BRAIN TUMOURS IN CHILDHOOD

For general information on brain tumours, please refer to the Summer 2006 POHN Newsletter found on our website (www.kidscancer.bc.ca, Network Newsletters)

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ACUTE MANAGEMENT

Children should be referred to a tertiary centre specialising in pediatric brain tumours management once a brain tumour has been diagnosed. Usually there is a role for a neurosurgical procedure such as relief of raised intracranial pressure by endoscopic third ventriculostomy, biopsy or resection. In the acute management of raised intracranial pressure dexamethasone may be indicated preoperatively to decrease oedema or anticonvulsants for management of seizures. If there is evidence of pending herniation (cushing’s triad as indicated by high systolic blood pressure and widened pulse pressure, bradycardia and abnormal breathing), a fixed dilated pupil, decreased level of consciousness, and/or decerebrate posturing, consider 20% mannitol +/- intubation on the way to the operating room.

ADVANCES IN THE BIOLOGY OF BRAIN TUMOURS AND RECENT DISCOVERIES

Medulloblastoma
Molecular advances in understanding these tumours have lead to the proposal that there are four groups of medulloblastomas based on their molecular signature and the aberrant signalling pathway involved. These groups appear to have distinct clinical manifestations and behaviour that have been reproduced in retrospective studies. The categories have been labelled group A (WNT), group B (Sonic Hedgehog), group C and group D. WNT signalling pathway aberration is related to Beta catenin mutations leading to increased protein synthesis and cell cycling; it is associated with loss of chromosome 6. Clinically the WNT type tends to occur in older children and has an excellent prognosis. Unfortunately it represents less than 20% of patients diagnosed. The Sonic Hedgehog pathway aberration is secondary to a PTCH mutation and associated with loss of chromosome 9q. This group, like the WNT group, is usually associated with a good prognosis. Historically, it has been shown that the subgroup of medulloblastomas with desmoplastic histology has a better prognosis. This subgroup is most often found in the group B Sonic Hedgehog category. Group B is also commonly found in those with an underlying genetic predisposition syndrome called Gorlin syndrome. Groups C and D are associated with neuronal and photoreceptor differentiation, loss of chromosome X, 8 or 17p and gain of chromosome 18 or 17q. Group D tumours have mainly classic pathology but can be anaplastic. They are more often metastatic at diagnosis, occurring in all age groups but more commonly in children. They have a worse prognosis than groups A and B. Type C represents almost 50% of cases and is particularly common in children and infants. It appears to be associated with the highest recurrence rate and particularly poor prognosis. These findings have yet to be validated in a prospective fashion. However, we expect this information will allow us to develop rapid testing to identify these groups, and tailor therapy according to molecular signatures such as providing less intense therapies and therefore fewer side effects for those with the WNT signature as well as developing novel and more intense therapies for those with, for example, Type C signatures.

Figure from M Taylor et al: The molecular subgroups of medulloblastoma: the current consensus. Acta Neuropathol, Dec 2011.
Ependymoma
Recent discoveries have delineated the ependymoma genome with nine different types of ependymoma, and four different molecular signatures for supratentorial and posterior fossa types. This has lead to the development of human ependymoma mouse models for the first time. Based on molecular profiling, different types of ependymoma may be emerging. One type in particular appears to be more commonly occurring in the lateral recess, and be associated with metastases at recurrence and a worse prognosis. Chromosomal gain of 1q, telomerase expression and upregulation of tyrosine receptors, particularly EGFR, have been associated with poor prognosis. These findings have yet to be validated in a prospective fashion but are confirming our suspicion that not all ependymomas will behave the same based on their genetic makeup. In addition these findings are leading to the development of novel agents to combat ependymoma.

Glioblastoma
Once again molecular signatures enlighten us in this disease, revealing that pediatric and adult glioblastoma are different, explaining why some cases of pediatric glioblastoma can be cured with chemotherapy following resection.

Conclusion
Management of these malignant tumours is continuing to progress with the exploration of the following:

- Lowering doses of radiation in patients with medulloblastomas who appear to have a good prognosis on clinical grounds
- Addition of chemotherapy during radiation in poor risk medulloblastoma and high grade glioma
- Addition of chemotherapy in ependymoma in high risk patients

In infants and young children, we continue to fine tune the intensive chemotherapy approaches, with excellent prognosis in some subgroups of medulloblastoma without the damaging effects of radiation to the developing brain. We look forward to ongoing developments in research that will allow us to cure more patients and minimise the long term cost to the patients who survive this disease.

The Role of Radiation Therapy in the Treatment of Pediatric Brain Tumours

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Successful treatment of pediatric brain tumours generally involves a multidisciplinary approach with surgery, chemotherapy and radiation therapy (RT). RT to the tumour bed is often important to reduce the risk of tumour recurrence. However, RT can be associated with significant long-term side effects, and much has been done in the past 10 to 20 years to reduce the amount of RT given or even avoiding RT completely in the treatment of tumours such as medulloblastoma in very young children. Our ability to target tumours and spare surrounding normal tissues has also improved significantly.

RT involves targeting the tumour with very high energy X-rays. Diagnostic MR imaging can be “fused” with planning CT scans to ensure that the pre-operative location of the brain tumour is carefully identified for RT treatment planning. Generally children are treated with 3-D conformal therapy”. This involves “aiming” RT from multiple different directions so that the high dose RT treatment volume conforms to where the tumour is located. Brain tumours often infiltrate surrounding normal tissue for some distance beyond the main tumour itself and a “margin” of normal tissue also needs RT to treat microscopic spread of disease.

