Brain Donation in Normal Aging Procedures, Motivations, and Donor Characteristics From the Biologically Resilient Adults in Neurological Studies (BRAiNS) Project

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Medical autopsy rates have been declining for the past several decades, yet, for more than a decade, the University of Kentucky Alzheimer’s Disease Research Center has been recruiting healthy older adults into a program involving annual assessments of mental status, biannual medical and neurological exams, and prearranged post-mortem brain examination. The present article focuses on the characteristics of these donors to explore potential factors that contribute to the decision to donate. The motivations of this unique group of individuals could serve to inform physicians who request autopsies for medical and research purposes. Over 500 volunteers who have enrolled in this program are well-educated community-dwelling adults over the age of 60. They are generally motivated by personal experiences with Alzheimer’s disease, referral by someone already enrolled, and a desire to promote scientific knowledge. These volunteers’ reasons suggest that rates of tissue donation or autopsy for basic research and investigations of causes of death might be increased by providing individuals and families with information concerning the medical and scientific value of the procedure. Within research settings, encouraging participant recruitment of friends or family members would likely increase tissue acquisition rates.

Key Words: Alzheimer’s disease, Autopsy, Organ donation, Senile plaques, Neurofibrillary tangles, Cognition

The acquisition of brain autopsies for research purposes is an important endeavor in research on aging. This process is crucial for understanding the morphological and biochemical changes occurring with normal brain aging and for comparison of these alterations in the central nervous system (CNS) associated with dementing conditions. Though procurement of CNS tissues from normal individuals is recognized as an important component of research, information is lacking about how this goal might be accomplished.

Two literatures that shed light on this problem concern autopsy requests for postmortem diagnosis and cadaver organ donation. There are similarities and dissimilarities in these literatures in relation to the acquisition of normal brain specimens. Recent literature regarding autopsy referrals has predominantly focused on pathological diagnoses as opposed to the investigation of normal tissues for research.
Some of the reasons most often cited for the agreement to perform an autopsy in a hospital setting include the identification or confirmation of the cause of death, advancement of medical knowledge or medical education, and certification that appropriate medical care was provided (Grunberg, Sherrod, Muellenbach, Renshaw, Zaretsky, & Levine, 1994; Harris, Ismail, Dilly, & Maxwell, 1993; McPhee, Bottles, Lo, Saika, & Crommie, 1986). Consent for autopsy may be limited by public misconceptions that autopsies are more important or informative in forensic cases than in deaths that are due to medical disorders (McManus & Wood, 1996). With organ donation, motives tend to be less concrete and are related to personal values and attitudes (Horton & Horton, 1991), often in regard to transplantation (Chabalewski & Norris, 1994). Barriers to obtaining permission for autopsy are also important. Physician attitudes and training as well as families’ beliefs and needs appear to contribute to the decision to permit an autopsy. McPhee and colleagues (1986) suggested that barriers to obtaining consent for autopsy include concerns about possible body disfigurement, a family member’s stress surrounding the death and granting of permission, other family members’ objections, and a general lack of information about the autopsy procedure. Physicians also often fail to request an autopsy. Apparent barriers to approaching a family for autopsy permission include a fear of litigation, discomfort on the part of the physician, beliefs regarding the family’s reaction, and the lack of training in obtaining consent as well as in the importance of an autopsy (Grunberg et al., 1994; Katz & Seidel, 1990; McManus, Suvalsky, & Wilson, 1992; Rosenbaum, Burns, Johnson, Mitchell, Robinson, & Truog, 2000; Souza & Rosner, 1997; Wilkes, Link, Jacobs, Fortin, & Felix, 1990). McPhee (1996) and others (Schneiderman & Gruhn, 1985) have suggested the need to improve communication between families and physicians as well as the need to educate all parties concerned on the importance of autopsy. Given the motivations for postmortem evaluations in a hospital setting and organ donation, it is not surprising that obtaining autopsies from normal individuals for the expressed purpose of research presents a unique problem beyond that of pathological diagnosis of conditions contributing to mortality.

