Prevention Task Force: Orlando: brief report and vision for the future

In the Prevention Task Force we had an outline agenda that included a few presentations and these are appended. This will enable delegates who attended to disseminate the information beyond those who were able to make this meeting date Monday 6th May: 7am Hibiscus Room Hilton Hotel time 7am-8am. Delegates present included the six speakers who were Vera Lopes (Brazil) Jyotsna Murthy (India), Azeez Butali (Nigeria & Iowa), Ron Munger (Utah, USA) and Peter Mossey (Scotland, UK). All speakers are happy that we share their short presentations with a brief report of the Task Force meeting.

The meeting acknowledged that only a small subset of those interested in the issue of aetiology/ prevention of orofacial clefts would be present at the meeting and the prevention message can be widely disseminated and was mentioned at various subsequent sessions throughout the Orlando meeting.

The 'Beyond Eurocleft' title was interpreted as using the Eurocleft as a model to refer to as the objective is (a) widespread dissemination beyond the Eurocleft project in all geographic areas in the world and (b) succession planning – there is a requirement for a new generation of scientists and researchers to be equipped with the skills and the enthusiasm to continue pursuing cleft research.

Major themes in cleft research

The two major themes in cleft research, both of which can be interpreted broadly are (1) improving access to care for CLP patients and this means gold standard of care for not only surgical interventions, but also multidisciplinary treatment involving a broad range of health care specialties and (2) improving knowledge on aetiology/causation and risk factors. The ultimate goal of such research is to identify possibilities for primary prevention.

The aspects raised in the presentations that are relevant to future dialogue and, hopefully, collaborative efforts are as follows:

1. Birth Defects surveillance: it is important that the prevalence of orofacial clefts in different parts of the world is known and that good infrastructure for ascertainment is developed and this is an issue not only for the developing world. The importance of accurate figures on birth prevalence is particularly relevant when preventive interventions are planned as it is important to measure efficacy. This is highlighted in recent examples of folic acid food fortification programmes.

2. Environmental factors: better methods are required for measurement of environmental factors with a shift towards biomarkers as opposed to questionnaires for precision of measurement and in OFC it is important that aspects of nutrition, environmental exposures, behavioural factors and medical history are well recorded.

3. Genetic factors: through GWAS the landscape of genetic predisposition has changed significantly over the last five years and ever-improving high throughput molecular genetic technologies and computational facilities make the possibility of identification of genetic predisposition much more accessible and tangible. The GWAS studies to date suggest that there are different genetic markers predisposing to cleft lip and palate in different populations and possibly in different ethnic groups and different families also.

4. GEI/GGI/Epigenetics: future studies will concentrate much more on interactions between genetic and environmental factors, interactions between genes in the same or different pathways and epigenetic factors such as DNA methylation and its influence on phenotype.

Implementation agenda: There was general consensus that we need to move to an implementation agenda in our research and that collaborative studies have the potential to accelerate the progress of research in field of cleft lip and palate.

Some issues identified over twenty years ago are still being debated in the context of OFC and an example of this is whether or not folic acid and/or multivitamins have protective effects when considering prevention of cleft lip and palate. For example is folic acid effective in (a) preventing both occurrence and recurrence to the same degree, (b) preventing cleft lip with or without cleft palate versus cleft palate (or both), and (c) whether there is a dose response effect, i.e. whether it requires a higher dose of folic acid to be effective for OFC prevention than for NTD prevention? Superimposed on this is whether multivitamins or trace elements might also contribute to protection.

Where do we go from here? Vision for the future:

1. Improved research methods. The aim is to improve the tools that we have for identifying genetic predisposition to clefts - and if we can measure environmental exposure precisely through biomarkers and also identify predisposition by phenotyping, there is an inevitable move towards the principle of personalised or stratified prevention.

2. Collaboration: it is also much more likely that combined efforts between scientists working in different countries and in multidisciplinary teams are more likely to be able to develop the expertise to answer complex questions in polygenic multifactorial disorders.

3. Large numbers of subjects: whether it be population based or family based study methodologies, large numbers, replication datasets and different ethnic groups and populations will be important.

4. Co-operation between clinicians and scientists: every patient encounter is an opportunity to collect information whether it be for a DNA sample, a biomarker or questionnaire information and if all teams could adapt this collaborative strategy and use a system for common core protocols or minimum datasets when developing these research strategies.

5. Involvement of young researchers: it would be extremely beneficial to the aims and objectives of prevention to have a policy for targeting and involving younger colleagues to be able to develop succession planning in the field.

Existing datasets and initiatives: there are already many national and international initiatives that attempt to address the agenda of primary prevention and it would be useful to involve them in a large international network and to build up a directory of resources of what samples are available. One such organisation where this is being done and could be enhanced is the NIH funded FaceBase Initiative.

Beyond orofacial clefting and birth defects: there are other areas of research that could be usefully pursued in parallel with the orofacial clefting research. Examples being low birth (or small for gestational age) studies, issues of co-morbidity, studies on maternal metabolic diseases,

cardiovascular disease, diabetes and obesity and cancers could all yield synergistic data that would be beneficial in our future research.

Geographic representation: we should strive to ensure that the Prevention Task Force achieves broad representation and a good communication system is established, beginning perhaps with a website, but also social media could be used to facilitate discussions. A matrix could be set up that lists every country and seeks to ensure that there is participation at least in an email distribution list for exchange of ideas and knowledge and notification of future events, research funding, etc. The broad geographic divisions are as follows:

1. **Latin-speaking America**
2. **English-speaking America**
3. **Africa**
4. **India**
5. **Far East**
6. **South-East Asia**
7. **Australia/New Zealand**
8. **Middle East**
9. **Europe**

Vision for the future: the mark of success for the future prevention network is that we would

1. Achieve a functional working group that participates actively in a discussion forum
2. By discussion, collaboration and dialogue the group would identify a list of research priorities
3. Among these research priorities there would be a clear translational / implementation agenda
4. having identified the research priorities the appropriate expertise would be identified for each of the projects
5. Collection of DNA / biological samples in biobanks using standardised protocols
6. Ethical principles adhered to: while there will be differences in different countries, the basic principles of research ethics will be similar and it may be possible to facilitate the process of identifying and securing ethical permission to carry out these studies
7. Ultimately, we should aim to demonstrate using sound research methodologies, whether there is progress in achieving primary prevention within a generation in most (if not all) countries in the world.

In the shorter term work with WHO, CDC and existing agencies to establish what is possible in terms of measurement of primary prevention. In the short term examine how prevention of clefts might fit in with strategies surrounding the millennium development goals (MDG) and research initiatives such as Horizon 2020.

APPENDIX: The following were present or represented:

Savita Hariharan (India); Gayatri Moghe (India); Puneett Batra (India); John Thompson (New Zealand) Peter Fowler (New Zealand); Kirsten Molsted (Denmark); Regine Steegers (Netherlands); Corstiaan Bruegem (Utrecht, Netherlands); Mekonen Estete (Ethiopia); Mary Marazita (Pittsburgh, USA); Marie Tolarova (USF, USA); Concha Martinez (Madrid, Spain); Cynthia Cassell (CDC, Atlanta); Christy McKinney (University of Washington); Jeniffer Dutka (Brazil); Temis Maria Felix (Brazil); Ratna Dissanayake (Sri Lanka); Parakrama Jekoon (Sri Lanka); Donna Fox (Brazil); Amit Kumar Jaiswal (CMC, India); Paulina Aburime (Nigeria) and Jane Figueiredo