Continuing Medical Education Programmes

**Symposium on β-Thalassemia**
*Sunday, 20th November, 2011*

**Symposium on Intellectual and Developmental Disabilities**
*Tuesday, 22nd November, 2011*

Activity Report

**3rd Asian Workshop on Genomics and Community Genetics**
19-25th November, 2011
(Sri Guru Ram Rai Institute of Medical & Health Sciences, Dehradun)
Sponsored by
Pasteur Institute, France and Wellcome Trust, UK
Supported by
Department of Medical Health & Family Welfare,
Government of Uttarakhand, Uttarakhand, India

Dr. Sujata Sinha, MD
Workshop Organizing Secretary
Pathologist, Govt. Doon Hospital, Dehradun
26th December, 2011
Introduction

Thalassemias and other inherited hemoglobin disorders recognized as major public health problems, underscoring the impact of genomics in public health. In the wake of adoption of resolution by the central government to eradicate thalassemia in January 2011, it is now imperative that the States assess and prepare a strategy and program for thalassemia.

Increasing number of children with Intellectual & Developmental Disabilities (IDDs) are presenting for intervention. Advances in genomic studies have unraveled etiologies for many birth defects and syndromes and the concept of early intervention in the management of disabilities is gradually gaining pace in tertiary medical and non-medical centers. The establishment of Early Intervention Center at Govt. Doon Hospital has been a major step in the inclusion of disability within the public healthcare system.

The CME programmes provided an opportunity to discuss the impact and role of genetics in improving the outcomes in birth defects with some of the best international faculty, research leaders in their respective fields. The Workshop faculty included several experts on thalassemia and on IDDs. Professor Sir David Weatherall who unfortunately could not come but nevertheless had provided material for his talk which was delivered on his behalf by Dr. Nancy Olivieri. With funding support from the NRHM, Uttarakhand we could invite few more experts for the CME programmes.
The Workshop on Genomics and Community Genetics, an international teaching program sponsored by the prestigious Pasteur Institute, France, was held for the first time in India in Dehradun. The 3rd Asian edition supported by the Department of Medical Health and Family Welfare incorporated programmes and activities addressing public health issues related to genetics. ‘Public health genomics...improving outcomes in maternal and child health’ was adopted as the theme for these activities. The field of Public Health Genomics (Genetics) is a relatively new discipline emerging after the Human Genome Project and the term came into standard usage after an expert Workshop on ‘Genome Based Research and Population Health’ held at Bellagio, Italy in April 2005. The Public Health Genomics was thus defined as the effective translation of genome-based knowledge and technologies for the benefit of population health. Maternal and child health continue to be an area of priority and concern in developing countries including India and hence ‘Birth Defects’ contributing to about one third of all childhood deaths, was chosen as focus area for this initiative. 70 percent of these birth defects can be prevented or improved by simple interventions. Birth defects represented by two groups of disorders – Beta-Thalassemia and Intellectual & Developmental Disabilities were chosen as focus areas for deliberations.

Eminent faculty, research leaders in their respective fields, drawn from various countries including France, Australia, United Kingdom, Canada, Singapore and India was spread over seven days and included lectures, tutorials, interactive sessions, an online course on bioinformatics and a presentation.
by each of the fellows on his area of research interest. 20 fellows selected from Indonesia, Philippines and different parts of India after a meticulous selection procedure. The goal was to stimulate basic research that incorporates clinical in this field in developing South and South East Asian countries that incorporates clinical, diagnostic, prognostic potential and to encourage the development of local and regional genetic laboratories and to identify future regional leaders in both fundamental and applied human genetics.

This report provides a brief on the activities focusing on the above mentioned public health issues during the Workshop and also includes a summary of the talks delivered during the thalassemia symposium. The report will serve as a resource document for formulation of policies and implementation of strategies on Thalassemia and Intellectual & Developmental Disabilities.
Activity Report

The Workshop was inaugurated on the 19th, November at Sri Guru Ram Rai Institute of Medical & Health Sciences, Dehradun. On the occasion The Educational Abstracts Book was released by Shri Piyush Singh, IAS, Executive Director, NRHM, Uttarakhand. Prior to that, Molecular Research Laboratory was inaugurated by Prof Ken McElreavey and Prof Alan Bittles in the Biochemistry Department of the Institute. The laboratory is the first set up in