Autopsy in Alzheimer’s disease (AD) patients is primarily directed toward the neuropathological confirmation of the clinical diagnosis. Even with the accuracy of clinical diagnosis ranging from approximately 80% to 90% (Blacker, Albert, Bassett, Go, Harrell, & Folstein, 1994; Galasko et al., 1994; Katzman, 1988; Kukull, Larson, Reifler, Lampe, Yerby, & Hughes, 1990; Victoroff, Mack, Lyness, & Chui, 1995), definitive diagnosis of AD requires neuropathological confirmation. In addition to establishing a diagnosis of AD or another dementing condition, autopsy provides tissue samples for analyses focusing on the potential pathophysiological mechanisms and causes of AD. Therefore, autopsy in AD is often the core element for research in the Alzheimer's Disease Research Centers (ADRC) funded by the National Institute on Aging. Many of the ADRC projects involve study of the AD brain for structural, biochemical, and clinical clues regarding the nature of this disorder and, similar to medical autopsies, provide a definitive diagnosis for the family. Through the cooperation of family members of the AD patient, the ADRCs have been able to study a large number of brains from victims of AD and associated disorders. However, there has been a critical shortage of control brains from prospectively evaluated cognitively normal individuals available for neuropathological and biochemical comparison with tissues from demented individuals. Only a very modest number of postmortem studies of the aging brain have appeared in the literature, and many have not included prospectively studied older adults with “normal” mentation (Davis, Schmitt, Wekstein, & Markesbery, 1999). Given that senile plaques and neurofibrillary tangles (hallmarks of AD) in varying densities in the brain have been described in normal older adults, the association of these changes due to aging, dementia of the Alzheimer’s type, and possible “preclinical” AD is unclear. Recent research suggests that clinically identified change in memory without other symptoms of dementia often evolves into clinical AD within a few years (Morris et al., 2001). Brain donation from well-studied, nondemented individuals can further our understanding of the brain changes in aging and dementing conditions.

Since 1989, we have recruited neurologically normal older adults who have agreed to donate their brains following death. This report describes some possible motivations for and against older adults granting permission for brain donation in a normal aging population that could serve as the basis for other research projects investigating changes in the brain associated with the aging process. We propose the term brain tissue acquisition, as the act of donating normal brain tissue for research purposes possesses qualities of both autopsy and organ donation. Understanding the factors behind this decision-making process are important, because there is a shortage of control brains nationally. Further, the national autopsy rate (in general) has been in decline over the past several years (Powers, Powell, Schlough, & Whitehouse, 1989), and an organ-donor shortage also exists (Jaynes & Springer, 1994).

Methods

Participants

For the last 16 years, the University of Kentucky Sanders-Brown Center on Aging has maintained a pool of research volunteers. This pool consists of 4,131 persons over the age of 60 who reside in the immediate geographical area of the ADRC and have agreed in principle to be research participants. This pool was initially created in 1984 by contacting registered voters in this region. General characteristics of this group of individuals are shown in Table 1. Recruitment for the current project began in the Fall
of 1989. In the Fall of 2000, members in this study submitted names for the project and voted to call this project the Biologically Resilient Adults in Neurological Studies (BRAiNS) program.

The present sample of community-dwelling volunteers reflects 504 persons over the age of 60 who were recruited from 1,305 contacts by letter and from 393 contacts through personal referrals and media publicity from the overall group. The majority of the research volunteer group members at the time of study enrollment were married, were between the ages of 60 and 97, and considered themselves to be in good health (see Table 1). Given resource limitations, a decision was made to follow a maximum of 500 living individuals in this cohort at any given time. Participants who die or are lost to follow-up are replaced to maintain this level of study enrollment. Replacement of individuals in this cohort continues to be based on local media presentations.

Procedure

To recruit persons for this project, we sent a personal letter from the ADRC to persons in the research volunteer pool explaining the critical need for understanding the cause or causes of AD. It also summarized how these goals might be promoted through the study of brain tissue from a normal older person. The letter specifically informed potential participants that they would be asked to take annual mental-status examinations to document the absence of cognitive symptoms normally associated with dementia and to agree to “donate” their brain following their death. This letter also specifically stated that the autopsy would be performed at no cost to the volunteer and that the brain donation was not disfiguring and that it would not require a change in either the type of funeral the individual desired or the timing of the funeral.

Within approximately 1 week following the receipt of the letter, each potential volunteer was contacted by telephone. At this time the potential participant was provided with an opportunity to ask questions about study procedures and autopsy. They were then asked questions based on NINCDS/ADRDA criteria (McKhann, Drachman, Folstein, Katzman, Price, & Stadlan, 1984) related to their mental and physical condition to determine their study eligibility. If it was mutually agreeable, a home visit was made with the individual to review and sign the informed-consent document, a donor card (Figure 1), and to obtain baseline mental-status testing.

Immediately after death, please call Dr. David R. Wnekstein. He can be reached 24 hours a day, 7 days a week, at one of the following numbers:

- During office hours: (859) 323-6040
- Nights at his home: (859) 269-4454
- If no answer: (859) 323-5321 and ask for pager #2239

Please call as quickly as possible after the time of death. Your role in this process is vitally important to the success of the research. Thank you for your cooperation.
tory of neurological disease, major psychiatric illness, or substance abuse were excluded from the study. Eligibility was further determined from mental status scores (e.g., a Mini-Mental State Exam score above 24; Folstein, Folstein, & McHugh, 1975). Volunteers who qualified as donors and consented to the study procedures are retested on an annual basis and receive biannual neurological and physical examinations. They are also contacted by telephone at 6-month intervals in an effort to maintain contact and determine that there have been no significant changes in their health status.

