FOLLOW-UP OF CHILDREN EXPOSED TO IONISING RADIATION FROM CARDIAC CATHETERISATION: THE COCCINELLE STUDY

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Cardiac catheterisation has become an essential tool in the diagnosis and treatment of children with a wide variety of congenital and acquired forms of cardiovascular disease. Despite the clear clinical benefit to the patient, radiation exposure from paediatric cardiac catheterisation procedures (CCPs) may be substantial. Given children's greater sensitivity to radiation and the longer life span during which radiation health effects can develop, an epidemiological cohort study, named Coccinelle or 'Ladybird' (French acronym for '*Cohorte sur le risque de cancer après cardiologie interventionnelle pédiatrique*'), is carried out in France to evaluate the risks of leukaemia and solid cancers in this population. A total number of 8000 included children are expected. Individual CCP-related doses will be assessed for each child included in the cohort. For each CCP performed, dosimetric parameters (dose–area product, fluoroscopy time and total number of cine frames) are retrieved retrospectively. Organ doses, especially to the lung, the oesophagus and the thyroid, are calculated with PCXMC software. The cohort will be followed up through linkage with French paediatric cancer registries.

CONTEXT AND OBJECTIVE

Over the last 20 y, there has been a marked increase in the number of diagnostic medical procedures that require ionising radiation. Especially, there has been an increase in the frequency of relatively high-dose procedures such as computed tomographic (CT) scanning, and cardiac catheterisation procedures (CCPs). CCPs are medical interventions in which fluoroscopy is used to guide small devices (e.g. placing a catheter in a blood vessel) to obtain images of blood vessels, heart chambers and valves. In addition to their use for diagnosis, interventional or therapeutic procedures are performed in hospitals to correct congenital heart defects (CHD) using devices, such as balloons and stents. Therapeutic procedures mainly involve dilatation of vessels or valves and occlusion of abnormal communications. CCPs are currently performed in a dedicated laboratory or cardiology services with sophisticated X-ray interventional equipment and specially trained staff to ensure successful outcome and minimal patient risk. However, increased radiation exposure can easily occur due to either prolonged fluoroscopy time (FT) or to the large number of cine imaging to record the whole procedure.

The radiation exposure issue in CCP is particularly relevant for children because of their higher radiosensitivity compared with adults and their longer mean lifetime expectancy during which radiation health effects can develop. However, information on cancer risks associated with CCP during early childhood remains limited, and the authors have stressed the utility of setting up epidemiological studies on the

cancer risks associated with radiation exposure during CCP⁽¹⁾. Such a study is more feasible today than in the past as the long-term outcome of the underlying cardiac diseases has improved greatly in the past decade, and now excellent long-term survival is the rule, rather than the exception⁽²⁾.

In this context, an epidemiological cohort study, named Coccinelle, is carried out in France to evaluate the risks of leukaemia and solid cancers in this population⁽³⁾.

MATERIALS AND METHODS

Population and setting

The study population consists of patients who underwent at least one CCP (either for diagnostic or therapeutic purposes) before the age of 10 y and from 1 January 2000 through 31 December 2013. Because of the lack of a national adult cancer registry, only children exposed very young are included in the study. Cancer incidence data will be available for at least 10 years after inclusion through the French pediatric cancer registries.

CCPs in children are predominantly performed in tertiary hospitals in France. Fifteen centres have been identified, all members of the French national network for Complex Congenital Cardiac Defects-M3C, which treats ~80 % of the children with CHD in France. In all, 4500 children recruited from the 2 centres coordinating the M3C network (Hospital 'Necker Enfants malades', Paris, and Surgical Center Marie Lannelongue, Le Plessis-Robinson) have already

been included in the cohort. Recruitment is ongoing in these two centres, and it is currently extended to other centres of the M3C network. The study is expected to finally include ~8000 children. This estimation is based on the average number of paediatric CCP performed in the two coordinating centres.

