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“Donating our bodies to science”: A discussion about autopsy and organ donation in Turner syndrome

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Abstract

At the Third Turner Resource Network Symposium, a working group presented the results of collaborative discussions about the importance of autopsy in Turner syndrome (TS). Considerable gaps in understanding the causes of death in TS can only be closed by more frequent death investigations and autopsies. The presentation included an overview of autopsy methods, strategies for utilizing autopsy, and biobanking to address research questions about TS, and the role of palliative care in the context of autopsy. This review highlights strategies to promote autopsy and tissue donation, culminating with an action plan to increase autopsy rates in the TS community.

Keywords

autopsy; molecular autopsy; palliative care; postmortem examination; sex chromosome abnormality syndrome; Turner syndrome

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CONFLICT OF INTEREST

None.

1 | INTRODUCTION

The Third Turner Resource Network (TRN) Symposium convened in Arlington, Virginia on July 15–17, 2018 to discuss the molecular mechanisms, medical treatment challenges, and epidemiology of health problems that affect individuals who live with Turner syndrome (TS). Unlike the 2016 International Turner Syndrome Meeting, which was intended to revise clinical practice guidelines, the primary purpose of the 2018 symposium was to develop an interdisciplinary strategy to advance TS-related science. The TRN Symposium was coordinated with the Turner Syndrome Society of the United States (TSSUS) Annual Conference, so that individuals with TS, families and advocates were available to attend as engaged contributors.

After preliminary collaborative discussions led by Dr. Angela Lin, the coauthors of this review took part in one of several breakout sessions at the TRN Symposium. They addressed the role of autopsy, a question that originated from individuals and families with TS. This review summarizing that session will (a) inform clinicians and researchers about the importance of autopsy in TS, (b) discuss the role of autopsy to obtain data about causes of death in TS, and (c) raise awareness about the value of organ and tissue donation for research in the TS community. The primary aim of these efforts is to increase autopsy rates among people with TS.

The session began with an introduction by Barbara Flink, who inspired the conversations that led to this session. Dr. Melisa Crenshaw presented a general overview of autopsies, including indications to request an autopsy, approaches to end-of-life discussions, and some technical aspects of autopsy. Dr. Siddharth Prakash and Dr. Adrianna San Roman then presented strategies for utilizing autopsy to address research questions about TS that require innovative methods for pathologic and molecular analysis of tissues. In these analyses, the working group considered costs, availability, best practices, barriers, and potential roles of institutions compared with commercial facilities, and a comparison of conventional autopsies to noninvasive or minimally invasive autopsy techniques. Dr Kimberly Earle concluded the session with an evaluation of important end-of-life issues involving autopsy and a discussion of the potential roles of palliative providers in end-of-life decision-making. These issues are frequently associated with death and life-threatening illness, but may also arise during discussions throughout a person's life. When initiated by a thoughtful provider as part of health maintenance, conversations about autopsy and organ or tissue donation may become an important element of wellness care.

2 | PERSONAL INSIGHTS

Barbara Flink, a 63-year-old woman with TS and long-time TSSUS activist, is a passionate advocate for autopsy. Inspired by frank conversations with her family, she felt compelled to begin planning to donate her own body for TS-related research. She was disappointed to realize that there was no facile mechanism to prepare for autopsy and no easy path to research. Prolonged advocacy by Ms. Flink and other women with Turner syndrome, as well as their families and providers, were the major influence that led to the creation of this working group on autopsy. Clinicians know that many more TS families contend with

painful, but important private discussions about autopsy and tissue donation but do not verbalize their feelings. Contemplating issues surrounding autopsy may be overwhelming to TS families who face crises such as a neonatal death or a new diagnosis.

3 | DEFINITION AND BACKGROUND

An autopsy is a set of techniques that are used to determine the cause of death. The term “molecular autopsy” is intended to highlight a set of specialized sample preparation methods and molecular assays that are not typically used in comprehensive death investigations (Ackerman, 2005). The principal difference between a conventional autopsy and a molecular autopsy is the addition of molecular techniques to measure DNA, RNA, or protein expression or epigenetic modifications in order to determine disease mechanisms.

