Neurocognitive function in same-sex twins following focal radiation for medulloblastoma

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Increased neurotoxicity and poor long-term neurocognitive outcome of preschool children treated for brain tumors have led to innovative therapeutic strategies in order to delay or avoid the use of craniospinal radiation and to improve survival. Because these protocols are relatively new, few data exist regarding cognitive outcome. We conducted a twin case–control study to investigate neurocognitive and behavioral outcome in a preschool patient who was 16 months old at diagnosis of medulloblastoma and was treated with surgery, chemotherapy, stem cell transplant, and focal radiation to the tumor bed. Stability and change over two assessments were compared for the patient and her nonaffected twin for standardized measures of cognitive function and experimental measures of parent–child interaction, social competence, and goal-directed play. A striking finding was improvement in intelligence, receptive language, and visual-motor functioning in the affected twin from 12 months to 24 months after treatment. Improvement in ratings of parent–child interaction and social competence for the affected twin was also evident. These findings are notable compared with the potentially devastating impact of craniospinal tumor, and this study is among the first to document the relative benefit of focal radiation in sparing cognitive function, albeit in a single case study.


Keywords: focal radiotherapy, medulloblastoma, neurocognitive outcome, preschool children

The majority of brain tumors in preschool children are aggressive neoplasms with a propensity for widespread neuraxis dissemination, which often require radiotherapy for control.1–3 However, young children with brain tumors are vulnerable to significant neurotoxicity and intellectual impairment after treatment with craniospinal radiation,1,4–9 and attempts have been made to avoid this therapy.10–13 Contemporary treatment studies for preschool children increasingly rely on primary postoperative chemotherapy intended to delay or eliminate the need for radiation.10–13 Although improved intellectual outcome has been documented for survivors treated without radiation, protocols have demonstrated variable efficacy for disease control when treatment involved chemotherapy only, particularly for children with postoperative residual and/or disseminated
disease. Hence, some protocols have included second-
look surgery, high-dose chemotherapy, stem cell trans-
plant, and focal radiation therapy in an effort to improve
treatment efficacy while minimizing adverse neurocogni-
tive late effects for patients with residual tumor or dis-
ease progression.13 Few data exist regarding the impact
of focal radiation on cognitive function: In a single study,
full-scale IQ was 1 standard deviation below normative
means in a group treated with radiation to the posterior
fossa.14 Serial and comprehensive neurocognitive evalu-
ation is critical in this vulnerable group of young patients
to evaluate the potential benefit of such new strategies in
sparing cognitive function.

Comparing the cognitive functioning of twins with
overlapping genetic backgrounds and comparable socio-
economic, prenatal, perinatal, and family history, but
discordant for a brain tumor, can provide important
preliminary information on neurocognitive late effects
of focal radiation.13 Twin case-control studies have doc-
umented poor spine and upper and lower limb growth,
and deteriorated intellectual ability in twins treated with
craniospinal radiation relative to their nonaffected
sibling, after treatment with a protocol including focal
radiotherapy. If focal radiation has an adverse impact
on early neurocognitive functioning, then over time the
affected twin treated should demonstrate poorer perfor-
manee in cognitive and behavioral function relative to
her nonaffected twin.

Materials and Methods

We saw the dizygotic same-sex preschool twins for
neurocognitive and behavioral assessment on two occa-
sions: (1) 21 months after diagnosis of a posterior fossa
medulloblastoma for the affected twin (and 12 months
after the completion of focal posterior fossa radiation) and
(2) 12 months later. The twins were 16 months of age
at the time of diagnosis. The Wechsler Preschool and
Primary Scale of Intelligence—Revised (WPPSI-R) was
used to assess intelligence. Receptive and expres-
sive language ability was evaluated using the Peabody
Picture Vocabulary Test—Third Edition (PPVT-III) and
the Preschool Language Scale (PLS). The Beery Visual-
Motor Integration Test (VMI) was used to evaluate
visual-motor integration. Further, well-validated and
reliable experimental tests of parent–child interaction,
social competency, and goal-directed play were used.19
For these videotaped observational measures, children
engaged in a number of tasks with their mother, with the
examiner, or by themselves, and relevant behavior was
recorded. All the experimental measures predict later
cognitive and social skills in young children at biologi-
cal risk over and above the contributions of intelligence
measures.19

