Training Syllabus
LABORATORY SYLLABUS

Syllabus for Training in Inborn Errors of Metabolism for Scientists and Medically Qualified Laboratory Staff

This syllabus is intended as a guide. Whilst the training should be comprehensive, it is recognised that not all subjects can be covered in the same detail. Changes may also be necessary to meet local needs.

APPENDIX: INBORN ERRORS OF METABOLISM

L.1 KNOWLEDGE

L.1.1 Physiology and Biochemistry

Basic biochemistry.

Structure/function relationships of the cell

- membranes, nucleus, cytoplasm, Golgi apparatus, endoplasmic reticulum, mitochondria, lysosomes, peroxisomes.

Enzymes/proteins

- the nature of proteins and enzymes, structure/function relationships, cellular distribution, function, mechanisms of action, control of enzyme activity, synthesis, processing, targeting, turn-over, measurement principles.

Mechanisms of inheritance and an understanding of molecular genetics

- molecular basis of gene expression, gene to protein pathways, the genetic code, mutations in genes, transcription, translation, post transcriptional modification, post translational modifications, effects of mutations on proteins/enzymes, analysis of mutations, frequency of genetic diseases, heterozygote detection, principles of prenatal diagnosis, population genetics, inheritance patterns, basic linkage (RFLP) analysis, mitochondrial DNA.

The normal physiology and biochemistry, including changes during childhood, of:
- fluid and electrolyte balance.

- acid - base regulation
- intermediary metabolism including blood glucose and metabolic response to fasting, lactate, ammonia, aminoacids, organic acids and fatty acids.
- oxidative phosphorylation and the respiratory chain
- lipids and lipoproteins
- cholesterol and other sterols
- lysosome and peroxisome metabolism
- purines and pyrimidines
- porphyrins
- calcium metabolism
bilirubin
trace metal metabolism
relevant aspects of brain metabolism including neurotransmitters. The role of the blood brain barrier
enzyme biochemistry and tissue expression

L.1.2 Knowledge of Laboratory Procedures

- reagent preparation, storage and handling
- sample preparation, isolation, concentration, purification
- stability/storage of patient tissues and other specimens
- cell/organelle isolation
- bioassays
- spectrophotometry
- fluorimetry
- luminescence
- immunoassay
- radionuclides (including safety)
- electrophoresis and related techniques (e.g., isoelectric focusing)
- gas chromatography
- HPLC
- mass spectrometry
- cell culture
- protein chemistry
- DNA extraction and banking
- PCR, Southern, Northern, Western analysis
- ASO mutation detection (ARMS)
- mutation detection/screening

L.1.3 Knowledge of Paediatric Metabolic Disease

- The pathological and biochemical changes, clinical symptoms, investigations and management in metabolic disorders of these pathways and organelles, as listed in the appendix.
- Treatment measures. An understanding of the measures used for the treatment of metabolic disorders including:
  - dietary management, metabolic inhibitors, metabolic activators, plasma exchange/plasmapheresis, chelation, organ transplantation, enzyme replacement, gene therapy

L.1.4 Ethics

- Ethics of research in research
- Process of informed consent
- Issues governing the ethics and consent for trials

L.2. SKILLS

L.2.1 Investigative skills

Laboratory investigation of metabolic causes of:

- Acute encephalopathy
- Neurological disease to include retardation, regression, fits, movements disorder, myopathy, etc
- Liver disease including acute liver failure
- Hepatosplenomegaly
- Cardiomyopathy
- Eye disease
- Nutritional status and growth
- Dysmorphic patients
- Skeletal disorders
- Skin disorders
- Renal disorders including the Fanconi syndrome
- Muscle disease

L.2.2 Technical Skills

Investigations of inborn errors of metabolism. Experience and understanding of the principles and performance of methods and interpretation of results with emphasis on defects of:

- amino acid metabolism, (incl. ammonia)
organic acid metabolism
carbohydrate metabolism and glucose homeostasis (glucose, FFA, lactate, ketones)
fatty acid oxidation (carnitines)
fat metabolism
purines and pyrimidine metabolism
neurotransmitter and biogenic amine metabolism (CSF and other fluids)
vitamin and coenzyme metabolism
peroxisomal disorders (VLCFA, pristanate, phytanate, etc)
mitochondrial disorders
lysosomal disorders
glycosylation disorders:
hereditary disorders of electrolyte and trace element metabolism including calcium, phosphate and magnesium, forms of rickets and osteopenias.

Laboratory diagnostic experience. Interpretation of obtained data is an essential part of the diagnostic task.