Data available for the cohort

Electronically stored patient records from the departments of paediatric cardiology of tertiary hospitals in France are being searched to identify the children to be included. The minimum data set includes the following information: identification of the patient [file number in the centre or service, full name, sex, date and place of birth and characteristics of the CCP (date of the procedure, age, weight, underlying disease, type of procedure, technical details including but not limited to FT and dose–area product (DAP)].

Follow-up of the children

Health status will be followed up by assessments in the future and every 5 y from 2016. The vital status of each child will be identified by cross-linkage with the national vital status registry [Répertoire National d'Identification des Personnes Physiques (RNIPP)].

Up to age 15, follow-up of cancer incidence will be performed through cross-linkage with the paediatric cancer registries [Registre des Tumeurs Solides de l'Enfant (RTSE) and Registre National des Hemopathies de l'Enfant (RNHE)], which since 1990 and 2000, respectively, have recorded all cases of childhood (i.e. under 15 y old at diagnosis) leukaemia and cancers in France. Above the age of 15 y, follow-up will be based on mortality status as France has no national cancer registry for adult cancers. Follow-up of morbidity through data from the medical insurance system (specifically, the SNII-RAM, an inter-health insurance scheme information system) may be available in the future.

Dose assessment

Individual CCP-related doses are being assessed for each child included in the cohort. Exposure parameters (DAP and FT) are retrieved from the dose-recording system. The DAP, which represents the dose in air measured at a given distance from the X-ray tube multiplied by the area of the X ray at that distance⁽²⁾, is used as a surrogate for radiation exposure⁽⁴⁾. Organ doses, especially to the lung, the oesophagus and the thyroid are then calculated with PCXMC 2.0—STUK⁽⁵⁾. For specific CCP, the doses received at different organs are also evaluated using anthropomorphic phantoms⁽⁶⁾.

Radiation exposure outside the participating centres will not be considered. However, it is planned

to address the children's exposure to CT scans, which account for a major contribution to their medical exposure dose. Our data will be cross-matched with data from the childhood French CT scan cohort ('Cohort Enfant Scanner') set up by the IRSN^(7, 8) for the children included in both cohorts. For children who underwent CCP in centres not participating in the 'Enfant Scanner' scanner, it will be necessary to go back to medical files to obtain information about the CT scans performed.

Ethical aspects

The French national data protection authority [Commission Nationale Informatique et Liberté (CNIL)] (no. 911112 of 12 December 2011) has approved the study and the conditions of storage of personal data and use of anonymised dosimetric and clinical data.

RESULTS

Up to now, 4500 children have been already included in the cohort, but recruitment is still ongoing at the national level. On average, each child has undergone 1.3 CCP, for a total of >5000 procedures performed between 2000 and 2013. Nearly half of these were performed during the child's first year of life. The main procedures investigated are as follows: diagnostic, patent ductus arteriosus (PDA) closure, atrial septal defects (ASD) closure, balloon valvuloplasty, balloon angioplasty and electrophysiology procedures.

Dosimetric data were analysed for 801 procedures performed between 2010 and 2011 at 'Necker Enfants malades' hospital⁽⁶⁾. For diagnostic procedures, the mean effective dose value was 4.8 mSv (min: 0.3 mSv; max: 23 mSv). For therapeutic procedures, the mean effective dose value was 7.3 mSv (min: 0.1 mSv; max: 48.4 mSv). In order to evaluate the impact of ionising radiation on organs surrounding the heart, specific CCPs were simulated on physical phantoms using thermoluminescence dosimeters. Results showed high doses to organs located within the primary beam (lungs and oesophagus) compared with the other investigated organs (Table 1).

DISCUSSION

CCPs play a crucial role in the diagnosis and treatment of congenital heart diseases. The justification of these procedures is clear: they make it possible to avoid complicated invasive surgery. These procedures are, however, among the radiological procedures with the highest patient radiation dose. Several assessments of cancer risk after CCP derived mainly from studies of Hiroshima and Nagasaki A bomb survivors are available. In particular, Ait-Ali⁽²⁾ estimated a lifetime attributable risk of death from cancer equal to 1 in

Table 1. Mean absorbed doses to lungs, oesophagus, breasts and thyroid for two diagnostic procedures and three therapeutic procedures (from Barnaoui, 2014).