Volunteers who remained eligible after their initial screening also signed a form (in addition to the consent document) indicating their agreement to donate their brain and, in most cases, other organs to the Sanders-Brown Center on Aging. Volunteers also agreed to inform significant others including their next-of-kin, physician, and funeral director concerning their donation decision and enrollment in the study.

As a part of the screening and recruitment procedures for this study, all potential participants (members of the research volunteer pool) who were contacted by telephone were also asked questions to understand their reasons for agreeing or not agreeing to participate.

### Results

To date, 1,507 of the research volunteers have been contacted about the brain donation program, and 583 (38.7%) have enrolled as donors. Direct mailings resulted in an 18% enrollment rate (186 of 1,031 letter or phone contacts enrolled after meeting criteria) and an additional 397 enrolled through referrals from study participants and local media coverage of the program. In the direct mailing, 274 persons were unable to be contacted by telephone to set up a home visit. The primary reasons were that these people had either died or moved away from the area or the telephone number was no longer valid. Of those who agreed to donation, 255 (50.7%) did so because they had family (39.9%) or friends (10.7%) with AD. The second most common reason provided was the personal referral by another participant (31.8%), and the third was the donor’s decision on cremation (15.5%) or closed casket funeral (1.8%) after death, and the perception that the brain donation would not interfere with this plan. Other reasons included the donor’s previous relationship with either the University of Kentucky (14.3%) or the health care community (12.3%) or a concern about their own memory (6.2%). Note that these proportions do not equal 100 given that some volunteers provided more than one reason for enrolling in the project.

Of the 843 persons contacted by mail who were not enrolled, 19% (161) were ineligible because of health reasons or exclusion criteria. Refusal without a reason was indicated by 432 (51.2%) of the contacts. An additional 10% (84) stated they would agree, but that family members objected. Other reasons for refusal included objections to the testing (6%, or 51), the perception that they were “not healthy enough” (103, or 12.2%), and the fact that some (1.4%) had already agreed to donate their bodies for medical research through another department at the medical school. In the case of the personal and local media referrals, only 75 of the 393 contacts could not be enrolled primarily because of our exclusion criteria.

Since the inception of this program, 38 of the volunteers (7.5% of the group) have withdrawn from the project. The most common reasons for discontinuation were for personal reasons including a change of mind regarding autopsy (31.5%), moving out of the area (39.5%), family pressure about the postmortem examination (13.2%), and declining health requiring institutionalization (15.8%).

### Discussion

The recruitment method used in the BRAiNS project appears to be successful as measured by the
numbers of brain donations acquired for autopsy. To date, there have been 131 deaths and 114 autopsies (87% autopsy rate). A description of the autopsy findings in the first 59 cases in this series has recently been presented (Davis et al., 1999; Schmitt et al., 2000). Given the declining trend for autopsy in the hospital setting, the willingness to enroll in an autopsy program that does not provide a diagnosis of medical conditions is unique and may reflect several factors. It also differs from the autopsy components of many ADRCs because the majority of these volunteers do not develop clinical symptoms of dementia. Further, this project and its procedures helped in the development of another study of brain aging with the School Sisters of Notre Dame (Nun Study; Butler & Snowdon, 1996).

The typical donor in the present study was a woman aged 70–79 with 13 or more years of education who reported “excellent” or “good” health. The primary motivating factor for agreeing to postmortem examination was personal knowledge of a person with AD. This motivation is undoubtedly the expression of a desire to help others by finding a cause, cure, or treatment for AD similar to attitudes that promote autopsy in the hospital setting (McPhee et al., 1986; Connell, Ave, & Holmes, 1994).

It is also possible that the donors in the present study are motivated by values and attitudinal factors. Altruistic values (Horton & Horton, 1991), a sense of purpose and fulfillment (Clancey, 1994), and something good (life) coming from tragedy (death; Clancey, 1994; Eizenga & Luukkonen, 1993) have all been found to be related to organ donation. These variables may be related to our volunteers finding purpose in their own deaths with their donation. On the basis of these observations, a second project designed to assess altruism in some of our volunteers is underway.

In viewing brain acquisition in relation to organ donation, another reason for success could be the donor card that is provided to the volunteer. The possession of a donor card has been found to be a predictive factor of organ donation (Horton & Horton, 1991). This concurs with McPhee’s (1996) call for improved communication and education for both health care professionals and the public about the importance of autopsy. With this in mind, our ADRC routinely provides information regarding the use of the requested brain tissue to health professionals and the public through the ADRC newsletter and patient-education materials. We also provide regular study updates through newsletters and presentations to our volunteers (and prospective volunteers) concerning research on AD. Imparting knowledge through these means (with accompanying coverage in the local news media) may be a factor in maintaining and recruiting additional volunteers for brain acquisition.