Case History

Affected Twin Case History

The affected twin was born at 36 weeks by induced vagi-
nal delivery and weighed 3 pounds 11 ounces. Because
of her low birth weight, she received neonatal intensive
care unit intervention, including respiratory support
and tube feeding. She remained hospitalized for 2 weeks
after birth. Her early developmental motor milestones
(i.e., sitting alone, crawling, and walking) were all met at
the expected ages; however, her early language develop-
ment was delayed prior to tumor diagnosis.

At 16 months of age, the affected twin presented with
a 3-week history of intermittent vomiting and irritabil-
ity, progressive ataxia, and lethargy. A CT scan demon-
strated a midline posterior fossa mass with marked
dilation of the lateral ventricles and compression of the
fourth ventricle. The tumor was incompletely resected:
there was tumor invasion of the brainstem along the infe-
rior margins of the fourth ventricle bilaterally that pre-
cluded total resection. An external ventricular drain
was first inserted, and 11 days later a left ventriculoperi-
toneal shunt was placed to address hydrocephalus. Patho-
logical evaluation was consistent with medulloblastoma,
with tumor cytogenetics abnormal with hypertriploidy
and cerebrospinal fluid positive for tumor cells. Based on
these findings and combined with the presence of resid-
ual tumor, she was treated with MOPP chemotherapy
(mustard IV, vincristine, procarbazine, and prednisone).
Subsequent imaging revealed response to therapy, with
a small residual in the area of the foramen of Luschka
remaining.

In order to avoid/delay craniospinal radiation, she
was treated with high-dose chemotherapy (intensifica-
tion with busulfan/thiotepa) followed by autologous
stem cell rescue at 20 months of age and then with 5,400
cGy/30 daily fractions via focal stereotactic intensity-
modulated radiation therapy (IMRT) to the surgical cav-
ity plus a 1.5-cm margin (Fig. 1). Although the affected
twin lost many of her developmental motor milestones
during treatment, she recovered all of them by 6 months
posttreatment. Follow-up MRI showed no evidence of
residual or recurrent disease. Both Italian and English
were spoken in the home. The affected twin was 37
months old at the time of the first neurocognitive assess-
ment and was 49 months old at second assessment. Thus,
she was evaluated approximately 12 and 24 months after
completion of radiotherapy.

Nonaffected Twin Case History

The nonaffected twin was born at 36 weeks by induced
vaginal delivery and weighed 4 pounds 14 ounces. She
was monitored in hospital for 3 weeks after birth due to
her relatively low birth weight. The nonaffected twin’s
early developmental motor milestones (i.e., sitting alone,
crawling, and walking) were mildly delayed; she sat at 8
months and walked at 15–18 months. She demonstrated
significant speech-language delay and has been seen for
Sensive language function across both assessments. The PLS index of receptive language was significantly higher than the expressive language index for both twins. The nonaffected twin demonstrated stable low-average performance on receptive language tasks across both assessments. Consistent with the pattern observed for intellectual measures, the affected twin demonstrated improvement in expressive and receptive language from the first to the second assessment. Both twins demonstrated average receptive vocabulary (PPVT-III). The nonaffected twin’s scores were higher than the affected twin’s and showed substantial improvement in relative functioning from the first to the second assessment.

Visual-motor integration (VMI) improved for both twins across assessments (Table 1), from low-average to average ability. The affected twin demonstrated higher test scores compared to her sister at both time points.

