simd workshop: thursday, march 9

Biochemical Genetics: From Mechanisms to Diagnosis and Management of Genetic Disease

Congenital Disorders of Glycosylation (CDG): Have you seen them? H. Freeze. The Burnham Institute, La Jolla CA.

Four new Congenital Disorders of Glycosylation (CDG) were identified last year. Patients have a broad range of symptoms: variable psychomotor and mental retardation, dysmorphia, multiple organ complications, coagulopathy, neuropathy, and hypoglycemia. Two decades of clinical experience in Northern Europe has netted most of the ~300 known patients. The 40 CDG patients identified in North America in the last 5 years are probably only the "tip of the iceberg". About 1% of the genome involves the biosynthesis and/or recognition of glycosylated molecules, and mutations in them are likely to have serious consequences. Currently, CDG includes 7 specific defects, mostly affecting the biosynthesis of N-linked oligosaccharides found on essentially all cell surface and secreted proteins. These defects include lesions in: interconversion of monosaccharide precursors, their transport into the Golgi apparatus, specific glycosyltransferases for precursor oligosaccharide synthesis and others that remodel protein-bound sugar chains.

Most known patients with severe psychomotor and mental retardation are deficient in phosphomannomutase (*PMM2*, CDG Ia). In contrast, phosphomannose isomerase deficient patients (*PMI1*, CDG Ib) have completely normal development and neurologic features, but show gastrointestinal disorders, hepatic fibrosis, coagulopathy, and hypoglycemia. Mannose therapy is effective for these patients. Other patients with a glucosyl transferase deficiency (*ALG6*, CDG Ic) make non-glucosylated lipid precursor oligosaccharides, and have milder symptoms that resemble CDG Ia. In contrast, patients with either of two defects (*ALG3*, CDG Id; and *DPM1*, CDG Ie) that compromise the same step in precursor sugar chain assembly are more severely retarded than CDGIa patients. A deficiency in GDP-fucose transport into the Golgi apparatus causes mental retardation, leukocytosis, recurrent severe infections and fever. Oral fucose therapy relieves all of these symptoms and provides a medically stable base for improved motor and mental development.

Increased awareness of and screening for CDG in North America will identify more patients with known defects and may unveil entirely new disorders. Mentally retarded adults and children with developmental delay who lack a definitive diagnosis should be screened for CDG. In most cases, isoelectric focusing analysis of serum transferrin is pathognomic for altered glycosylation. Standard biochemical and/or genetic analysis can pinpoint known defects and new causes of CDG. Recognizing the many faces of CDG together with frequent, broad-based screening is essential since some patients can benefit from simple therapies. (Supported by RO1DK55615 and March of Dimes 1-FY99-205.)

The Impact of Recombinant DNA on Inborn Errors of Metabolism. Stephen Cederbaum. Departments of Psychiatry and Pediatrics, UCLA, Los Angeles.

The revolution in DNA technology has altered completely the understanding of genetic disease and the practice of our profession. The effect has been particularly profound on those disorders and processes about which our understanding had previously been most limited. In contrast, the enzymatic defect for most known inborn errors had already been elucidated and our understanding of the pathophysiology and the approach to treatment has been based on the level and flux of metabolites in the body. This relatively advanced state of their biology allowed the genes for many inborn errors to be among those cloned first in the DNA era. These cloned genes proved to be valuable tools in the research enterprise and elucidated the mechanisms of mutation, the normal regulation of gene expression and much about the demographics and anthropology of populations as demonstrated by the flow of gene mutations. Mutation hunting became increasingly easy with the constant technological progress. Because of this, genotype-phenotype correlation became a mantra. These correlations often proved both obvious and unhelpful clinically. Increasingly, genotype analysis is being restricted to confirmation of the diagnosis and for prenatal diagnosis. In the future, DNA diagnosis may be most useful in those disorders, such as those in the electron transport part chain in which biochemical diagnosis has proven to be the least satisfactory and specific. Gene therapy is the holy grail toward which modest progress is continually made.
These exciting and sometimes controversial observations will be discussed in this presentation.