Diagnosis at the metabolite level
- Chemical diagnosis of defects of intermediary metabolism, storage diseases and monitoring of treatment
- simple screening tests and TLC
- gas chromatography/mass spectrometry for organic acid analysis
- automated amino acid analysis
- specialist assays of intermediary metabolites and carnitine
- loading and function tests
  - fasting test for disorders of intermediary metabolism
  - allopurinol test
  - glucagon test
  - tests for co-factor responsive disorders (such as B12 test for MMA)
  - protein, amino acid, MCT, LCT, glucose loading

Diagnosis at the enzyme level
- Determination of enzyme activities
- tissue culture and enzyme assay for selected disorders
- white cell enzyme assays

Diagnosis at the DNA level
- protein and DNA analysis by blotting techniques, PCR and related methods.

Techniques of whole population neonatal screening for phenylketonuria, neonatal hypothyroidism and other disorders including interpretation of test results and involvement in follow-up testing.

Quality assurance:

- Quality assessment and accreditation according to accepted norms such as ISO 9000, CCKL guidelines and good laboratory practice.
- Standardisation, calibration and evaluation of analytical techniques.
- Technical performance schemes and proficiency testing.

Experience of patient care including:

- attendance at ward rounds in General Paediatrics and Neonatal Special Care
- attendance at relevant specialist clinics
- participation in clinical care of patients with inborn errors of metabolism as a consultant to clinical colleagues.

L.2.3 Management skills

- Understanding of management skills required for development and use of resources in the metabolic laboratory, including budget control, contracting, strategic planning and writing a business plan.
- Experience of day to day running of a paediatric metabolic laboratory service, occupational health and safety matters, chemical safety, radiation safety, physical safety, biohazards and related legislation
- Human resources management including staff selection, training and conflict resolution
  Structure and function of local, regional and national health provision organisation

L.2.4 Academic skills

- Critical evaluation of scientific and laboratory results from literature review and audit
  An understanding of the methods used to establish evidence based practice
- Manuscript preparation
- Oral presentation skills
**L.2.5 Teaching skills**

- Formal and informal teaching skills at undergraduate and postgraduate level
- Development of core teaching material to enable participation in teaching programmes on a regular basis
- Organisation of scientific teaching programmes

**L.2.6 Organisational skills**

- Routine departmental tasks including duty rotas, teaching programmes and postgraduate meetings

**L.2.7 Research skills**

- Design of scientific studies including medical statistics and grant application preparation
- Data organisation and presentation
- Computer literacy

**L.3. ATTITUDES**

**L.3.1 Professional**

- Appreciate the patient and families and non-specialist colleagues understanding of metabolic disease
- Working in partnership with others who care for the children such as multi disciplinarianteams and parent groups

**L.3.2 Communication**

- Effective communication and appropriate approach to clinical, nursing and supplementary health professionals, general medical and university colleagues, pathology staff and hospital managers.

**L.3.3 Education**

- Commitment to continuing self-education and to teaching others

**L.3.4 Support**

- Understanding and positive approach to the supervision of junior laboratory staff
- Recognition of and coping with stress in self and others

**L.3.5 Academic/Research**

- Innovative attitude to scientific problems
- Supportive to / active in research
- Collaborative attitude to local, national and international colleagues

**L.3.6 Managerial**

- Interest in the overall organisation of departmental activities
- Understanding approach to local management structure
- Constructive attitude to the process of decision making
- Acceptance of shared responsibility for the use of resources
- Ability to respond effectively to laboratory related complaints

**APPENDIX**

**INBORN ERRORS OF METABOLISM**

- Disorders of aminoacid and peptide metabolism
  - Phenylketonuria including the management in pregnancy, homocystinuria, MSUD, etc
- Disorders of organic acid metabolism (propionic acidaemia,methylmalonic acidaemia,etc)
- Hyperammonaemia and urea cycle disorders
- Disorders of carbohydrate metabolism (Glycogen storage disease, galactosaemia, fructosaemia,etc)
- Disorders of fatty acid oxidation (MCAD,LCHAD, etc)
- Disorders of ketone body metabolism
- Lysosomal storage disorders (MPS, etc)
- Disorders of lipoproteins and lipid metabolism
- Peroxisomal disorders (Adrenoleucodystrophy, Zellweger’s syndrome, etc) Disorders of purine and pyrimidine metabolism
- Disorders of calcium metabolism
- Disorders of metal metabolism (Wilson’s disease, Menkes syndrome, etc) Congenital lactic acidoses and metabolic myopathies
- Porphyrias
- Disorders of cholesterol, sterol and bile acid metabolism
- Disorders of vitamin metabolism (biotin, cobalamin, etc)
- Defects of membrane transport (lysinuric protein intolerance, etc)
- Defects of glycosylation
- Defects of connective tissue