Procedure Phantom [age (y); weight (kg)]	Dose (mGy)			
	Lungs	Oesophagus	Breast	Thyroid
PAH Phantom (1 y; 10 kg)	13.3	10.6	4.2	1.3
EMB + Coro Phantom (10 y; 32 kg)	42.7	26	21	1
VSD Phantom (0 y; 3,5 kg)	61	53.8	33	37
PDA Phantom (5 y; 32 kg)	14.6	10	4	2
ASD Phantom (15 y; 55 kg)	2.2	3.7	0.8	0.7

Diagnostic procedures: PAH, diagnostic of pulmonary arterial hypertension; Emb + Coro, endomyocardial biopsy associated with a coronarography.

Therapeutic procedures: VSD, ventricular septal defect; ASD, atrial septal defects closure and PDA, patent ductus arteriosus closure.

1717 (0.06 %) for boys (from 0 to 15 y) receiving an average of 7.1 mSv and equal to 1 in 859 (0.12 %) in girls receiving an average of 9.4 mSv during CCP. These cancer risk assessments could be criticised because of concerns about how applicable the findings are to the relatively low doses of radiation, such as those from CCP, and to exposure of non-Japanese populations. Another important limit in the cancer risk assessments is the lack of consideration of the clinical characteristics of patients in such an evaluation. These individuals, especially patients with CHD, can present important comorbidity factors.

Epidemiological studies may be able to assess directly the question of whether cancer risks are increased after CCP in childhood and young adulthood. Until now, only two cohort studies have assessed the association between the risk of cancer in children and radiation exposure during paediatric CCP. MacLaughlin studied 4891 Canadian children who had undergone at least one CCP before the age of 18 y between 1946 and 1968 and did not demonstrate a significant increase in leukaemia or in any other tumours in this population⁽⁹⁾. A second study, conducted by Modan, examined the records of 674 children who had undergone ICP for CHD between 1950 and 1970 and showed an excess number of solid cancers and of lymphomas⁽¹⁰⁾.

Methodological limitations (no estimation of the doses received, types of CCPs used unknown) might explain the inconsistency of these results.

More precise estimates might be available with the epidemiological Coccinelle study carried out in France and specifically designed to provide further knowledge on the potential cancer risk associated with paediatric CCP. However, even with complete and accurate follow-up, it must be acknowledged that this study by itself will have limited statistical power. The size of the French cohort ($n = 8000$ children) was estimated based on the average number of CCPs performed in the two main centres (Hospital Necker Enfants malades and Surgical center Marie Lannelongue). As indicated in (3), this sample size will be sufficient to detect an overall excess risk of 1.7 for all cancer incidence, but smaller levels are expected. A similar study is currently being conducted in the UK by Dr M. Pearce, University of Newcastle, and the feasibility of a pooled analysis to increase the statistical power of these individual studies is under discussion.

CONCLUSION

Technological advances have made it possible for CCP to play a therapeutic as well as a diagnostic role. In various CHD, it can allow surgical procedures to be postponed or even replaced. But, CCP can also involve potentially non-negligible doses of radiation to the patients. This issue is particularly relevant for children as they are relatively more sensitive to ionising radiation than adults are and have longer mean lifetime expectancy. This cohort study is specifically designed to provide further knowledge on the potential cancer risk associated with paediatric CCP. In the meantime, it will provide comprehensive information on typical levels of doses for paediatric interventional CCP in France. Finally, this study aims to provide answers on individual variability in cancer risk, and in particular on the effect of age at exposure. It complements the studies on CT scan studies whose major limitation is indication bias due to the lack of information about the reasons for scans^(8, 11, 12). Overestimates of cancer risks could have resulted if the CT scans were performed either because of suspected cancer (reverse causation) or for diagnosis or monitoring of conditions themselves related to increased cancer risk (confounding bias). In the framework of the Coccinelle study, the reasons for CCP are well known and the possibility for reverse causation will be minor.

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