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Prospective Collection of Tissue Samples at Autopsy in Children with Diffuse Intrinsic Pontine Glioma

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Abstract

BACKGROUND—Brain tissue obtained at autopsy has been used in research for non-oncological disorders. However, this tool has never been systematically used in large investigational studies for cancer. We conducted a prospective, multicenter study to assess the feasibility of tissue collection at autopsy and its suitability for molecular analyses in children with diffuse intrinsic pontine glioma.

METHODS—Tumor tissue was collected at diagnosis, if clinically indicated, or at autopsy. Normal brain tissue was also collected at autopsy. The integrity of DNA and RNA was evaluated in all samples. Logistical data about autopsies were recorded. The feasibility of tissue collection at autopsy was assessed for patients treated at a single institution over a 43-month period.

RESULTS—Tumor samples were collected at diagnosis ($n=3$) or at autopsy ($n=38$) at 29 centers across the US; samples were obtained at diagnosis and autopsy in two cases. The median interval from death to autopsy was 7.7 hours. DNA and RNA with minimal or partial degradation, which were suitable for genome-wide analysis, were obtained from 100% and 63% of tumor samples, respectively. At the coordinating institution, approximately 40% of parents consented to autopsy and 40% declined. During the study period, 12 autopsies were obtained from patients who did not receive therapy at the coordinating center.

CONCLUSIONS—Multicenter, biological studies based on tissue obtained at autopsy are feasible in children with brain cancer. Our experience established a new paradigm for brain tissue collection which may increase the potential for research studies in patients with cancer.

Keywords

autopsy; brain; children; diffuse intrinsic pontine glioma; molecular studies

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Brain tumors are the second leading cause of death among children with cancer.¹ Likewise, primary and metastatic brain cancer account for a disproportionately high share of the mortality among adults with cancer.^{1, 2} Following breakthroughs in the use of targeted therapies for other cancers in adults,^{3, 4} there has been a huge effort to better understand the biology of aggressive brain cancers with the hope that it may lead to the design of more rational and better therapies. Recent studies have described detailed molecular analysis of glioblastoma (World Health Organization [WHO] grade 4), the most lethal brain cancer in adults.^{5, 6}

Diffuse intrinsic pontine glioma (DIPG) is one of the deadliest brain tumors in children.⁷ Despite the use of radiation therapy (RT) with or without chemotherapy, the long-term survival of affected children has remained < 10% for the past 30 years.⁷ Radical (> 90%) resection of DIPG is not feasible as the tumor is an infiltrative neoplasm arising within the pons. Although tumor biopsy can be safely obtained for histological confirmation,⁸ it is rarely recommended because of lack of benefit to patients. Likewise, autopsy is hardly ever performed in these patients. Histological review of DIPG at diagnosis or at autopsy invariably demonstrates a high-grade glioma, particularly glioblastoma.^{8, 9} Since tumor tissue for research studies is hardly available, little is known about the molecular characteristics of DIPG.¹⁰⁻¹³ A recent single-institution study reported genome-wide DNA abnormalities in 11 children with DIPG; nine of the tumor samples were collected at autopsy.¹⁴

Although autopsy was standard practice until the middle of the twentieth century, its frequency among adults has declined steeply in Western countries.^{15, 16} Autopsy rates among children have declined less dramatically compared to adults.^{17, 18} Autopsy has been shown to be a valuable tool in obtaining brain tissue for research purposes in several devastating disorders in adults and children.¹⁹⁻²² However, no study to date has ever addressed the feasibility of systematic collection of brain tissue at autopsy and the suitability of this tissue for molecular studies focused on cancer.

Here we describe a successful prospective clinical trial in which tumor and normal tissue samples were collected from children with DIPG at diagnosis, when clinically indicated, or at autopsy at multiple centers throughout the continental United States. Our primary goal was to increase the understanding of the molecular mechanisms of tumorigenesis in DIPG to provide the opportunity to target specific genetic aberrations within this cancer. Our experience established a new paradigm for brain tissue collection which may increase the potential for research studies in patients with cancer.

MATERIAL AND METHODS

After approval by the St. Jude Children's Research Hospital Institutional Review Board (IRB) in June 2006, we prospectively collected tumor and normal tissue samples from patients of any age with a clinical and radiological diagnosis of DIPG, including secondary DIPG after RT. Patients with high-grade glioma originating outside the brainstem and non-high-grade glioma arising within the brainstem were excluded. At the time of IRB approval, we also obtained permission to include tumor samples collected at autopsy before activation of the study. Magnetic resonance imaging of the brain at diagnosis or during therapy was centrally reviewed by one investigator (A.B.) to confirm the diagnosis of DIPG. Tumor samples underwent central histological review by a senior neuropathologist at the coordinating center.