Another possible reason for success in recruiting older adults for a prearranged autopsy program is simply that a request was made. The topic of autopsy is often difficult for both physicians and families, and therefore often avoided (Rosenbaum et al., 2000). McPhee and colleagues (1986) found that the single most common cause for not having an autopsy performed was simply the failure of professionals to request one. This also appears to be the case for African American families, who were less likely to be approached for organ donation than the families of White patients, and consent to organ donation varied by type of death, geographic location, and type of hospital (Guadagnoli, McNamara, Evanisko, Beasley, Callender, & Poretsky, 1999). It is possible, therefore, that our request communicates value to an older adult, especially in a society in which emphasis is placed on youth. For example, McPhee and colleagues (1986) found that the majority of autopsies (62%) were performed for the pediatric hospital service. It is unclear, however, whether more autopsies were being requested by physicians from this service or by families. An autopsy request from our ADRC may therefore communicate the importance that is placed on health issues and quality of life for the elderly by physicians and scientists.

In considering demographics of our participants, it is important to note that the majority of the volunteer pool consists of well-educated, middle- to upper-class Whites. Other cultures or groups may not value autopsy as highly. For example, in a study of Mexican Americans, Perkins, Supik, and Hazuda (1993) found that this group questioned the medical benefits of autopsy and were less willing to grant autopsies that benefited only people outside the family. Religious beliefs were also in opposition to autopsy. Many individuals in this group placed great importance on the whole, “unmutilated” cadaver and believed that the soul lingered in the cadaver for a period of time after death. Clearly, autopsy would interfere with these beliefs. Further, requesting autopsy before death, as in this study, was often believed to hasten death. Organ donation in this Hispanic population has been possibly affected by culture also, as most organ procurement workers are Caucasian (Rene, Viera, Daniels, & Santos, 1994). Consideration of the culture (including ethnicity and religion) of the population from whom tissue is being requested is therefore important in the design of successful recruitment procedures. Multilingual informed consent forms and patient-education materials may facilitate cross-cultural communication about the benefits of autopsy and the specific medical procedures involved. However, Rosenbaum and colleagues (2000) found in a recent survey of U.S. teaching hospitals that fewer than 6% offered multilingual forms.

Family objections are often reported in the literature as reasons for autopsy rejection. Ten percent of respondents who initially contacted did not agree to autopsy because of family objections and some enrollees later withdrew consent for a similar set of reasons. One recent survey (Sanner, 1994) found that 62% of respondents were willing to donate their own organs, while significantly fewer (39%) were willing to donate organs of a family member. In regard to autopsy, however, the proportion of autopsy acceptance for self and family members was similar.
Sanner (1994) suggested a range of positive opinions toward postmortem procedures of autopsy, organ donation, and dissection. It is possible that the request for brain donation represents yet another point on this continuum. Family opinion obviously plays a much larger role when autopsy is not requested until after a patient death. In these cases, the amount and type of information provided, or withheld, about the autopsy procedure may increase family distress (Rosenbaum et al., 2000). Involving family members in advance planning has been suggested as one intervention for educating significant others (Connell et al., 1994; McPhee, 1996).

Data from a similar project have shown that the rate of brain donation among older adults is associated with chronological age (Kaye, Dame, Lehman, & Sexton, 1999). In Kaye and colleagues’ project, persons over the age of 85 are almost twice as likely (62%) to consent to brain donation when first approached about donation when compared with their younger counterparts of ages 65 to 75 (36%). Factors such as religion, religious affiliation, and socioeconomic status did not dramatically contribute in this decision to donate.

The success of the current recruiting efforts at the Sanders-Brown Center on Aging and prominent features of the sample obtained suggest that autopsy and tissue donation requests benefit from consideration of the target population’s demographic characteristics, values, beliefs, and religious constraints. Clinicians and researchers are likely to obtain increased donation rates by asking potential donors before death or illness, whenever possible. Providing information emphasizing the donation’s advancement of medical or scientific knowledge, potential benefit to others with specific illness, and specific types of donation (e.g., brain only or whole body) at the time of the request might tap into the reasons commonly endorsed by volunteer donors. Directly addressing cultural or religious concerns with the procedure in the primary language of the potential donor would increase the relevance of the information presented. Finally, offering donor cards and encouraging or facilitating family discussion of the decision to undergo autopsy or tissue donation is likely to increase volunteer acquisition and retention.

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