INDICATIONS

IN ADULTS  Various aneuploidies of the sex chromosomes are the most common chromosome abnormalities encountered in autopsies of adults. The Turner (usually 45,X but mosaicism is common) and Klinefelter (47,XY) syndromes are two examples (1). Deletions or unbalanced translocations and inversions are rarely seen in autopsies of adults because patients with these abnormalities seldom survive into adulthood. Approximately 1/500 adults carries a genetically balanced abnormality of chromosome structure. These balanced chromosome anomalies may affect the reproductive history of an individual, but rarely affect the phenotype (2). Some adults have sporadic chromosome changes as part of a chromosome breakage syndrome such as Fanconi anemia (3), ataxia-telangiectasia (4), Bloom syndromes (5), and others.

Chromosome analysis may be done at autopsy to eliminate a specific clinical diagnosis. Thus, establishing that the karyotype of the deceased is normal can be useful. Chromosome studies may be done at autopsy to establish the karyotype of specific tissues when chromosome mosaicism is suspected (6). Cytogenetic studies may be useful in the same setting to help resolve issues of malignant disorders. Chromosome studies can help establish the presence of an abnormal clone, classify neoplastic disorders, assess disease progression, and detect the emergence of therapy-related neoplasms. More than 200 different chromosome abnormalities have been strongly associated with specific malignant disorders (7-9). In these cases, it is important that the tissue(s) selected for chromosome studies be derived from the neoplasm in question. Sometimes autopsy chromosome studies are done as part of research protocols.

IN NEONATES, INFANTS, AND CHILDREN  Chromosome analysis should be done when malformations correspond to well-established chromosome syndromes, especially when the diagnosis is doubtful. The syndromes associated with aneuploidy are the most common and easily recognized at autopsy. Three of the more frequently encountered conditions in autopsies of newborns are the Down (trisomy 21) (10), Patau (trisomy 13), and Edwards (trisomy 18) syndrome (11). Presence of ambiguous genitalia is also a common indication of a genetic problem and may be a clue to gonadal dysgenesis, true hermaphroditism, and other abnormalities or gene mutations involving the sex chromosomes (1,12).

As a group, deletions, translocations, and inversions are the most common chromosome abnormalities in newborns; they also are the most difficult to recognize clinically. Anomalies of chromosome structure can involve more than one chromosome and they can involve any part of any chromosome. Structural anomalies in neonates are often private mutations (i.e., found only in the deceased or some of their blood relatives). For this reason, genetic imbalances resulting from structural anomalies are inconsistent among individuals and the clinical presentation is generally nonspecific. Because structural anomalies usually are associated with multiple congenital anomalies, postmortem chromosome analysis may be done in severely malformed neonates. Three rare syndromes that involve abnormalities of chromosome structure and may be encountered at autopsy of neonates are Cri du Chat (13), Wolf-Hirschhorn (14), and Langer-Giedion syndromes (15), but many others are known.

It is particularly important to do chromosome studies of a neonate when the family has a history of frequent spontaneous abortions, as the results can be useful in genetic counseling of living relatives (2). Structural abnormalities of chromosomes can be familial when one of the parents is a balanced carrier. When this occurs, the parents of the deceased and other relatives may be at considerable risk to produce abnormal offspring and this information is important in family planning and the application of prenatal genetic testing with future pregnancies (2).

IN SPONTANEOUS ABORTIONS  Chromosome analyses on spontaneous abortuses can be an emotional benefit to patients, both in having the cause of death explained or in ruling out an identifiable inherited abnormality. Chromosome studies of spontaneous abortions may be done to define the cause of fetal demise, collect information on familial chromosome anomalies, and identify molar pregnancies (16,17).

From 1991 to 1993, we studied 1,502 spontaneous abortuses; some were associated with recognizable fetal tissue but others did not contain discernible fetal tissue. We successfully completed chromosome studies on 1,164 of these specimens: 414 (36%) had a chromosome abnormality. Chromosome anomalies in abortuses with identifiable tissue included any
kind of autosomal trisomy (47%), triploidy (17%), and 45,X (Turner syndrome, 16%). The remaining chromosome anomalies included unbalanced translocations, aneuploidy of multiple chromosomes, mosaicism, tetraploidy, and balanced translocations. These results are consistent with other investigations of spontaneous abortions (16).

Of the 33 abnormal spontaneous abortuses without recognizable fetal tissue, we found 5 that had triploid karyotypes. This karyotype is often associated with partial hydatidiform moles. In the remaining 28 spontaneous abortuses, 6 carried anomalies which could have been familial. Familial chromosome anomalies would include any unbalanced or balanced structural abnormality. In these cases, family members and subsequent pregnancies should be studied because of the risk that a similar chromosome abnormality will recur. Chromosome abnormalities identified in the remaining cases included trisomies and monosomies, and were the probable cause of fetal demise.