Review of the literature revealed surprisingly few publications about the frequency and circumstances of autopsies in TS. Institutions with centralized medical databases have reported limited observations about causes of death in TS, but have not systematically analyzed autopsy data. Statistics reported by TS clinics are likely to underestimate mortality rates because they exclude many adults with TS who do not receive regular follow up care. Congenital heart defects, hypertension, stroke, liver disease, and cancer are all prevalent in TS, but specific causes of death remain largely unknown. Thus, there are considerable gaps in our understanding about causes of death in TS that can only be closed by more complete death investigations and increased autopsy rates.

The consensus of the working group is that all families should be provided with an opportunity to request a complete autopsy after the death of an individual with TS. If the death is definitely explained by a preexisting defect, such as a severe congenital heart defect or aortic aneurysm, then a postmortem examination may not be prioritized or routinely performed. However, even if the cause of death is clear, anyone has the right to request the clinical care team or pathologist for an autopsy. It is usually the responsibility of the attending physician to make a formal request for autopsy and to obtain informed consent. The family then proceeds to make final arrangements with a funeral home in coordination with the pathology department. If the pathologist or coroner is not helpful or supportive, families should contact the TSSUS Professional Advisory Board, who will assist in advocating for autopsy. If the end of life is sudden and unexplained, then an autopsy is usually performed as part of the regular protocol for death investigation. The chief medical examiner, or coroner, always becomes involved if the death involves a person not being treated by a physician for a known medical condition, if the death occurs less than 24 hr after hospital admission, or if the death occurs during a medical procedure. Pathologists may travel to outlying hospitals to perform the autopsy, or hospitals may refer cases to tertiary care centers where the autopsy may be performed by clinicians with specialized expertise in TS.

When a person wishes to donate her body as an altruistic gift for research, the decision should be made as early as possible, before the crisis of a sudden death or a prolonged illness. For research purposes, a rapid autopsy within 5 hr of death can provide tissues of sufficient quality for RNA studies or creation of patient-derived cell lines.

The hallmark of autopsy is the gross examination and histologic analysis of tissues. Autopsies can provide valuable opportunities to investigate tissues that may not be accessible in life, but are commonly affected in TS, including cord blood, CSF, liver, lung, bone marrow, skin, heart, brain, inner ear, aorta, intestine, uterus, and kidneys. In TS, cardiovascular disease is a focal point of autopsy, because CV conditions are the most frequent cause of death in adult women with TS (Power, Langlois, & Byard, 2014). The anatomic and functional characteristics of bicuspid aortic valves, which are found in one-third of cases, have implications for the prognosis of cardiac and vascular disease. Other congenital defects, such as thoracic aortic aneurysms, coarctation, ventricular septal defects, partial anomalous pulmonary venous return, and persistent left superior vena cava, are also common in TS and should be documented. Autopsies can determine the proximal causes of death from coronary artery disease or aortic dissections, including complications such as myocardial infarction, stroke or visceral malperfusion. In addition, examination of other tissues, such as thyroid (autoimmune disease) and gonad (gonadoblastoma) can identify previously unsuspected causes of death that are relatively frequent in or specific to TS.

Ear and hearing problems are a major cause of morbidity in TS, but are incompletely understood because of restricted access to inner ear tissues and inadequate animal models (Fish et al., 2009; Hultcrantz, Stenberg, Fransson, & Canlon, 2000; Probst, Cooper, Cheung, & Justice, 2008). Rapid specimen retrieval and fixation, within 10 hr postmortem, is essential for preservation of ear structures (Liu, Schrott-Fischer, Glueckert, Benav, & Rask-Andersen, 2017; Stenberg et al., 2001). TRN researchers will share their expertise with biobanks and pathologists to develop standardized protocols for inner ear tissue retrieval, providing a new resource to investigate the pathophysiology of hearing loss in TS.

