Early detection, health promotion and prevention: From preconception to early childhood

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Goals

- Define the issues
- Where were we?
  - Historical perspective
- Where are we now?
  - How far have we come
- Where can we go?
  - Future Challenges
Impact of genetic disease in pediatrics

- Congenital anomalies (a.k.a. birth defects)
- Developmental delay, mental retardation
- Autism
- Disorders of growth
- Any combination of the above
- Common pediatric disease: asthma, diabetes, inflammatory bowel disease, etc.
Approximately 3-4% of all live born children have a major birth defect
- Approximately 120,000 babies born each year in U.S.
- Hospital costs alone for all birth defects at all ages = $2.6 billion (MofDimes2007): does not include physician and outpt costs

The leading cause of infant deaths:
- 20-30% of all infant deaths and 30-50% of all deaths occurring after the newborn period attributed to congenital anomalies

Approximately 5-fold relative increase in death rate for children with a reportable birth defect, including chromosome abnormalities
Mental Retardation
(adapted from Chelly J, et al. EJHG, June, 2006)

- Reported estimates:
  - 0.3-0.5% moderate and severe (IQ<50)
  - 1-3% mild (IQ 50-70)
  - 30% excess males>females

- Causes:
  - Environmental
  - Chromosomal
  - Monogenic disorders (1177 Mendelian traits in OMIM; 282 MR genes identified)

- Precise cause identified in
  - 50% moderate to severe MR
  - Less often in mild MR
Autism

- **Prevalence**
  - 0.1-0.3% narrow phenotype
  - 0.3-0.6% broader ASDs

- **Strong genetic component**
  - British twin study: 60-92% concordance in monozygotic twins vs. 0-10% dizygotic twins (Bailey A, Psychol Med, 1995)

- 10%: “syndromic”: Fragile X, Rett syndrome, Tuberous Sclerosis, Neurofibromatosis 1

- Multicenter autism studies
Prior to 1960’s

- Diagnosis
  - Mainly by physical examination and developmental evaluation

- Treatment
  - Symptomatic, surgical, or not possible

- Etiology unknown
1960’s-1970’s

- Improved diagnostic capability
  - Chromosome testing: postnatal and prenatal
  - Metabolic testing: PKU and other conditions
- Continued delineation of birth defects, genetic conditions
- Special education programs- children with developmental disabilities now in educational system
- Newborn screening
  - Mandated and funded by state legislatures
  - PKU and hypothyroidism
  - Presymptomatic therapy for prevention of mental retardation
  - Successful public health initiative for treatment of conditions associated with mental retardation/developmental disabilities
- Underlying basis of many conditions still unknown
1980’s-2000: era of molecular genetics

- Identification of genes associated with conditions that cause birth defects, genetic disease, developmental disorders
- Improved diagnostic testing with confirmation of diagnosis, presymptomatic testing, and carrier testing
- Improved understanding of gene function and gene/environmental interactions
  - A prerequisite to development of therapy based on etiology of the condition
Preconception

- Folic acid supplementation for prevention of spina bifida, anencephaly
  - Up to 70% prevented with 400 micrograms folic acid daily
- Improved maternal nutrition, treatment of underlying medical conditions (hypertension, epilepsy, etc.)
- Identification of causes for prematurity and recurrent pregnancy loss and early treatment
- Family history: define possible increased risk for birth defects/developmental disabilities
  - Helps guide pregnancy surveillance, identifies women at increased risk for pregnancy complications, helps guide delivery planning
- Preimplantation diagnosis
Pregnancy

- Family history review: medical, developmental, ethnicity
  - Helps define risk and pregnancy surveillance
- Maternal serum screening
- Prenatal testing: chorionic villus testing and amniocentesis (often reassuring)
  - Genetic conditions, infections, anemia and other blood disorders
  - Imaging: ultrasound and MRI
- Expectant medical management
Birth and newborn period

- Identification of birth defects and abnormalities of fetal growth
- Identification of serious metabolic disorders that present in first week of life that can cause significant disability and may be fatal if not treated promptly
- Expanded newborn screening
  - 6-29 conditions: metabolic, endocrine, infectious, sickle cell disease, cystic fibrosis
  - Differs by state
  - Funding generally available for initial screening, but not confirmation of diagnosis, treatment, or follow-up
Early childhood

- **Diagnostic**
  - Further identification of medical, growth, and developmental abnormalities
  - Often requires specialized genetic testing not easily accessible by primary care physicians and often not covered by insurance - potentially cause inequity in medical care based on ability to pay

- **Treatment**
  - Often requires coordination of care between multiple specialists and primary care physician
  - Partnership between the medical team, school system/EIP, and home
Molecularly based therapies

- Clinical trials have begun
  - Down syndrome
  - Neurofibromatosis, type 1
  - Fragile X syndrome
  - Tuberous sclerosis
  - Angelman and Prader-Willi syndromes
  - Muscular dystrophies
Future challenges

- Diagnostic testing: continue to improve and increase ease of testing and access
  - Presymptomatic testing for common childhood conditions (diabetes, asthma, obesity) with anticipatory lifestyle adaptations
- Newborn screening: standardize testing in the U.S. and fund diagnosis, treatment, and follow-up adequately
- Educate: primary care physicians, non-genetic specialists, families, schools, support organizations
Future challenges

- **Care:** “It takes a team”
  - Very time and labor-intensive and not adequately funded or covered by insurance

- Develop national patient registries in anticipation of new clinical trials

- **Cost**
  - Diagnosis
  - Treatment
  - School programs
These are our children and this has relevance for us all

- An extraordinary time in maternal and child health and genetics
- With increased knowledge comes opportunity and also obligation
- Our children are relying on us to make the right decisions