Below various activities conducted are briefly outlined

1. CME Programmes
   Symposium on β-Thalassemia-20th November, 2011, Hotel Madhuban
The CME programme on thalassemias was, organized in association with Dehradun Chapter of Indian Academy of Paediatrics, had nine lectures. The keynote address on global burden of thalassemias was delivered by Prof Nancy Olivieri on behalf of Prof. Sir David Weatherall. The session on genetics included talks on fetal hemoglobin, role and effect of alpha globin genes and population genetics of thalassemia. The other session included talks on strategies for dealing with thalassemia as a public health problem, diagnostic and screening strategies, cost effective iron chelation therapy and growth monitoring of thalassemic patients. An update on stem cell therapy concluded the session.
The CME programme on developmental disabilities was organized in association with Latika Roy Foundation. The keynote address was delivered by Prof Alan Bittles, Adjunct Professor and Research Leader, Centre for Comparative Genomics, Murdoch University, Perth. The session on genetics included talks by Dr G.K. Chetan from NIMHANS Bangalore who discussed the genetics of mental retardation and Prof Rajiva Raman talked on genetics of hyperhomocysteinemia affecting developmental defects like neural tube defects. Dr. Peter Corry discussed common genetic conditions encountered in children of Asian descent. The clinical session consisted of talks on evaluation of microcephaly, a common condition encountered in an EIC and a detailed account of evaluating a child with Autism by Dr. Sharmila Mukherjee. Dr. Shubha Nagesh provided the perspective of the Latika Roy Foundation.

A total of 86 participants registered for both the symposia. About 120 delegates including faculty and fellows and few invited guests attended the thalassemia symposium. And about 80 delegates attended the IDD symposium. Each talk was followed by lively discussions indicating the engagement of the audience.
2. **Clinics:**

**Thalassemia clinic**, at Doon Hospital- 20th November, 10.00 am to 12.00 noon.

15 thalassemic patients with their parents attended the clinic

Experts- Prof Nancy Olivieri, invited faculty and renowned expert clinician on thalassemia from University of Toronto, Canada examined and assessed 6 patients in detail with a purpose to educate the clinicians present. Dr. Sangeeta Kumar, Thalassemia paediatrician, Incharge of the Thalassemia Care Center, run by VRTWS at Mata Anandmayee Hospital, Varanasi was the other expert. Dr. D.S. Rawat, Senior Paediatrician, Doon Hospital, Dr. Yatish Goel, senior practicing paediatrician and Dr. B.P.Kalra and Dr Anil Rawat, faculty members, Department of Paediatrics, HIHT, Dehradun were present at the clinic.

Dr. Iva Chandola, of IMA Blood Bank Dehradun co-ordinated the clinic.

**Developmental Disability Clinic**- 17th and 18th, November, 2011,

Doon Early Intervention Center, Doon Hospital.

Dr. Peter Corry, from Bradford, England, an expert on developmental disabilities and neuro
disability with vast experience on Asian children conducted the clinic at the EIC. He evaluated 6 patients selected for review and discussion. The Clinic was co-ordinated by Dr. Sebastian Gruschke, Project Head of Doon EIC and was attended by the entire team of Doon EIC staff. Dr. Alpa Gupta, Paediatrician, Himalayan Institute of Medical Sciences, also attended the clinic.

3. **Session with parents of thalassemic children to initiate formation of patient support organization. 20th November, Doon Hospital Conference Room.**

Dr. J.S. Arora, Secretary, National Thalassemia Welfare Society and Secretary, Federation of Indian Thalassemics and Dr Alok Ahuja, senior pathologist, Dehradun, addressed the parents of thalassemic children and encouraged them to come together to form a patient support organization which shall work together with doctors and administrators to ensure optimal care for thalassemics in the State.

4. **Meetings:**

An informal dinner meeting between officials of State Health administration and WHO panel members and faculty to discuss need and strategies for incorporating genomics into public health system in Uttarakhand was held on 22nd November from 8.00-10.pm.

Members representing the State Health department present at the meeting were- Shri Piyush Singh, Mission Director, NRHM (Uttarakhand), Dr. Anil Shah, Additional Director, DOMHFW, Dr. B.C. Pathak, CMS, Govt. Doon Hospital.

Prof Alan Bittles and Dr. Hilary Burton, Director, were the WHO panel members on Grand Challenges in genomics in Developing Countries along with the faculty Dr. Sujata Sinha, Dr. Reena Das along with Dr. Geeta Khanna, senior practicing Paediatrician, Dehradun.

