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Assessing Cerebrospinal Fluid Flow Dynamics in Pediatric Patients with Central Nervous System Tumors Treated with Intraventricular Radioimmunotherapy

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Abstract

Background: The incidence of abnormal CSF flow dynamics in the pediatric population with CNS tumors prior to intraventricular therapy has not been described.

Methods: We performed a single-institution, retrospective review of patients with primary or metastatic CNS tumors treated between 2003-2018 (15 years). Patients underwent 111-indium diethylene triamine pentaacetic acid injection into the CSF intraventricular space followed by nuclear medicine imaging at 90 minutes, 4, 24, and 48 hours (if required). CSF flow was classified as normal, delayed, asymmetric or obstructed.

Results: 278 CSF flow studies were performed in 224 patients, 202(90%) <18 years of age. 116(52%) patients had metastatic CNS neuroblastoma, 57(25%) had medulloblastoma, and 51(23%) had other histologic types of CNS tumors. Of the 278 studies, 237(85%) were normal, 9(3%) required neurosurgical intervention, 25(9%) were delayed, and 7(3%) were asymmetric.

Conclusions: Abnormal CSF flow and necessity of neurosurgical intervention must be considered when attempting to ensure appropriate intraventricular therapy in the pediatric population.

Introduction

The success of intraventricular compartmental therapies, bypassing the blood-brain barrier, in part depends on adequate drug distribution throughout the thecal space. Several techniques may be used to assess cerebrospinal fluid (CSF) dynamics in the central nervous system (CNS) including phase contrast and time-spatial labeling magnetic resonance imaging (MRI). Radionuclide shuntography using Tc-99m diethylenetriamine pentaacetic acid and serial imaging is another reliable way of evaluating CSF dynamics, although there is a general lack of guidelines regarding this procedure or consensus on image interpretations.(*1*) We undertook this study to define the incidence of normal, delayed, asymmetric or obstructed CSF flow in a large pediatric population with CNS tumors prior to the administration of intraventricular therapy.

Methods

We performed a retrospective review of patients with primary or metastatic CNS tumors treated at Memorial Sloan Kettering Cancer Center (MSK) over a 15-year period (2003-2018). Patients were the subjects of MSK IRB-approved protocol 16-1466, a Study of the Reliability of In-111-DTPA studies. Pediatric patients under consideration for trials incorporating radioimmunotherapy were required to have CSF flow studies documenting the absence of obstructive hydrocephalus and adequate CSF flow. All patients had an indwelling intraventricular catheter with either an Ommaya reservoir or programmable ventriculoperitoneal shunt with ventricular location of the catheter confirmed on MR or CT. The intraventricular catheter was accessed by the pediatric team (oncologist or nurse practitioner) in the presence of a Nuclear Medicine physician. The same clinician then used a 25ga needle under sterile conditions; clear CSF was aspirated confirming ventricular access. Intraventricular injection of approximately 0.2-

0.3 mCi 111-indium diethylene triamine pentaacetic acid (DTPA) was performed followed by autologous CSF flush. Imaging was obtained using a Skylight dual-head gamma camera system (Philips Inc., Bothell, WA). Whole-body conjugate (anterior, posterior and bilateral images of the head as well as anterior and posterior images of the spine were acquired. The first non-dynamic set of images was obtained within 90 minutes and up to 4 hours post injection; this window was chosen to accommodate patients who often required general anesthesia for the scan, or depending on scanner ability. Patients then underwent follow-up nuclear medicine imaging at 24 hours and 48 hours (if necessary). Distribution of the 111-In-DTPA was assessed on serial imaging and officially read by a board-certified Nuclear Medicine physician and reviewed by the Pediatric Oncology team. CSF flow studies were classified as normal if tracer flowed down the thecal sac in the first scan, and distribution over the convexities and systemic clearance on the 24-hour scan (Fig 1a). CSF flow was considered obstructed in the absence of tracer down the thecal sac on any scans (Fig 1b).

asymmetric if one side of the brain had preferential uptake of tracer (Fig 1c) or delayed if the tracer was slower to distribute over the convexities (Fig 1d).