Autopsy may also provide valuable and unique opportunities to address other questions related to TS. Many girls and women with TS do not complete surveillance imaging during their lifetimes due to cost and difficulties in accessing care. Some congenital cardiovascular defects, such as atrial septal defects and anomalous pulmonary veins, may be missed on routine imaging. Can we determine the true prevalence and severity of these problems? Prospective collection of various tissue types in women with TS is currently limited to easily obtainable tissues, like blood and skin, or the rare surgical specimen, which is insufficient for the breadth of biological samples required to understand the molecular biology underlying TS phenotypes. Can we understand how TS genotypes are linked to organ and tissue phenotypes using gene expression or epigenetic assays (Trolle et al., 2016)? Many TS phenotypes are caused by developmental defects that occur during embryogenesis. Researchers are unable to access tissues at the appropriate timepoints to study why these defects occur. It is still difficult to harvest sufficient numbers of cells from a living donor to create stem cell lines. Creating induced pluripotent stem (iPS) cell lines from adult tissues like skin and blood can allow researchers to recapitulate changes that occur during development and study why development of some tissues does not occur normally in TS (Ardhanareeswaran, Mariani, Coppola, Abyzov, & Vaccarino, 2017).

Autopsy also provides important resources to investigate somatic mosaicism, a frequent modifier of TS phenotypes that may influence susceptibility to TS-related conditions. Mosaicism complicates efforts to correlate peripheral blood genotypes to phenotypes and

can really only be assessed completely by a full-body sampling of postmortem tissues. This data may stimulate research to determine how the burden of mosaicism influences disease susceptibility, and whether mosaicism may be more prevalent in TS than previously thought.

Lewis identified seven potential barriers to requesting an autopsy: reluctance to permit invasive procedures, practical issues, and logistics of requesting an autopsy, preference to retain organs for burial, emotional distress, lack of communication between families and providers, lack of insight into the value of autopsy, and systematic professional or organizational obstacles (Lewis et al., 2018). The question about who should interpret and disseminate autopsy results, and whether genetic test results need to be made public, present formidable obstacles. A team-based multidisciplinary approach involving providers and forensic pathologists facilitates outreach to family members and can be effective to inform families about the cause of death and to counsel surviving relatives about their risks (Cann et al., 2017). However, these types of interventions are not widely available. Many forensic centers lack sufficient multidisciplinary teams to counsel families and conduct research studies. There are also substantial legal and procedural barriers to molecular autopsy studies, which may vary according to jurisdiction (McGuire et al., 2016). Individuals who die out of the hospital are even less likely to receive a complete or molecular autopsy. Chronic underfunding and staff shortages at hospitals and morgues compound these challenges.

To address these issues, TSSUS will identify model institutions where autopsy and organ or tissue donation proceed smoothly. One example of a successful biobanking effort is the network for Pancreatic Organ Donor (nPOD) research group (<https://www.jdrfnpod.org/>). nPOD banks pancreatic tissues of patients with type 1 diabetes for research. While the program is focused on one organ, nPOD essentially draws on resources from all organ procurement agencies. Key strategies to promote organ donation in nPOD include designating an “on-call” agent to facilitate appropriate tissue transfer and empowering families to alert clinicians to their participation in the biobank. A premortem document signed by the donor and a telephone number for families to call at the time of death greatly facilitate the autopsy/ biobank process, and their importance cannot be understated. The nPOD leadership is available as a resource to TRN.

4 | MINIMALLY INVASIVE AND MOLECULAR AUTOPSY

Due to the emergence of minimally invasive and molecular techniques, a complete autopsy is frequently not necessary to determine the cause of death. Needle biopsies can obtain sufficient tissue from most organs for histologic and molecular analysis (Table 1; Byass, 2016). Pathologic changes can be readily identified in MRI or CT images, which may be used to target biopsies and minimize the impact of autopsy (Blokker, Wagenveld, Weustink, Oosterhuis, & Hunink, 2016). The principal strategies that are utilized in molecular autopsies are whole exome sequencing, karyotyping and SNP array genotyping, which are already used in people with TS. These molecular techniques work with very small amounts of tissue and can even be used on some archival samples of formalin-fixed tissues from prior autopsies. Thus, minimally invasive approaches have the potential to expand the use of autopsy by providing revolutionary options for families who are concerned about invasive

procedures or potential disfigurement (Table 2; Ben-Sasi et al., 2013; McPherson et al., 2017).