The meeting ended on a general consensus to make strategic efforts in Uttarakhand to incorporate genomics in public health practices. Programmes on Thalassemia and Birth Defects addressing maternal and child health will be ideal to start with.

5. **Preparation of resource material**

**Educational Abstracts Book-**

The book contains abstracts and write-ups on most of the talks and in addition a few Write-ups and articles providing insights in the subjects.

A DVD set of recording of all talks delivered at the symposia has been prepared as Educational material.
6. Media Coverage
The Workshop and the CME programmes were well covered in the print and electronic media. (clippings attached)

Proceedings of the thalassemia symposia highlighting the public health aspects and basic concepts of disease recognition, management, population health and genetics, carrier detection and control strategies are compiled below as a resource material for the Department of Medical Health & Family Welfare, Uttarakhand.

Symposium on β-Thalassemia-20th November, 2011, Hotel Madhuban

The Symposium was inaugurated by Shri Piyush Singh, Mission Director, NRHM, Uttarakhand. In his brief address he expressed the hope “that the Workshop shall throw up some of the solutions which we can convert into policy "

Session I: Molecular genetics of β-thalassemia

Thalassemias and the global burden of disease
Professor Sir David Weatherall, Oxford Institute of Molecular Medicine Talk Delivered on his behalf by Dr. Nancy Olivieri

Key Points.

  Frequency of Birth Defects worldwide 7.9 million/yr causing 3.3 million deaths. 25% of diseases comprised 5 diseases-congenital heart defects (1 m births), neural tube defects (324000), Hemoglobinopathy (including Thalassemias (308000), Down’s Syndrome (217000) and G6PD deficiency (177000) with 60.2% in Low income countries and 33.5% in middle income countries. Thalassemia and Hemoglobinopathy comprise five of the commonest birth defects and commonest single gene disorder

- Development of control programmes required.

- Education and training of ‘core’ clinical, laboratory and nursing staff for adequate management of thalassemia is extremely important

- For prevention, education and screening of population and decision on means of control are important. Patient societies can play a significant role.

- Thalassemia in Asia characterized by – heterogeneity in presentation, presence of E-Beta thalassemia, environmental factors like Malaria and lack of recognition of thalassemia and lack of resources to tackle it;

- Ethical issues in genetics – Patriarchy, social customs, arranged marriages, consanguinity affect the prevalence of thalassemia.
• Governmental recognition of the problem and policy to provide support make the key difference to solving the problem
• Asian Thalassemia Network has been formed and has started making impact in the South east asian countries.

Deletional and triplicated α-chain allele prevalence and impact on the clinical assessment of α- and β-thalassaemia
Assoc. Prof. Sam Chong, National University, Singapore

Genomics of fetal hemoglobin and the clinical implications for β-thalassemia
Dr. Roshan Colah, ICMR National Institute of Immunohaematology, Mumbai, India

The above two talks focused on the factors that affect the severity of the disease. Alpha thalassemia or alpha genotype and Fetal Hemoglobin levels greatly affect the thalassemia phenotype. They are called the secondary genetic modifiers of the disease. Primary modifiers are the beta globin gene mutations themselves.

- Triplicated alpha genes are responsible for severe types of beta thalassemia while single gene deletions give rise to milder phenotype. Thus their recognition is important in predicting phenotypic severity.
- Alpha thalassemia is prevalent in Indian population and thus contributes greatly to phenotypic heterogeneity
- High Fetal hemoglobin level are associated with milder forms of the disease

(The talks focused on highly scientific content related to alpha genotypes genes or genetic determinants that lead to variation or increase in Fetal hemoglobin. These are important areas of research currently as their understanding can lead to better management or amelioration of the disease)

Population genetics of β-thalassemia in the Indian subcontinent
Dr. Sujata Sinha, Thalassemia Working Group, Varansi and Govt. Doon Hospital Dehradun, India

- Natural selection against Malaria is the major evolutionary force determining high frequency of thalassemia in malaria endemic regions further modified by population movements, founder effects, social customs, marriage practices.
- Mapping of gene frequencies at state level with incorporation of ethnic data with an understanding of underlying population subdivisions is required for effective control strategies.
- Systematic collection and generation of data at state level is required for effective care and control. It can be achieved through ThalInd the web based database system for thalassemia in India which is intended to support the national thalassemia network.