Results

278 CSF flow studies were performed in 224 patients, 202 (90%) < 18 years of age. 116 (52%) of patients had a diagnosis of metastatic CNS neuroblastoma, 57 (25%) had medulloblastoma and 51 (23%) had other histologic types of CNS tumors. There were no complications (i.e. extravasation, infection, inability to acquire or remove CSF) associated with the administration of 111-indium diethylene triamine pentaacetic acid (DTPA). In general, Ommaya catheters and ventriculoperitoneal shunts with programmable valves were equally easy to access, although a

greater CSF volume removed for standard assays (i.e. cytology, cell count, total protein levels) was more readily obtained from Ommaya catheters. In addition, Ommaya catheter administration did not require shunt valve adjustments, making them less cumbersome for both patients and staff. Further, despite full programming of a ventriculoperitoneal shunts in the highest setting (i.e."off") residual tracer activity is still visualized in the peritoneum at 24 hours (Fig 2). Of the 278 flow studies, 237 (85%) were normal, (figure 1a) and 41 (15%) were abnormal. Of the 278, 25 (9%) were delayed (figure 1b), 9 (3%) were obstructed requiring neurosurgical intervention (figure 1d), and 7(3%) were asymmetric (figure 1c). Obstruction was evident for those scans that had no distribution down the thecal sac by 4 hours, with little or no change seen at 24 or 48 scans. Surgical correction to lyse adhesions or shunt revision to correct occlusion was required to establish flow in these instances.

For delayed scans, tracer resorption into the systemic circulation took > 24 hours and was evident by scans obtained at later intervals (i.e. 48 hours). We note the 24 hours drainage over the convexities is the rule for cysternogram (when lumbar injection is performed); in contrast for Ommaya shunt studies, delayed flow was noted by both decreased flow over the convexities at 24 hours accompanied by decreased resorption into the systemic circulation.

Asymmetric distribution of tracer was evident on scans obtained at 24 hours, where one hemisphere had preferential uptake compared to the other. No surgical procedure was performed to address delayed or asymmetric CSF flow.

Discussion

CSF dynamics have clinical, surgical and therapeutic implications. For many years, contrast myelography was the procedure of choice to assess CSF flow, later replaced by radionuclide cisternography, particularly when detecting CSF fistulous tracts.(*2*) Radionuclide imaging has often employed technetium 99m (99mTc)DTPA or 111InDTPA.(*2,3*) More recently, phase – contrast magnetic resonance imaging is a noninvasive imaging technique that enables quantitative measurements of CSF flow.(*4*) While this technique has been validated, a single injection of In-111-DTPA followed by serial images over 1-2 days provides additional therapeutic information by depicting the rate of CSF flow throughout the thecal space, the time to tract over the CNS convexities, and the time to systemic absorption. These studies simulate the dynamics that may be predicted with radioimmunotherapy. Further , the use of In-111-DTPA imaging demonstrates the amount of therapeutic activity that may or may not be asymmetrically distributed , or lost in the peritoneal cavity as with VP shunts, with obvious therapeutic implications.

Several pathologic states are known to disrupt CSF flow dynamics, including the presence of bulk leptomeningeal deposits, post surgical adhesions, and Chiari malformations.(*4*) More recently, MR studies have shown that anatomic differences among normal healthy subjects affect CSF bulk flow including lordosis and kyphosis; spinal cord eccentricity in the healthy human spine result in subject-specific patterns of bulk flow recirculating regions.(*5*)

Several methods to bypass the blood brain barrier and improve the effectiveness of macro-molecule drugs for CNS tumors have been attempted, with intraventricular administration of

chemotherapy and radioimmunotherapy being among the most common. More recently, the study of interstitial fluid of the brain tissue and CSF , as well as the glia-lymphatic system and perivascular spaces for waste clearance have been recognized as important links to the transport of solutes in the CNS.(*6,7*) Data further support the perivascular spaces lining the leptomeninges provide an avenue of transport deep into the brain via CSF.(*8*) Asymptomatic patients with no evidence of hydrocephalus on neuroradiographic imaging may have altered CSF flow dynamics that have therapeutic implications for intraventricular therapy.