It is possible to calculate the statistical probability that future pregnancies of a couple will involve a chromosome abnormality based on the karyotype of the spontaneous abortus and the parents. In general, if the spontaneous abortus has an abnormal karyotype and the parents have a normal karyotype, the risk for a future abortion due to chromosome abnormalities is about 1%. Prenatal studies are often recommended in subsequent pregnancies when the spontaneous abortus has a trisomy or monosomy that has been associated with a classic syndrome.

Complete and partial hydatidiform moles are genetically aberrant conceptuses that have the potential to develop into malignancies (17). Usually, complete moles have a diploid karyotype with only paternal chromosomes. Most partial moles have 69 chromosomes (triploidy), including 23 of maternal origin and 46 of paternal origin. Differentiation between complete and partial moles is important, as the two entities have different potentials for clinical persistence, malignant transformation, recurrence, and presence of a fetus. The complete mole consists of abnormal, cystic choriocarcin villi with no fetal tissue present. Retained fragments after an incomplete spontaneous abortion may evolve into choriocarcinoma. The risk of recurrence is about 1%. The partial mole also has cystic choriocarcin villi, but a fetus is always present initially. The fetal tissue may or may not survive up to the time of diagnosis. The recurrence risk for triploid partial hydatidiform moles is unknown. Subsequent pregnancies should be studied with either finding.

Any structural chromosome abnormality found in a spontaneous abortion requires chromosome studies on the parents to determine whether the abnormality is familial or a de novo mutation (2). When the spontaneous abortus has a duplication or deletion not found in the parent, the recurrence risk is <0.5%. Thus, during subsequent pregnancies, studies are not strongly indicated. When the spontaneous abortus has an unbalanced inversion, and one parent is the carrier, recurrence risk in subsequent pregnancies ranges from 0.5% with a paracentric inversion to 5–10% with a pericentric inversion. In the latter case, prenatal studies are indicated for all future pregnancies. If the spontaneous abortion has a translocation, either balanced or unbalanced, prenatal studies would be indicated only if one of the parents carries the balanced translocation.

Approximately 80% of spontaneous abortions without recognizable fetal tissue in our study were chromosomally normal females. We suspect many of these studies were done on maternal cells. This potential for maternal contamination points out the importance of attempting to collect specimens that contain fetal tissues. When unidentifiable tissue is all that can be collected, the cytogenetic laboratory should attempt to further isolate embryonic or extra-embryonic tissue using a dissecting microscope. The rationale to do chromosome analyses on unidentified tissue is not always clear. In our study, only 11 of the 33 products of conception had chromosome anomalies, which may have explained the fetal demise or may have led to useful chromosome studies on the parents.

COSTS

Since cytogenetic studies are expensive, they should be applied to autopsies in a frugal manner, but they certainly are indicated if chromosome analysis is the only means to obtain pertinent medical information. The cost of chromosome analysis varies among cytogenetic laboratories and ranges from a few hundred dollars to over $1,000, depending on the type of tissue studied.

SPECIMEN COLLECTION, TRANSPORT, AND PROCESSING

Most cytogenetic studies require living tissues to obtain successful cell culture for chromosome studies (18). For this reason, it is important to use sterile procedures to collect specimens. Whole blood and other tissues have been cultured successfully from mailed-in specimens for clinical purposes. Thus, it is not necessary for the autopsy pathologist to have ready access to a cytogenetic laboratory. Since living cells are involved, it is important to transport specimens to the cytogenetic laboratory within 1 or 2 d. Moreover, exposure of the specimen to temperature extremes (freezing or >30°C) can prevent a successful chromosome study. The specimens should not be frozen or packed on ice for delivery.

The cytogenetic laboratory is often used to culture cells from autopsies with evidence of a molecular or biochemical genetic disorder. In these cases, it is important that the prosector informs the cytogenetic laboratory about the need for molecular or biochemical testing. This will ensure that the cytogenetic laboratory processes the specimen correctly and forwards the cultured cells to another laboratory for appropriate genetic or biochemical testing.

The following procedures may be used to prepare and mail specimens collected at autopsy for cytogenetic studies. When other tissues are needed, the collection procedure and mode of transportation should be discussed with personnel from the cytogenetic laboratory to enhance chances of a successful result.

**BLOOD** Blood is generally the preferred specimen for chromosome analysis when a congenital disorder is suspected and it is possible to collect an appropriate specimen. Obtain 5–10 mL of unclotted, uncontaminated blood in a sterile fashion. Mix the blood sample with 1 mL of sodium heparin in a small sterile vial and send it to the cytogenetic laboratory.

In the cytogenetic laboratory, the cells are incubated for 66–72h at 37°C with a T-cell mitogen such as phytohemagglutinin...