcification and we therefore consider ligamentum arteriosum calcification to be a common normal finding.

Conclusion

In the post-mortem setting, ligamentum arteriosum calcification is a common finding in children < 8 years of age. It can be better identified on post-mortem computed tomography (CT) than radiographs, and is more frequently coarse and easily identified when present. Radiologists new to reporting post-mortem paediatric CT studies should recognise this as common normal finding to avoid unnecessary further unnecessary investigations at autopsy.

Figure Captions:

Fig. 1: The variety of calcification patterns seen in ligamentum arteriosus calcification on non-contrast post-mortem computed tomography (CT) within different patients in this study cohort. (a) Axial and (b) sagittal post-mortem CT image in a 7 year old male patient reviewed on bone windows demonstrating coarse curvilinear/linear calcification present from the proximal descending aorta to the superior aspect of the pulmonary artery (white arrow). (c) Axial post-mortem CT image, reviewed on bone windows in a 2 month old male child, demonstrating very subtle punctate calcification in the region of the proximal descending aorta (white arrow).

Fig. 2: Presence of ligamentum arteriosus calcification in a 4 month old male child on both (a) frontal post-mortem chest radiography (calcification superimposed at the costovertebral junction) and (b) coronal section post-mortem computed tomography (white arrows).

Fig. 3: Imaging performed in a 1.4 month old X child with (a) frontal post-mortem chest radiography and (b) coronal section post-mortem computed tomography demonstrating the more common situation where there is calcification seen on the CT study (white arrows), but not the radiography.

Fig. 4: Bar chart demonstrating the frequency of ligamentum arteriosus calcification (%) against age, illustrating a peak frequency at approximately 6 to 7 years of age, followed by a gradual downward trend with ligamentum arteriosum calcification observed after the age of 12 years.

Fig. 5: An 18 month old female child died of likely acute hypoxia/ischaemia secondary to probable seizure due to a granule cell dispersion developmental anomaly in the brain. Post-mortem computed tomography reported a small dense focus between the pulmonary artery and arch/descending aorta which was suggested to be a patent ductus arteriosus clip. At autopsy, the ductus arteriosus was described as obliterated by hyalinised fibrous tissue showing dystrophic calcification. This histology image acquired with Elastic van Gieson staining demonstrates characteristic approximation of the intimal cushions. The intimal cushion is shown by the white arrows, lining the lumen of the ductus arteriosus. As the ductus arteriosus 'closes', there is fibrous obliteration of the lumen, and fibrosis and calcification of the tunica media.

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Table 1:

Frequency of patients with ligamentum arteriosum calcification, according to age groups.

The frequency is calculated by dividing number of patients in each age group against the total number of patients per age cohort. Patients aged 1 year old belong to the 0 – 1 year age bracket, those who are aged 1 year and 1 day would belong to the higher 1 – 2 year age bracket. This principle is followed for the remaining subsequent age cohorts. CI, confidence interval (lower limit set to 0).

Age (years)	Number of patients	Number of patients with ligamentum arteriosum calcification observed	Frequency % (95% CI)
0 – 1	118	29	24.6 (17.3 – 33.5)
1 – 2	28	15	53.6 (34.2 – 71.9)
2 – 3	13	4	30.8 (10.4 – 61.1)
3 – 4	14	7	50.0 (24.0 – 75.9)
4 – 5	9	3	33.3 (9.0 – 69.1)
5 – 6	5	3	60.0 (17.0 – 92.7)
6 – 7	3	2	66.7 (12.5 – 98.2)
7 – 8	8	2	25.0 (4.4 – 64.4)
8 – 9	5	1	20.0 (1.1 – 70.1)
9 – 10	2	0	0.0 (0.0 – 80.2)
10 – 11	2	0	0.0 (0.0 – 80.2)
11 – 12	3	1	33.3 (1.8 – 87.5)
12 – 13	2	0	0.0 (0.0 – 80.2)
13 – 14	2	0	0.0 (0.0 – 80.2)
14 – 15	3	0	0.0 (0.0 – 69.0)
15 – 16	2	0	0.0 (0.0 – 80.2)
16 – 17	1	0	0.0 (0.0 – 94.5)
Total	**220**	**67**	**30.5 (24.5 – 37.1)**

Table 2:

Retrieved papers that included calcification frequency utilising a paediatric cohort. *XR = radiography; CT = computed tomography*

First Author Surname	Study Type	Sample Size	Imaging Modality	Age Range	Number of Patients with Ligamentum Arteriosum Calcification	Calcification Frequency (%)
Bisceglia et al, 1991 **[3]**	Retrospective	53	CT	1 month – 20 years	7	13.2
Beluffi et al, 1998 **[4]**	Retrospective	38 476	XR	Preterm – 16 years	31	0.1
Proisy et al, 2015 **[5]**	Retrospective	69	CT	Infants – 8 years	42	60.9
Hong et al, 2012 **[6]**	Retrospective	500 (Non-contrast CT: 164 Contrast CT: 336)	CT (500) XR (476)	0 – 20 years	All CT: 117 Non-contrast CT: 62 Contrast CT: 55 XR: 17	All CT: 23.4 Non-contrast: 37.8 Contrast CT: 16.4 XR: 3.6