Our results show mechanisms that may affect the distribution of therapies in the CSF space even in the absence of radiographic findings suggestive of altered CSF dynamics in up to 15 % of patients with CNS tumors. This has therapeutic implications as for treatment such as radioimmunotherapy , contact with the target antigen is necessary for radionuclide tumor ablation. Among these exist patients in whom no therapeutic drug would have been successfully distributed throughout the thecal space in the absence of a neurosurgical procedure to address flow dynamics. Explanations to account for asymmetrical distribution of tracer are largely considered to be related to the presence of tumor deposits or from prior therapies resulting in adhesions or vascular insult (i.e. post-surgical or radiation therapy induced changes), although innate interpatient variability is still possible. These results support baseline isotope tracer studies for any patient in whom intraventricular therapies are being considered, not only for malignancies but several other neurodegenerative conditions with proposed therapies circumventing the blood-brain barrier (i.e. amyotrophic lateral sclerosis, Alzheimer's and Parkinson's disease, lysosomal storage diseases.)

Conclusions

Abnormal CSF flow studies are noted in 15% of pediatric patients with CNS tumors, including 3% of patients who will require a procedure to improve adequate flow prior to receiving intraventricular therapy. These results have implications for successful delivery of intraventricular therapies.

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Key Points

Question: What is the incidence of normal, delayed, asymmetric or obstructed CSF flow in the pediatric population with CNS tumors prior to intraventricular radioimmunotherapy.

Pertinent Findings: Abnormal CSF flow studies are noted in 15% of pediatric patients with CNS tumors; 3% of patients will require a procedure to improve adequate flow prior to receiving intraventricular therapy.

Implications for Patient Care: Because adequate CSF flow is important to the successful therapeutic use of chemotherapy and radioimmunotherapy, oncologists should consider demonstrating normal distribution prior to these interventions.

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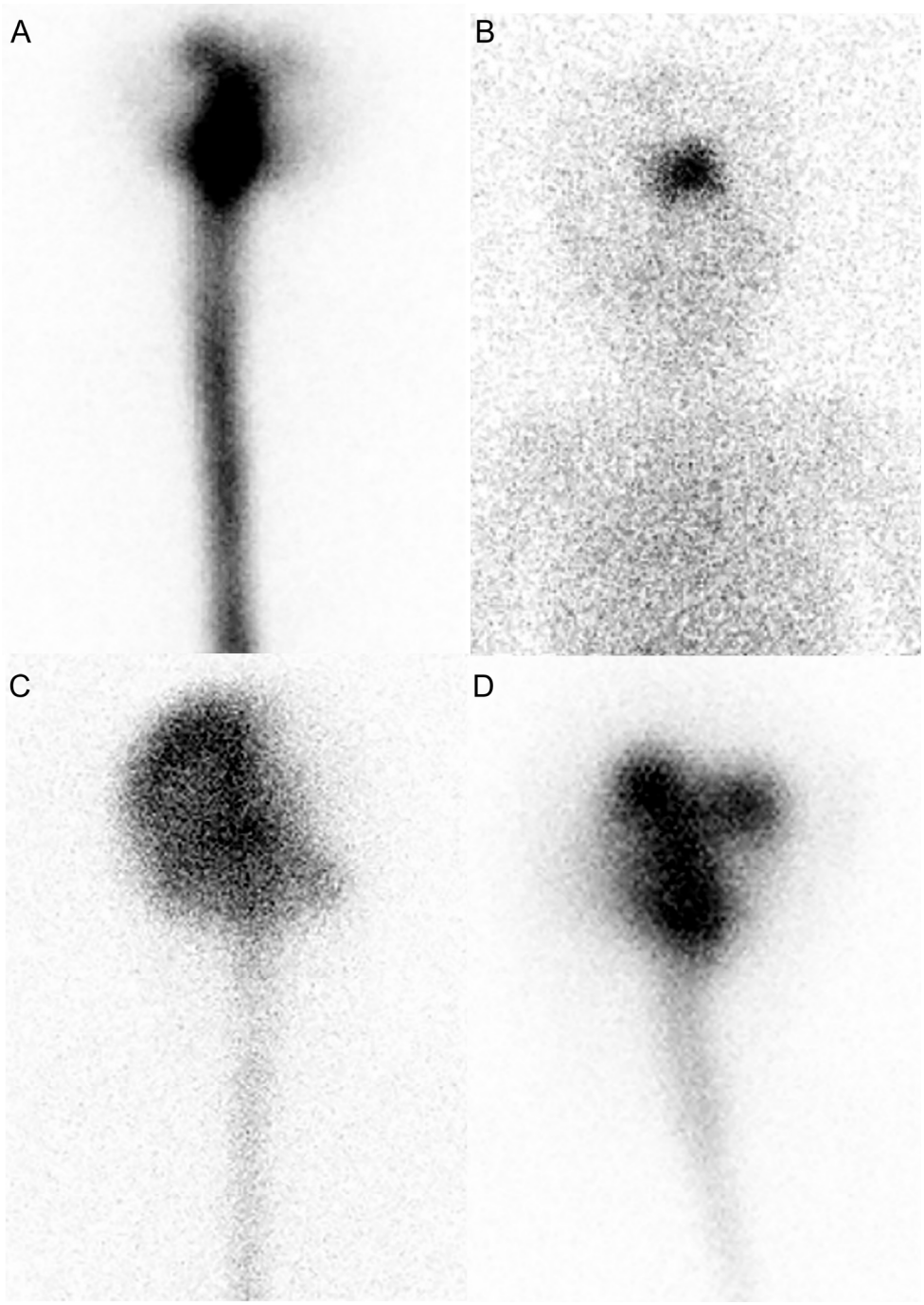

