workshop c1: saturday, march 11

Prenatal Dysmorphology

Skeletal abnormalities/short bones. D. Krakow[1,2,3], R.S. Lachman[1,2], and D.L. Rimoin[1,2]. [1]Research Institute and [2]Departments of Obstetrics and Gynecology and [3]Pediatrics, Cedars-Sinai Medical Center, UCLA School of Medicine, Los Angeles California.

With increasing utilization and improved resolution capabilities of ultrasound, there has been an increase in the recognition of prenatal onset skeletal dysplasias and dysostoses. The skeletal dysplasias/dysostoses are a genetically heterogenous group of disorders, many of which present in the prenatal period. Most of these cases arise in families with no family history of skeletal dysplasias. When evaluating a fetus with short "long bones" the difficulty arises in determining a precise diagnosis by ultrasound. Through the International Skeletal Dysplasia Registry (ISDR), we have ascertained over 800 cases of prenatal/perinatal cases of skeletal dysplasias. In a retrospective review, we correlated the accuracy of the referring versus the ISDR final diagnosis. We found that the correct diagnosis was made in approximately 35% of the referred cases. Aside from the difficulty of assigning precise diagnoses within the group of skeletal dysplasias, many of the referred cases represented early IUGR or genetic syndromes. In this retrospective review, the most commonly seen prenatal-onset skeletal dysplasias were osteogenesis imperfecta type II, achondrogenesis and thanatophoric dysplasia. The ISDR has now prospectively analyzed ultrasound images in almost 90 prenatal cases to determine if our correct prenatal diagnoses rate. A correct diagnosis was established in almost 75% of the cases. We found that the criteria we employed which aided in the diagnosis included: determining lethality, size, shape and mineralization of the long bones, location of the bony alterations, evaluation of the vertebral bodies and pelvis, facial features and other organ system abnormalities. We did not find that an absolute long bone measurement correlated with a specific skeletal dysplasia diagnosis. While we believe that for counseling purposes a final diagnosis should be made based on clinical findings, radiographs, and histomorphology, obtaining an accurate prenatal differential diagnosis can be most helpful. It allows families to make choices based on more accurate information, and it aides in choosing appropriate diagnostic testing for both clinical use and research purposes.

Prenatal Dysmorphology – Additional Laboratory Evaluations. S. Schwartz. Center for Human Genetics, Department of Genetics, Case Western Reserve University and University Hospitals of Cleveland, OH

The vast majority of prenatal diagnosis studies are undertaken to rule out a chromosomal abnormality. Sometimes, however, abnormal ultrasound findings or other indications might suggest a condition that is not detectable cytogenetically. Due to increasing technology, many of these conditions can be detected using additional, more specialized testing. Two examples of the more common additional tests used in prenatal diagnosis are FISH to detect subtle chromosomal changes not detectable by routine cytogenetics and molecular (DNA) testing to test for specific genetic conditions.

Heart defects detected by ultrasound are probably the most frequent indication for FISH studies prenatally. Approximately 29% of sporadic nonsyndromic conotruncal cardiac defects have been determined to have a deletion in 22q11, and detected by FISH with the TUPLE1 probe. Although this is the most common inherited cause of a congenital heart defect, other causes have been detected, including deletions leading to Williams, Miller-Dieker and Smith-Magenis syndromes. The 22q11 deletion has been seen associated with polyhydramnios, as has the deletion seen with Miller-Dieker syndrome. There are numerous prenatal indications for the use of molecular testing for specific conditions. Uniparental disomy (UPD) for certain chromosomes is commonly performed in a variety of situations. Intrauterine growth retardation (IUGR) could be the result of UPD 14. Omphaloceles are associated with Beckwith-Wiedemann syndrome, sometimes caused by UPD 11. UPD testing is also warranted in cases of a mosaic trisomy found by CVS if followed by a normal karyotype by amniocentesis, or when certain translocations are found by amniocentesis or CVS. When maternal serum screening reveals very low levels of unconjugated estriol (uE3) testing is often performed for Smith-Lemli-Opitz (SLO) syndrome using molecular analysis and steroid sulfatase (STS) deficiency utilizing FISH. Ambiguous genitalia can also suggest molecular testing to rule out such conditions as SLO, congenital adrenal hypoplasia, BWS, as well as possible alterations in SRY or SOX9. Another common ultrasound finding is echogenic bowel and, although often associated with Trisomy 21, if a normal karyotype is found, molecular testing for Cystic Fibrosis is warranted.

The detection of a normal karyotype might only be the beginning of a search for a cause of a prenatally detected abnormality and there are a variety of additional tests that can be done. During the course of this talk I will attempt to review the different methodologies available for further testing and the efficacy and appropriateness of the various tests.

Prenatal dysmorphology: Evaluation and management. B.D. Hall. Univ. of Kentucky, Lexington, KY.

The diagnosis of prenatal dysmorphology can be divided into two functional categories. The first category is indirect prebirth evaluation (IPE) utilizing ultrasound, amniocentesis, CVS, fetal echocardiography, and maternal/fetal gestational history. The second category is direct postbirth evaluation (DPE) which includes physical exam, photographs, and laboratory studies such as chromosomes, metabolic, molecular, skeletal x-rays, ultrasounds/CT-MRI scans, biopsy, and autopsy. Diagnostic skills have improved in IPE and DPE relative to detecting anomalies, but correctly diagnosing the specific etiological syndrome still leaves a lot to be desired. The most experienced prenatal ultrasonographers/radiologists have no more than an 80% accuracy rate for known skeletal dysplasias while accurate prognostication is no better than 60-70%. Our diagnostic problems in both IPE and DPE are not surprising since no diagnosis is forthcoming in 30-50% of term liveborn infants with multiple anomalies. In DPE the clinical geneticist/dysmorphologist role as the diagnostician is more effective while his/her role in IPE is mostly advisory in the sense of interpreting the overall meaning of what was seen and helping to formulate a differential diagnosis. Examples of diagnostic problems for IPE and DPE will be presented.