Flexibility was granted to physicians and other health care providers to discuss the issue of brain-only autopsy with parents at the time judged to be most appropriate, be it before or

after death. The process of consent to autopsy was variable and followed local and institutional regulations. In addition, consent for this research was obtained from parents in all prospectively collected tissue samples.

Protocol guidelines for tissue collection at autopsy recommended a brain-only autopsy as soon after death as possible. Autopsies were performed at 29 centers in 18 of the continental United States. Selection of these centers was based on their proximity to the place of death and availability of infrastructure to perform autopsy. Only four of the autopsies were performed in the coordinating center. Tissue samples were to be collected from the brainstem tumor and from normal brain. The cerebellum (if no tumor involvement was suspected) or the frontal lobes were chosen as the source of normal brain tissue. When possible, approximately 100-mg fragments of tumor and normal brain samples were to be snap-frozen in liquid nitrogen and stored at temperatures of -70°C or lower. The remaining samples of normal brain and tumor were processed for routine histological examination.

Clinical data and information about autopsy (place of death, interval between death and autopsy, location of autopsy, and processing of samples) were prospectively collected. The rate of consent to autopsy was investigated for all consecutive patients with DIPG treated at the coordinating institution who experienced disease progression during the study period.

Snap-frozen tissue samples were pulverized on dry ice. DNA was extracted as previously described.²³ RNA was extracted using Trizol (Invitrogen, Carlsbad, CA) according to the manufacturer's protocol. The integrity of DNA was evaluated by agarose gel electrophoresis and by labeling and hybridization to Affymetrix SNP 6.0 Gene Mapping arrays. RNA integrity was evaluated by using the Agilent Technologies (Santa Clara, CA) 2100 Bioanalyzer Lab-on-a-Chip system, which produced an RNA Integrity Number (RIN). RNA was classified as minimally degraded (RIN > 7.5), partially degraded (RIN 5-7.4), or degraded (RIN < 5). Logistic regression was used to investigate the association between RNA integrity and the interval from death to autopsy.

RESULTS

Tumor tissue was obtained from 38 patients with DIPG (median age at diagnosis, 6.1 years; range, 3-15.7 years) and from one patient with secondary DIPG. The secondary DIPG was diagnosed at autopsy in a 15-year old boy who had been treated with RT and chemotherapy for glioblastoma originating elsewhere in the central nervous system. Twenty-seven (69%) children were Caucasian, 6 (15.5%) were African-American, and the remainder were of other minority groups or of mixed race/ethnicity. (Table 1)

Three patients with DIPG underwent surgery at diagnosis for histological confirmation; two of them also underwent autopsy. Five autopsies had been performed as part of standard care before study activation. Thirty-three autopsies were performed between June 2006 and January 2010. Thirty-six autopsies followed failure of treatment for DIPG, one was obtained shortly after diagnosis of secondary DIPG, and one shortly after diagnosis of DIPG in a child who died of rapid tumor progression before treatment started.

Thirty-two (84%) patients who underwent autopsy died at home. Six patients died in the hospital where they were admitted to receive terminal care. The median interval from death to autopsy was 7.7 hours (range, 2.25 to 23 hours). Thirty-one (82%) autopsies were performed at academic centers and the remainder at community hospitals or private institutions. Liquid nitrogen was used to snap-freeze tissue samples from 28 (74%) autopsies. Tissue samples were stored at temperatures of -70°C or lower in all cases except one. Normal brain tissue from 33 (87%) autopsies was available for analysis.

Central histological review of three tumor samples obtained at diagnosis revealed anaplastic astrocytoma (WHO grade 3; $n=1$) and glioblastoma ($n=2$). Glioblastoma was the histological finding in 35 autopsies, including two obtained at diagnosis. One autopsy disclosed extensive tissue destruction and a tiny focus compatible with glioma and another autopsy revealed a diffuse infiltrative astrocytoma. Tissue for histological review was not available for only one case.