Observational measures were videotaped and scored by two coders who were blind to the medical status of the twins. Consistent with the pattern observed for the standardized tests, ratings of the affected twin’s behavior in the tasks of social interaction and competence improved across assessment sessions. Ratings of the quality of social play interactions for both parent and affected twin increased from the first to second assessment. The affected twin was rated as being more responsive to and socially engaged with her mother and more engaged with the toys she was playing with and her general environment. Ratings of the mother’s interactions corresponded with this pattern, with increased levels of warmth, supportive actions, and responsiveness noted for the second assessment relative to the first. Both child and parent ratings remained the same for the nonaffected twin: the quality of interactions between the nonaffected twin and the mother were rated as higher than those with the affected twin during the first assessment, but with the improvement noted for the affected twin, ratings were essentially the same for both twins at the second assessment. The affected twin also showed improved social competence across assessments, with increased use and
complexity of language and in cooperation and initiative from the first to the second assessment sessions. No increases in ratings of social competence were evident for the nonaffected twin. Finally, for independent exploratory play with novel toys, the affected twin and the nonaffected twin demonstrated similar frequencies of functional play during the first assessment. However, at the second assessment, the nonaffected twin showed increases in her level of play and engagement, and exploration of toys and her play was more advanced in terms of problem solving. In contrast, functional play in the affected twin decreased. These results are consistent with the parent report that with age the affected twin became more cautious and less likely to spontaneously engage in new activities without maternal support.

**Discussion**

This case study is the first to examine serial neurocognitive and behavioral outcome after treatment with focal radiation for medulloblastoma in a preschool child, relative to her twin sister. A striking finding was improvement in intelligence, language, and visual-motor functioning in the affected twin from 12 months to 24 months after treatment with focal radiation. The affected twin, for the most part, demonstrated higher standard scores than her unaffected sister, who demonstrated a normal rather than accelerated pace of development over the same time period. Further, improved functioning was also evident in ratings of parent–child interaction and social competence for the affected twin. The affected twin’s improvement likely reflected normalization of functioning after illness as her medical condition improved and she experienced increased opportunities that stimulated her behavioral and cognitive development.

Our findings are notable compared with the very poor intellectual outcome typically associated with craniospinal radiation in infants and young children. Focal posterior fossa radiation still encompasses substantial amounts of the cerebral hemispheres, including occipital and parietal lobes, thalamus, and diencephalon, and has been associated with relatively poor intellectual outcome. In the present case study, the affected twin was treated with IMRT, which yielded volumes restricted primarily to the tumor bed and involved dose modulation, sparing cerebral tissue from a significant amount of radiation. Hence, IMRT may be especially critical in preserving cognitive function and may be useful for addressing concerns regarding cognitive outcome in this vulnerable population.

Further, we found that measures of preschool children’s social and behavioral functioning, including parent–child interaction, social competence, and goal-directed play, are useful for demonstrating the social consequences of disease and are sensitive to improvement with normalization of function after treatment.
Hence, these measures may be useful in examining outcomes in larger samples of preschool patients. This would yield ecologically valid information, may be useful in predicting future cognitive and social functioning, and can provide important information for developing home-based interventions for young children. Comprehensive assessment of multiple areas is important because subtle deficits may emerge for patients treated with focal radiation that are not detected using only standardized cognitive tests, despite intact intellectual functioning.

Finally, our findings must be considered in the context of previous slight developmental delays for both twins, and their very poor expressive language, which may reflect the bilingual language environment in which the twins reside or may be a consequence of their birth history and low birth weight. However, the twins’ history reflects the reality that children with a range of premorbid backgrounds are treated for brain tumors, and the impact of treatment manifests within the context of their broader developmental functioning. Further, because of the case study design, we report qualitative descriptions of change over time. Certainly, the potential benefits of focal radiation require evaluation in larger patient series using quantitative analyses. Despite these constraints, our preliminary findings of improvement in intellectual, language, visual-motor, parent–child interaction, and social competence over time after treatment with focal posterior fossa IMRT are unique, and this study is the first to document minimal deleterious effects after treatment, albeit in a single case study.

References