Tissues that are obtained from autopsy are routinely examined for histology, using unique stains for each cell type and organ, for microbiology, if an infectious cause of death is suspected, or for tumor markers, if there is evidence of cancer (Rüegger et al., 2014). For individuals with TS, genetic analysis of the chromosomal complement is a critical component of autopsy. The karyotype or metaphase chromosome analysis, is the usual “gold standard” for diagnosis of TS, but is not always accessible from autopsy specimens due to the requirement for fresh peripheral blood and special cell preparations (Koooper, Faas, Feenstra, de Leeuw, & Smeets, 2014). Chromosomal microarray analysis (CMA) or single nucleotide polymorphism (SNP) microarrays are viable alternatives to karyotypes, because they can utilize purified genomic DNA from any tissue and may be ordered as clinical tests. CMA quantitates copy number changes throughout the genome and generates a “virtual karyotype” of the X and Y chromosomes to identify aneuploidy, detect previously unsuspected chromosomal structural variants, such as Y chromosome material, and quantitate the extent of mosaicism. Clinicians can follow up uncertain results from karyotypes or CMA using more sensitive and specific assays such as fluorescent in situ hybridization (FISH) or quantitative polymerase chain reaction (qPCR). These molecular probes are used to target specific regions of the genome to determine the structures of marker or ring chromosomes or to visualize structural rearrangements of the X and Y chromosomes, such as translocations. Genetic testing by whole exome sequencing, the most recent innovation that is relevant to autopsy, can detect rare mutations that cause disease (DNA) or provide highly accurate measurements of changes in gene expression that may be involved in disease (RNA). Exome sequencing is being used in molecular autopsies with increased frequency (Shamseldin et al., 2018; Yates et al., 2017). Sequencing of genomic DNA derived from tissues or cell-free DNA has no current role in the diagnosis or clinical management of TS, but is an active focus of research (Zhang et al., 2017).

Molecular techniques can be used to extend the techniques and findings of conventional autopsy. Between 5 and 10% of natural deaths remain unexplained even after a complete conventional autopsy (Oscar & Ramon, 2016). Many of these cases involve deaths of young people who have no apparent structural heart disease, but were found to have genetic mutations that predispose to sudden death by exome sequencing. The highest yield of rare pathogenic mutations is found in families with a history of sudden cardiac death, young persons without detectable physiologic findings on conventional autopsy, women with recurrent fetal demise and families with consanguinity. Causal genetic mutations are found in up to 50% of these cases, and an additional 30% were found to harbor rare genetic variants of uncertain significance that may actually be reclassified as pathogenic mutations over time (Rueda et al., 2017; Shamseldin et al., 2018). Individuals in the general population with similar risk profiles may benefit from genetic screening for early diagnosis and prophylactic therapies (Shanks et al., 2018). Therefore, molecular autopsy not only facilitates diagnosis, but can also prevent genetically triggered sudden deaths. TS is associated with a threefold increased risk for cardiovascular mortality, including unexplained sudden deaths in women who do not have structural heart or vascular disease. The incidence of preventable sudden deaths due to acute aortic dissections or long QT syndrome may be

increased in TS (Duijnhouwer et al., 2018; Trolle et al., 2013). In too many cases, families still learn about the diagnosis of TS at autopsy. Clearly, individuals with TS should be prioritized for molecular autopsy in order to investigate causes of sudden death.

How might molecular autopsy techniques apply to TS? Understanding key factors that mediate the profound variability of TS phenotypes, including mosaicism, and other risk-modifying genetic variants, was a central topic of the TRN symposium. Molecular techniques are readily applicable to detect mosaicism and gene expression in tissues that are not accessible during life. Therefore, molecular autopsies can provide critically important tools to investigate the molecular biology of TS. Questions that molecular autopsies can address include: which tissues require a second sex chromosome to complete normal development, or which genes are implicated in different TS phenotypes? To answer these questions, clinicians, advocates, and families should team up to ensure that we perform conventional and molecular autopsies on as many TS patients as possible. Success is more likely if providers establish relationships with families and take part in discussions with patients who face life-changing decisions that might include the possibility of sudden death, such as an impending surgery. Those preparatory discussions can promote collaborations between providers and families to facilitate tissue harvesting after procedures and increase the probability that autopsies may be performed.

