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- 04 University College London – Great Ormond Street Children’s Hospital (UCL)
- 05 Assistance Publique Hopitaux de Paris – Necker (APHP)
- 06 European Organisation for Nuclear Research (CERN)
- 09 University of the West of England (UWE)
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Introduction

This document reports the progress made in work package 9 of the Health-e-Child project up to month 24. The goal of this work package is to collect the necessary clinical, imaging and genetic patient data. This activity supplies core data for the three applications of disease modelling, decision support, and knowledge discovery. Biomedical data are collected for three disease groups, namely Paediatric Heart Diseases, Inflammatory Diseases, Brain Tumours [1].

Collecting as comprehensive as possible biomedical data for each patient entering the Health-e-Child system is critical. This step not only serves the purpose of testing the data integration mechanism, but also provides training and testing data for the construction of integrated disease modelling, decision support, and knowledge discovery systems.

Our three hospitals (IGG, Genoa; APHP, Paris; and UCL, London) are collecting patient data for Paediatric Heart Diseases and Inflammatory Diseases. Moreover, Brain Tumours study is ongoing only at IGG.

The following chapters deal with the three disease classes of Health-e-Child, it includes data collection status, problems encountered during the reporting period, and status with regard to Self Assessment Plan.



Data collection status

1.1. I.R.C.C.S. Giannina Gaslini (IGG)

1.1.1. Paediatric Heart Diseases

At **IGG** 75 patients (70 RVO - 39 ASD, 30 TOF, 1 PAPVR - and 5 CMPs being 2 hypertrophic CMP and 3 dilated CMP) have already been enrolled and for all of them clinical and imaging data have been gathered (including echocardiography for all of them and 13 cardiac MRI). Follow-up has been performed for 19 patients (3 CMP and 16 RVO patients). Blood samples for genetic test have also been collected for RVO patients (Constitutional Karyotyping was done for 59 patients and subtelomeric rearrangement of chromosomes was performed for 2 patients; screening of the three candidate genes was undertaken for 34 ASD, and 25 TOF and Array CGH analysis was performed for 59 patients); the first achieved data have been inputted in the database and released to IT partners. Further inputted data will be shortly released and sent. Meetings with IT partners were organised and undertaken in order to discuss the development of the decision support system.

Some interesting data have been found out and it is planned to go deep in details and verify the possibility of publications in medical journals.

1.1.2. Inflammatory Diseases

At IGG, At IGG 53 JIA patients were enrolled. 17 of these 53 patients have 1 year follow-up control. Overall 70 MRI, ultrasonography and radiographs have been performed. Regarding MRI, the data was counted for all patients (old and new protocols). With regard to imaging analysis we proposed semiquantitative MRI and US scores for JIA pathological findings (synovitis, bone erosions..ect.) to be used for vertical integration with other clinical and biological data. The process of validation of these scores is ongoing. Preliminary results in terms of reliability and construct validity of our MRI scoring system to assess structural damage to joints appear promising; however its suitability is yet to be tested in large-scale longitudinal studies.

Blood samples have been collected and stored in the biobank to perform immunological and genetic studies. With regard to genetic investigations the analysis of polymorphism of osteopontin and periostin genes is ongoing on the blood samples of all patients enrolled at IGG. Proteomic analysis is ongoing on synovial fluid and blood samples of 15 patients with clinical indication to perform arthrocentesis.

Clinical data of all patients enrolled in the three Centres (IGG, GOSH and APHP) have been inputted in a database created purposely for these patients and is located at Gaslini Institute.

1.1.3. Brain Tumours

The Brain Tumours study is ongoing at IGG. A total of 49 patients have been enrolled. The database for collection of clinical and imaging data was refined and validated.

Clinical data have been collected for all 49 patients and the Brain MRI has been performed in all children whereas imaging data have to be completed. The tumor tissue diagnosis have been performed in all cases as the tissue sampling of all 49 cases. RNA have been prepared from all 49 cases to be used for expression studies. Hybridization of chip arrays have been done using the Affimetrix Gene-Chip U133 Arrays (IGG). Tumour gene expression data (microarray) has been accomplished for 49 patients and the expression data is analysed by Siemens, DISI and UoA. From the same cases DNA extractions have been prepared at IGG from 38 tumor samples and 12 peripheral blood samples from the same affected patients



and sent to EGF. Those DNAs are used for mutation detection in selected genes. Sequence Analysis on PTEN, CDKN2A, PTPN11 and Netrin 1 is currently ongoing. In order to increase the statistical power of this study, it has been programmed to enrol more patient in the next period. For 14 patients, brain MRI studies were acquired after 2004 and are available as DICOM images. 6 of these 14 patients are among the 49 patients selected for the gene expression study.