Integrity of DNA and RNA samples

DNA with minimal degradation was isolated from tumor and normal brain samples obtained in 33 (87%) and 31 (94%) autopsies, respectively. (Table 1) The remaining samples yielded DNA with partial degradation. (Figure 1A) All DNA samples yielded call rates $> 89\%$ when labeled and hybridized to Affymetrix Single Nucleotide Polymorphism (SNP) 6.0 Gene Mapping arrays, indicating outstanding quality for genome-wide copy number analysis.

Minimally degraded RNA was recovered from 13 (34%) tumors and 19 (58%) normal brain samples obtained at autopsy, respectively. Eleven (29%) tumors and 7 (21%) normal brain samples showed partial RNA degradation but were considered suitable for Affymetrix Gene Expression array analysis on the basis of institutional experience. (Figure 1B) A shorter interval from death to autopsy was significantly associated with minimal degradation of RNA ($p=0.042$). Whereas RNA with minimal degradation was obtained from 70% of the autopsies performed within 5 hours of death, the yield of good quality RNA dropped to 21% beyond 5 hours from death.

Rate of Consent for Autopsy

During the study period, 53 children with DIPG ($n=51$) or secondary DIPG ($n=2$) who were treated at St. Jude Children's Research Hospital died after experiencing progressive disease. Consent for autopsy was not sought in 11 cases (20.8%) because of the primary physician's preference ($n=6$), loss of follow-up ($n=2$), or inability to reach the parents ($n=3$). The parents declined autopsy in 21 (39.6%) cases. Brain-only autopsy was obtained in the remaining 21 (39.6%) cases.

During the same period, 12 (36%) autopsies were obtained from children treated at other institutions and tissue was submitted to this study. Two of the 12 children had been seen at the coordinating institution for consultation at the time of tumor progression. The process of tissue donation was initiated by either the parents or the patient's local oncologist in 11 (92%) of these 12 cases.

DISCUSSION

This is the first prospective study of the feasibility of tissue collection at autopsy from a relatively large number of patients with brain tumors. Our findings demonstrate that systematic collection of tissue samples at autopsy in children with DIPG is not only feasible but yields DNA and RNA suitable for genome-wide studies. All tumors and normal brain samples yielded DNA of sufficient quality for use in genome-wide SNP array studies. RNA in 63% and 79% of tumor and normal brain samples, respectively, was suitable for genome-wide expression studies. Short intervals between death and autopsy were most likely to yield the best quality RNA. However, RNA with minimal degradation was recovered from a sample collected over 17 hours after death, indicating that samples suitable for genome-wide expression studies may be obtained even after longer intervals from death. Although one-third of the cases yielded degraded RNA, these samples could still be useful for other molecular studies (e.g., polymerase chain reaction amplification of smaller fragments to detect gene mutations).

It was also extremely gratifying to recover DNA and RNA of excellent quality from most tumor and normal brain samples, particularly taking into account that the vast majority of our patients received end-of-life care and died at home.

Since the advent of magnetic resonance imaging, DIPG has been diagnosed on the basis of its typical imaging characteristics.²⁴ Histological confirmation is currently recommended to rule out other types of brainstem neoplasm only when the tumors show atypical imaging characteristics. Our central review confirmed the diagnosis of high-grade glioma in all except two of the evaluable samples. In the latter two cases, treatment effect and sampling error likely restricted our ability for correct diagnosis. Although DIPG and secondary DIPG are likely to arise through distinct mechanisms of tumorigenesis, we included the latter group in this study because it provided a unique opportunity to compare the molecular characteristics of the two neoplasms.

The extent to which parents consented to autopsy in this study was of particular interest in view of recent controversy about pediatric autopsy and in view of concerns raised by parents about two incidents of undisclosed tissue retention in the United Kingdom.²⁵ Even more remarkable, in more than one-third of autopsies performed during the study period the patients had not been treated at the coordinating institution; the process of tissue donation was initiated by parents in at least seven of 12 cases. We attribute this success partially to growing awareness among parents of children with DIPG that further collaboration with researchers is needed to improve the outcome of children with this lethal cancer. This growing awareness has been particularly fostered by networks of parents and support groups in the United States. We took particular care to obtain parents' consent for the retention of their child's tumor and brain tissue for molecular studies. We also made every effort within the context of a multicenter study to share the clinical information obtained at autopsy with the parents. Of note, expedited IRB approval outside the coordinating institution was only required in one autopsy since all other participating institutions considered this brain-only autopsy part of standard care.

