Elective at Harvard Medical School

Report for the Mobbs Travelling Fellowship

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Acknowledgements

I would like to thank the Faculty of Occupational Medicine for sponsoring my elective at Harvard University, and my research in occupational medicine and genetics. In addition, more broadly, I would like to thank them for inspiring the next generation of doctors to specialise in occupational medicine.

Background

I first became involved in occupational medicine after completing courses in aerospace medicine at University College London, International Space University and NASA, and an internship at the European Astronaut Centre within the European Space Agency. There, I became involved in safety and evacuation procedures as well as selection criteria.

As part of my final-year medical elective this year, I was accepted at HMS where I met some of the founders of the Personal Genome Project (PGP), which inspired me to do more research into the link between genetics and occupational health. I think it is very important to promote the integration of new knowledge and techniques in occupational medicine for a more multi-disciplinary approach to solving the increasingly global challenges and to extend the applications within this field.

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The Personal Genome Project (PGP) was developed at Harvard Medical School (HMS) and is now the official reference for genetic information by the FDA. The PGP compiles the genomic information of up to 100 000 American volunteers as well as information on phenotype and medical records. To date, this is the largest project combining information on genotype and phenotype and opening the doors for a wide-range of research and data-mining, including in the field of occupational medicine.

Aims and objectives

In addition to my personal objectives to gain new skills and form new collaborations, the educational objectives of this elective project included:

i) To lead patient interviews, examinations and formulate management plans at the standard of Harvard's Advanced Medicine Clerkship and get experience in performing at subinternship (pre-junior doctor) level expected of advanced final year medical students. The clinical work had particular emphasis on occupational medicine, health assessments and certification.

ii) To work with members of the Personal Genome Project (PGP) and receive training in the using the PGP database, conducting specific searches and extracting data.

iii) To carry out an original piece of research into data analysis and applications of the PGP data for occupational medicine purposes, including looking at work patterns and links to gene expression and morbidity.

iv) To present the results at the end of the elective period to the host and home universities Harvard and UCL, respectively.

HMS elective

I spent part of the elective working at Massachusetts General Hospital (MGH) where I got a chance to interview and examine patients as well as formulate management plans and discuss them with my seniors. I also attended the daily Lunchtime Conferences and weekly Grand Rounds (Figure 1), which are particularly famous for being held at the Ether Dome, the first site where

ether was used as surgical anaesthetic in a public demonstration. The working environment was particularly orientated towards the training of academic clinicians and there were daily presentations on unusual clinical cases. This gave me the opportunity to make several presentations during my elective, including to my supervisor, the clinical team and the department. These were based on topics I had worked on prior, as well as during, my elective rotation.

Figure 1. Grand round at the Ether Dome, MGH, on next-generation genomics and proteomics (27.06.2013).

During my elective course I rotated through several different departments including: the department of genetics, neurology and paediatrics.

I worked with several members of the PGP team at the genetics department. They also introduced me to the consultancy-side of genetics, including new spin-off companies such as Abvitro. This broadened my knowledge and understanding of the use of applications for genomic sequencing. As part of my project work, I also spent time data-mining with statistical analysis on the PGP and NCBI databases. I received training in using the PGP data for specific searches, including looking at work patterns and links to gene expression and morbidity. I also attended a variety of outpatient clinics and took care of several inpatients on the genetics service. Since the genetics service is a consult service, I worked on the inpatient side as part of two of the departments frequently linked to genetics and holding many of their patients. These departments were paediatrics and neurology.

Several of the patients I saw were joint between genetics, paediatrics and neurology. In particular, there was an unusual case of a 34 week-old premature baby girl, born with intrauterine growth retardation, microcephaly and hypoplastic cerebellum from consanguineous first-cousin marriage. The results of extensive testing were inconclusive and the case was such a diagnostic mystery that I decided to look into some of the differential diagnosis. As part of my work, I made a presentation on cerebral creatine deficiency syndromes (CCDS) and the use of MRI for diagnostic purposes. Although CCDS typically presents beyond three months of age, earlier onset has been described and by adding spectroscopy to the MRI scan, this diagnosis could be easily ruled out/in. (In this case the diagnosis was ruled out as a creatine peak was present on MR spectroscopy whereas it would be expected to be absent in CCDS).

Genetics has also become increasingly important in neurology and especially neuro-oncology where certain mutations have been linked to better/worse response to chemo- or radio-therapy. For instance, in gliomas, the most common adult primary brain tumour, the O6-methylguanine-DNA methytransferase gene (MGMT) has been associated with improved outcomes and higher sensitivity to alkylating chemotherapy (Rivera et al., 2010). Gliomas have been shown to have a slightly higher incidence with certain industries e.g. workers from petrochemical refineries, firefighter, farmers and physicians, too (Carozza et al., 2000).

As part of my elective, I specifically looked at the application of genetics in occupational medicine. I was particularly interested at looking the potential link of cancer and obesity with night-shift and alternating-shift workers. I first became interested in the topic after reading Sahar and Sassone-Corsi's article in 2009 (Sahar and Sassone-Corsi, 2009). This link is thought to be

related to the different cytochrome p450 genes and gene expression that various in circadian cycles. I used the PGP database to gather information about the genetic (p450 polymorphisms) as well as the phenotypic (occupation and shift patterns) information of volunteers and looked at the correlation. The analysis is complicated because the p450 system is also involved in the metabolism of a variety of chemicals and drugs. For instance, the asthma drug theophylline has a narrow therapeutic index and is largely metabolised by the p450 system, which varies with the circadian clock. Therefore, careful consideration needs to be given to confounding factors, potential toxicities and chronotherapy. This requires a large number of records, which is why the PGP database is a particularly good source of information, and is continuing as several hundred more records of volunteers are going to be uploaded to the PGP in the next few months.

Reports and presentations on the work from the elective have already been submitted to the host and home universities, Harvard and UCL, respectively. As the work continues and more data is obtained, it is hoped that abstracts will submitted to further scientific meetings such as the European Society for Environmental and Occupational Medicine, the American Occupational Health Conference and the Faculty of Occupational Medicine.

Since completing the elective, I have started work on the Academic Foundation Programme (AFP). It is also hoped that the results will be presented at the next AFP meeting at the end of the year and the work will continue into the second year of the two-year AFP contract.

Conclusions

In addition to the clinical work during the elective, the personal research looking into the link of genetics and occupational medicine led me to a number of important conclusions. In particular, the reported link between changes in shift patterns and complex diseases such as cancer is likely to be related to genetic polymorphisms of cytochrome p450 enzymes and their regulation by the circadian rhythm. There are several important potential confounding factors to be considered in future work, which include patients' medications and chronotherapy as these can influence not only p450 levels but may also predispose to toxicities and confounding morbidities.

Summary

This elective was uniquely helpful in many ways: it not only allowed me to gain new knowledge and make new connections but also to contribute to the field of occupational health. This gain in knowledge, connections and research has not only been useful during my Academic Foundation Programme as a junior doctor but it will also be helpful to me in the coming years years and long-term future as I pursue a career in academic medicine. I aim to eventually establish myself as a specialist bridging the gap between occupational medicine and the new technological advances in personalised medicine (e.g. in genetic changes and targeted pharmaceuticals) and I will be always grateful for the support given to me by the Faculty of Occupational Medicine. The results of this elective are aimed to stimulate further research into the important applications of genetics to occupational medicine and to benefit the wider field of occupational health.

References

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