5 | BIOBANKING

Autopsy tissues and data should be widely available to the TS research community, in order to accelerate our efforts to understand TS-related conditions. Because TS is a rare disease, individual researchers in academia and industry face extraordinary barriers to collect sufficient biological specimens for rigorous research, which negatively impacts the possibilities for novel biological and therapeutic insights. Banking tissues and organs from women with TS can attract new researchers into the field by facilitating access to specimens, supporting hypothesis-driven research about TS and creating a resource to address future questions.

What would a successful biobank to support TS research look like? We envision that the biobank will be accessible to donors in all geographical regions at no cost. The biobank should be capable of maintaining multiple types of tissues that are relevant to TS-related disorders in long-term storage, using the best practices for sample collection and preservation. Ultimately, the biobank will also facilitate equitable distribution of samples for TS research. As no dedicated TS biobank currently exists, part of our mission was to identify accessible solutions for the TS community.

Some established biobanks already provide potential destinations for cells and tissues from TS autopsies. Three NIH Institutes fund the NeuroBiobank (NBB), a federated network of brain and tissue repositories that coordinates their distribution to researchers (<https://neurobiobank.nih.gov/>). Studies using tissues collected by the NBB have shown that the samples are of high-quality for gene expression analysis (White et al., 2018), and have been used to study mechanisms and biomarkers related to the high prevalence and early onset of Alzheimer's disease in individuals with Down syndrome (LeVine et al., 2017; Wilcock et

al., 2015). The TRN will work with the NBB to develop a customized protocol for collection of tissue samples that are relevant to TS. Individuals with TS can preregister with the brain donor project, a nonprofit partner of the NBB that facilitates the signup process for those interested in becoming a donor and provides awareness materials and messaging to patient advocacy groups. Upon death, the brain donor project coordinates with relatives to facilitate tissue collection for the NBB. The entire process is available at no cost to donors, the collection is not disfiguring, and the body is quickly returned to families for funeral arrangements. The NBB also collects tissues from healthy individuals to serve as research controls. Families of women with TS could consider this option to support the TS community. They are willing to accept fetal samples from miscarriage in addition to pediatric and adult tissues. An online system facilitates access to their catalog, and tissues are distributed based on the scientific merit of research proposals. The NBB will be useful for studies of mosaicism, genotype–phenotype correlations and research into abnormal functions of some organs in TS.

NIGMS funds the Coriell Institute Biorepository to collect biological specimens from individuals with various genetic conditions (<https://www.coriell.org/>). Coriell generates cell lines from donor-contributed blood and skin punch biopsies. Coriell mails a sample collection package to interested participants, who may donate tissues at a local clinic and return the samples by mail. The entire cost of donations, including reimbursement for sample collection if performed at a commercial laboratory, is usually free. Researchers may easily request cell lines from an online catalog to use in their research. The Coriell Biorepository will be most useful for genetics and molecular biology research into TS-related genes. We envision that TRN investigators will work with these or other vendors to establish repositories and protocols that accurately reflect TRN research priorities.

6 | THE ROLE OF PALLIATIVE CARE

Palliative care is provided for patients with a life-limiting diagnosis alongside any additional care and is independent of the intent to cure the disease, to continue life-prolonging care or to minimize suffering. Palliative care can begin at the time of diagnosis and continue through the end of life to offer supportive counseling, assist with difficult decisions, provide symptom management, and when needed provide comfort care at the end of life.

The core concepts of palliative care and palliative care decision-making can be applied to life situations that are relevant to TS, including prenatal diagnosis, perioperative evaluations and end of life discussions. Discussions about autopsy should be tailored to different life stages and disease severity (Table 3). A prenatal diagnosis of TS may occur in the context of abnormal screening results or the discovery of significant congenital defects. In these situations, the option to perform an autopsy may include plans for stillbirth and interventions that may be required in the immediate postnatal period. Discussions with adults should include quality of life assessments, management of TS-related conditions and related complications, and the possible need for interventions. A conversation about potential complications and risks for death provides an opportunity to consider end-of-life plans and may be an appropriate moment to introduce autopsy. Providing information about the logistics of autopsy in advance can reduce the anxiety of patients and caregivers. Positive

discussions about how to create a beneficial legacy, including the lasting contributions of autopsy and tissue donation, may be an integral element of these difficult conversations.