1.2. Assistance Publique Hopitaux de Paris – Necker (APHP)

1.2.1. Paediatric Heart Diseases

At **APHP**, the required number of patients have been recruited (66 with TOF and 33 with CMPs). For patients with TOF, a complete set of data have been obtained in 56 of the patients including imaging (echo for all, MRI in 56), and basic genetic study (standard karyotype). All of them had undergone full clinical evaluation, ECG monitoring and BNP dosage. For patients with CMPs, a complete set of data have been obtained including clinical examination, echo, and metabolic study. DNA sample has been stored. Histological data were obtained for the great majority of patients. Additional patients have been recruited for the study to increase the number of collected data. For this extra-group, some data are presently missing but will be obtained within the next two months. All together, 129 patients (80 with TOF or ASD and 49 with CMPs) have been recruited for the study.

1.2.2. Inflammatory Diseases

At **APHP** at the end of December 2007, 52 patients have been enrolled. Seven of them have had a one-year follow-up visit. Clinical data are available for all patients. All of them had undergone all imaging (including one-year control group) and for each patient, blood samples had been collected and stored in biobank to perform genetic study. This has been done in almost all cases for both parents as well. The question about how to transfer blood samples abroad for genetic analyses to be performed in Italy are going on (some specific authorizations are required).

1.3. University College London – Great Ormond Street Children’s Hospital (UCL)

1.3.1. Paediatric Heart Diseases

So far 58 patients have been enrolled in the study. MRI and echo data has been collected for all participants thus far. Forty eight Chest X-rays have been collected thus far. No genetic data is being carried out. Cardiac MRIs are continuously delivered to the IT partners (Siemens). Thus far, the IT partners have collected 54.

1.3.2. Inflammatory Diseases

At UCL, Regarding rheumatology, a research physiotherapist has been recruited and had started working for the project since July 2007. by the end of December 2007, twenty six patients have been recruited, which is on target with the initial objectives. 1st cohort of patients recruited was performed. Appointment of data Manager and Server is established for uploading study data. No patients had refused the enrollment in the study on Ethical grounds.



Problems encountered during the reporting period

1.4. IGG

No significant problem was encountered for Paediatric Heart Diseases, JIA and Brain tumours studies.

1.5. APHP

Regarding **Paediatric Heart Diseases** three patients had refused the cardiac MRI and 7 had contra-indication to undertake such a test.

Regarding the **JIA** study, the inclusion of patients is in progress. It has been possible to benefit from only 2 MRI slots per week until now, but from the beginning of January 2008 a third slot will be available weekly, which should allow us to recruit 48 more patients and to perform MRI again in the patients having a second visit one year after enrollment. Some data from the first patients (mainly ultrasounds) have not been properly recorded but now these data are systematically saved. It remains difficult at this stage to be sure that the way data are initially interpreted by radiologists is the same in the 3 participating centers and some formal quality assessment might be of interest. Some genetic analyses are to be performed in Italy. However, it is still to discuss the mode of sending the samples and there may be the need to obtain some additional authorizations in France.

1.6. UCL

Regarding the **JIA** study, the following problems have been underlined:

- Difficulty in finding appropriate patients with Hip and Wrist involvement that qualify according to recruitment criteria
- Parents choosing not to take part (unless outside school time, feel that child has already had enough tests and not able to tolerate any more).
- Difficulty with patients tolerating length of examination and/or contrast injection without GA.



Status with regard to Self Assessment Plan

According to the self assessment plan, data collection at the three hospitals at month 24 (4a data collection at the three hospitals at month 24 in Paediatric Heart Diseases; 4b data collection at the three hospitals at month 24 in Inflammatory Diseases; 4c data collection at IGG at month 24 in Brain Tumours) is to be evaluated [2].

The number of cases expected to be collected by the three hospitals by month 24 was at least 40% and at best 75% of the total in each subgroup.

In paediatric heart diseases, 87% of the patients were already enrolled at month 24, indicating that patient enrolment is well ahead of the original plan.

In the inflammatory diseases subgroup, 55% of the total were collected which is slightly below linear, but still within the margins we expected.

In the Brain Tumours subgroup, the data for all 49 patients that were selected for gene expression analysis already is completely collected at month 24. This constitutes 98% of the cases we had set as a target for month 30.



References

- [1] Health-e-Child "Project Proposal, Annex I: Description of Work, Project Phase II"
- [2] Health-e-Child D.1.5.a Self Assessment Plan