Session II: Clinical aspects: Diagnosis, Management & Control
Developing tool kits for improving care and prevention of hemoglobin disorders in low and middle income countries
Dr. Hilary Burton, Public Health Genomics Foundation, Cambridge, UK
May 2010 World Health Assembly resolution on birth defects has charged countries with the responsibility to address the huge public health burden associated with these conditions specially in low and middle income countries.

A health needs assessment based on basic demographic data (CBR/IMR/under 5 mortality rate), epidemiological information of the disease. (1.2/1000 births with pathological HB, 32500 births per year, 35-49 million carriers) is required, effectiveness and cost effectiveness of interventions and consideration of ethical, social and legal issues.

Engaging patients and patient organizations is important

Lack of epidemiologic data often comes in the way of convincing the governments but with a structured process lack of epidemiological data does not become a show stopper!

For beta thalassemia, the data may not be accurate but is enough to support that measures have to be taken at public health level.

Diagnosis of β-thalassemia – present protocols and newer technologies
Professor Reena Das, PGIMER, Chandigarh, India

- Carriers are reservoir of disease and thalassemia is one of the few genetic disorders where >95% carriers can be identified by simple blood tests.

- **Recommended blood tests for screening are:** Complete Blood Counts (CBC) with well calibrated counters followed by HPLC for HbA2 estimation. Elevated HbA2 is the diagnostic hallmark for diagnosis of a beta thalassemia carrier.

- **Naked Eye Single Tube Red Cell Osmotic Fragility Test (NESTROFT) can be used in settings with limited resources. It is positive in Iron Deficiency Anemia also**

- DNA based diagnostic work up to identify causative mutations is essential for prenatal diagnosis. Ideally the testing of the parents should be done before pregnancy.

- Two groups where screening for carriers is most cost effective is 1) Pregnant women during first Antenatal visit and 2) cascade or extended family screening i.e. relatives of the index case.

- Each state should have at least one apex genetic diagnostic laboratory.

- There are 8-10 centers in the country More training centers are required.

Effective Iron Chelation in Thalassemia
Prof Nancy Olivieri, Hemoglobinopathy Research Program, Toronto General Hospital, University of Toronto, Canada

- Iron is accumulated by increased iron absorption in Thalassemia major and by multiple transfusions.

- Patients receiving multiple blood transfusions are at risk of iron overload. One unit of PRBC delivers approx 200-250 mg of iron.
• Human body has no natural mechanism for excreting iron. Thus iron chelation therapy is necessary to prevent iron related tissue damage. Excess iron deposits in tissues and is toxic
• Complications- first and second decade- sexual maturity is affected-abnormal LH-Pituitary response- delayed menarche.
• Second and third decade: diabetes, liver fibrosis, cardiac failure, hypopituitarism
• Liver Iron Concentration is an adequate reflection of iron stores but is difficult to measure.
• Serum Ferritin is a very poor indicator of iron stores but is the only option in most cases especially in limited resources.
• Effective chelation therapy significantly improves patient survival. Desferal (Subcutaneous) has proven efficacy. Deferiprone (oral) has limited efficacy. Desferasirox (oral) shows promise of effective iron chelation

Monitoring growth and development in thalassemia
Dr. Sangeeta Kumar, Thalassemia Working Group, VRTWS, Varanasi, India

• Monitoring of growth and development is of paramount importance in management of Thalassemic child. Its a screening tool to diagnose complications at an early stage allowing early intervention to ensure optimal outcome.

• Thalassemics present with failure to thrive between 6 mths to 2-3 yrs. On treatment growth is good for initial 9-10 years then present with delay in growth and puberty with reduction in final height.

An update on the current status of stem cell therapy and gene therapy in the treatment of inherited hemoglobin disorders
Dr Anu Bashamboo, Paris, France

• Bone marrow transplant is effective and curative. But limited due to lack of matched donors.
• Gene therapy is in experimental stage.

During the Workshop session on “Role of Disease Registries in Community Genetics” on 24th November Professor Ken McElreavey delivered talk on DSD Registry and Dr. Sujata Sinha on ‘ThalInd-Developing a disease specific registry for India’. The talks generated great interest and enthusiasm. The concept of disease country specific disease registry ‘ThalInd’ for thalassemia in India was greatly appreciated.