The diagnosis of a terminal condition inevitably causes acute grief. Families and individuals with TS may initially feel overwhelmed by end of life choices, but become empowered as they work with providers to develop a plan. In addition to the routine postmortem evaluations, palliative teams encourage families to undergo formal counseling with a medical geneticist who is familiar with TS. An ideal postmortem session for parents or family members may include a healthcare team with the attending physician, geneticist, endocrinologist, cardiologist, and a spiritual or religious professional. By offering an outlet for their questions and thoughts, palliative care teams can relieve anxiety, promote quality of life issues, and provide additional options to enhance the legacy of a life, including contributions to research.

7 | FUTURE DIRECTIONS

Formulating specific contingency plans for in-hospital and out-of-hospital deaths is a primary objective of the autopsy working group. To solicit commentary and to publicize the value of autopsy to the TS community, the working group will circulate a survey about autopsy and organ donation to TS research registry participants. As part of this effort, they will identify stakeholders across the country who will advocate for autopsies and work with families to facilitate organ and tissue donation. For example, the TRN will work with nonprofit organizations such as nPOD and NBB to develop protocols for transfer of tissues or organs to research centers with specialized expertise in TS. The long-term goals of this effort are to promulgate a central registry of resources for tissue donation, a database to compile the results of completed autopsies, and a set of practice standards for autopsy to providers, families, and women with TS. The working group distilled these recommendations into a brief educational brochure about autopsy that will be disseminated to providers and families so that key stakeholders in the TS community can be empowered to improve autopsy rates.

8 | CONCLUSION

This review highlights strategies to promote autopsy and tissue donation in the TS community and to develop an action plan for overcoming formidable barriers to increasing autopsy rates. The potential value of autopsy and tissue donation extends to TS patients, families and stakeholders, who can benefit from end-of-life planning, and TRN researchers, who stand to benefit from the analysis of autopsy data and specimens. Discussions about autopsy were primarily initiated by women with TS and their advocates, who have long recognized the scientific value of autopsies and tissue donation. These topics may also be broadly applicable to other rare disease communities with similar priorities.

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“For many years, I have been interested in autopsy. My parents were both adamant that they wanted any usable body parts donated when they die, and we had many family discussions (some of them quite humorous) on the subject. I am a strong proponent that every family should have this kind of discussion about the inevitable long before someone is on their deathbed. My mother donated her body for anatomical study when she passed away five years ago which inspired me to want to donate my body as well... hopefully not any time soon.” -Barbara Flink, MS.

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TABLE 1

Tissue samples available from minimally invasive autopsy

Tissue	Relevance to TS
Peripheral blood	Karyotype
Cord blood	Prenatal or neonatal death
Brain, cerebrospinal fluid (CSF)	Stroke, moyamoya disease, neuroanatomic abnormalities
Middle and inner ear	Hearing loss, ear malformations
Liver	Fatty liver, steatosis
Lung	Bronchiectasis, abnormal pulmonary venous drainage
Bone marrow	Myelodysplasia
Skin	Lymphedema, vitiligo, nail dysplasia
Heart	Bicuspid aortic valve
Thyroid	Autoimmune hypothyroidism
Aorta	Thoracic aortic aneurysm, coarctation
Small intestine	Celiac disease
Ovaries	Gonadoblastoma, streak ovaries
Kidneys	Horseshoe kidney, other renal deformities
Pleural effusion or ascites	Chylothorax, cystic hygroma, other lymphatic abnormalities

TABLE 2

Comparison of conventional and minimally invasive autopsy

Conventional autopsy	Minimally invasive autopsy
Involves dissection	Does not utilize dissection
Examination and removal of entire organs	Small samples or biopsies of many organs
Limited to photographs and histology	Includes CT or MRI “virtuoscapy”

TABLE 3

Life situations that may prompt discussion about autopsy

Event	Example(s)
Fetal or neonatal death	Termination of pregnancy, stillbirth
Sudden or unexpected death at any age	Sudden cardiac death, aortic dissection
Pre-operative discussion	Cardiovascular surgery
End of life care decisions	Medical orders for life sustaining treatment (MOLST)
Educational session	TSSUS conference, scientific meeting
Estate planning	Legacy, living wills
Research	Cell or tissue banking, minimally invasive autopsy