Figure 1. (a) “Normal 111-indium diethylene triamine pentaacetic acid (DTPA) and nuclear medicine imaging over 48 hours in a pediatric patient with CNS neuroblastoma metastatic the brain; the patient was treated with surgery, radiation therapy and chemotherapy and was in a radiographic remission at the time of this study, with no evidence on neuroblastoma on MR

imaging. (b) Obstructed CSF flow seen at 24 hours after injection in a 3 year old with relapsed medulloblastoma; despite a normal MR . The patient underwent an endoscopic third ventriculostomy with lysis of adhesions that re-established adequate CSF flow enabling treatment with radioimmunotherapy; (c) Asymmetric CSF flow demonstrated with increased activity over the right hemisphere on the 20 hours scan after injection in an 8 year old male with recent right parietal craniotomy and resection of right frontal love metastatic lesions; MR was unremarkable for evidence of hydrocephalus or subdural fluid collections. (d) Delayed CSF with retention in the ventricle at 24 hours after injection in a 13 year old male with multiply recurrent medulloblastoma and known leptomeningeal metastases at the time of injection; at 4 hours after injection, images showed tracer accumulation predominantly in the basilar cisterns and ventricles, with decreased flow down the remainder of the thecal sac.

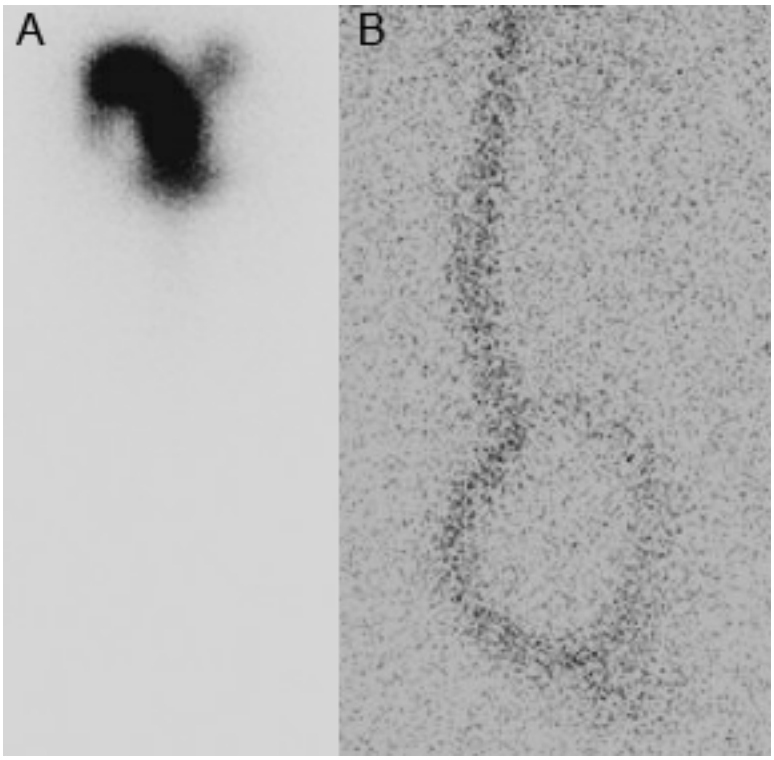

Fig 2. 111-In-DTPA injection through a programmable VP shunt; (a) Immediate post injection images show CSF accumulation in the basilar cisterns and ventricles with no evidence of obstruction; (b) immediate images show minimal radiotracer shunt catheter excretion in the peritoneum.