We prospectively studied the rate of consent and decline to autopsy among parents of children treated at the coordinating institution. An equal proportion of parents consented to autopsy and declined permission to the procedure. For ethical reasons, we did not seek the reasons for decline to consent. The attending physicians opted not to raise the issue of autopsy in 11% of cases treated at the coordinating institution. We attribute this percentage largely to the fact that end-of-life care and death uniformly occurred at the family's home; therefore, the pediatric oncologists were not in close contact with the families near the time of death. However, we cannot rule out the possibility that the physicians were uncomfortable about discussing the issue of autopsy in some cases. We have begun to interview the parents who consented to autopsy, having first waited several months. Bereaved parents frequently seek ways to move forward in their bereavement and to find meaning in their child's death.²⁶ Our hope is that these interviews will reveal parents' reasons for participating in the current study and whether they have experienced any regret about their participation.

Although the end-of-life process in children is quite distinct from adults, we believe that our success in collecting brain samples in children with cancer may encourage similar studies in adults with cancer and brain involvement. For example, recent studies have analyzed the molecular abnormalities in recurrent brain tumors in adults compared to samples obtained at diagnosis to better understand the mechanisms of tumor resistance.^{27, 28} Brain tissue collection at autopsy represents a valuable source for such studies.

The strengths of our study include its prospective nature, the conduct of autopsies in multiple centers across a large geographical area, the multicultural background of

participating families, the relatively large number of autopsies obtained, and the high yield of DNA and RNA suitable for sophisticated genome-wide studies. These features allow our findings to be generalized to other clinical settings in which tissue obtained at autopsy could be used in research designed to benefit children. Our study remains open with the purpose of collecting a larger number of tissue samples for analysis. Meanwhile, we believe that our experience may encourage others to seek tissue for research in other lethal brain disorders.

Condensed Abstract

Brain tissue obtained at autopsy has been used in research for non-oncological disorders. However, this tool had never been used before for large investigational studies focused on cancer.

We have shown that DNA and RNA suitable for sophisticated genome-wide studies can be successfully obtained in multicenter biologic studies based on tissue obtained at autopsy in children with diffuse intrinsic pontine glioma, a deadly pediatric brain cancer.

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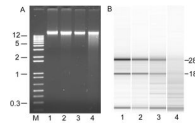


Figure 1.

Representative DNA and RNA extracted from tissue obtained at autopsy.

(A) Agarose gel electrophoresis of DNA extracted from two paired sets of normal brain and tumor (lanes 1-4). All lanes except lane 4 show minimal DNA degradation. Lane 4 shows partial DNA degradation. M indicates 1-kilobase ladder molecular weight marker. (B) RNA analysis (Agilent 2100 Bioanalyzer) of the same samples shown in A. Lanes 1 and 2 show minimal degradation (RNA Integrity Number [RIN] 8.9 and 8, respectively), lane 3 shows partial degradation (RIN= 6), and lane 4 shows degraded RNA (RIN= 2.2). Migration of 28S and 18S ribosomal RNA is indicated.

Table 1

Clinical Characteristics of Patients and Yield of Tissue Collected at Autopsy

Median Age at Diagnosis (range) ^z	6.1 years (3 to 15.7)
Race	
Caucasian	27 (69%)
African-American	6 (15.5%)
Other [†]	6 (15.5%)
Median Interval from Death to Autopsy (range)	7.7 hours (2.25 to 23 hours)
Histological Diagnosis	
Biopsy	Anaplastic astrocytoma (<i>n</i> =1) Glioblastoma (<i>n</i> =2)
Autopsy [§]	Glioblastoma (<i>n</i> =35)
Quality of DNA [¶]	
Tumor	Minimal degradation: 33 (87%) Partial degradation: 5 (13%)
Normal Brain	Minimal degradation: 31 (94%) Partial degradation: 2 (6%)
Quality of RNA [¶]	
Tumor	Minimal degradation: 13 (34%) Partial degradation: 11 (29%) Degraded: 14 (37%)
Normal Brain	Minimal degradation: 19 (58%) Partial degradation: 7 (21%) Degraded: 7 (21%)

^zOne 15-year old patient with secondary DIPG is excluded

[†]Other consists of mixed race or other minority groups

[§]One autopsy demonstrated extensive tissue destruction and one focus compatible with glioma and another autopsy revealed a diffuse infiltrative astrocytoma. Tumor tissue was not available for review in one case.

[¶]Including only samples obtained at autopsy