Sometimes, when it is safe to treat with narrower margins (for example, a tumour such as craniopharyngioma with a cystic component and well defined edges) special techniques can be used to spare surrounding normal tissue. These techniques include IMRT (Intensity Modulated Radiation Therapy where the treatment intensity varies at different depths), Rapid-Arc Therapy (a type of rotating IMRT), stereotactic RT (where a very small volume is precisely targeted) and proton therapy. We do not have a proton facility in British Columbia, but children, for whom this modality has an advantage, are sent out of Province for treatment at a Proton Facility. Protons are a type of particle therapy which has the same radiobiological effect as standard RT, but it is possible to make the treatment very highly focused. There is much debate about which treatment technique is best in some circumstances.

Different tumours require different treatment approaches with RT. Medulloblastoma (a small round blue cell tumour arising in the posterior fossa) in children aged 6 and older is generally treated with initial surgical resection, RT to the whole brain and spine, with a “boost” of extra RT to the posterior fossa where this tumour arose, together with chemotherapy. Ependymoma is also a posterior fossa tumour, but after surgical resection the patient is given very high dose RT to the posterior fossa alone, and the brain and spine are only treated if the tumour has already spread to those areas. Children treated in BC are usually enrolled in Children’s Oncology Group (COG) studies and, through these studies, we learn about the effectiveness of different treatment strategies and how to improve therapy.

Long term side effects of RT include developmental delay and neurocognitive deficits, damage to the pituitary with growth hormone and other hormone deficits, primary hypothyroidism and hearing problems. There is also a very small increased risk of strokes and second tumours arising within the RT field many years after therapy. The severity of these side effects depend on many factors, such as age at the time of therapy (young children often have serious learning disabilities after cranial RT), underlying patient genetic factors, the amount of RT given and time since treatment. It is becoming clear that as time from treatment increases, so does the risk of late effects for the survivor.

This is a complex subject and the website Pediatric Oncology Education Materials (POEM) contains information about the different childhood brain tumours as well as more general information about RT in the “Basic Oncology” section. There is also a “Late Effects” section which outlines some of the many chronic health problems that survivors of pediatric brain tumours may face.
Hearing Loss in Brain Tumour Survivors

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Radiation and chemotherapy can significantly impact the hearing of children undergoing treatment for CNS tumours. Therefore audiologic monitoring during and after therapy is standard of care for any patient who has received treatment with modalities that are known to cause hearing loss. The typical ototoxic treatments are those that include the platinum agents (cisplatin and to a much lesser degree carboplatin), as well as radiation therapy. Moreover, many of the supportive care medications that are needed during therapy, such as aminoglycoside antibiotics and Lasix, also damage the hearing of children. Therefore ongoing audiologic assessments are necessary and interventions are required in those who develop hearing loss to ensure optimal learning and development, as well as to facilitate socialization with peers.

Cisplatin is the most effective chemotherapeutic agent for many childhood brain tumours. Unfortunately, the biggest adverse drug reaction associated with cisplatin is sensineuronal hearing loss. This is irreversible and is due to direct damage to the inner hair cells of the cochlea. There is a very typical pattern seen on the audiograms of children with this toxicity, with initially the drop at high frequencies (8,000 Hz and above), but with each successive dose of cisplatin further drops are seen until the speech frequencies (500 – 6,000 Hz) become affected. It is estimated that 10-38% of adults who receive cisplatin have hearing loss. Unfortunately, children appear to be even more sensitive to this toxicity with up to 62% of children receiving cisplatin showing evidence of hearing loss. Moreover, the younger the child, the more frequent and more severe the hearing loss, with those under the age of 4 at the highest risk. The young child will also most likely have the most detrimental impact of hearing loss, given that speech and language have yet to be fully developed in this group. Recent evidence suggests that hearing loss appears to decline further years off therapy – which suggests that those who have had cisplatin in the past need ongoing audiologic follow-up years post therapy. Due to the awareness of this late effect, much research is being conducted to identify the causes and predictors of cisplatin-induced hearing loss, as well as the use of protective agents to prevent toxicity while achieving cure from the tumour.

Recently at BC Children’s Hospital, we identified 2 genes that appear to predict those who are at risk of cisplatin hearing loss. Using a case-control pharmacogenomics study, we enrolled children from British Columbia who received cisplatin and separated them into those with hearing loss (cases) and those with normal hearing (controls). We then collected DNA from these children and analyzed differences between the cases and controls at over 200 genes. Two genes were identified, COMT and TPMT, which appear to have different variants that were associated with risk of hearing loss. Specifically, those who had low functioning variants of these two genes appeared to have a very high rate of hearing loss. To ensure that these findings were real, these 2 genes were then investigated in a separate group of children from across Canada who received cisplatin. Again, COMT and TPMT proved to be associated with hearing loss. Therefore a test has been developed, which will be available in 2012, which can be used to predict hearing loss prior to the first dose of cisplatin being delivered. Those who test positive have a 93% probability of having significant hearing loss.

However, it is important to note that cisplatin remains a very important component of treatment of CNS tumours and cannot be removed from protocols without impact in cure rates. Therefore, other solutions are needed to try and minimize hearing loss. A current trial at Children’s Oncology Group (COG) is investigating the use of Sodium Thiosulfate (STS) as a protectant in those receiving cisplatin. This randomized control trial has nearly reached full accrual (136 subjects) and will hopefully have results by early 2013. If this agent shows effective protection of the hearing of these children, then it will become incorporated into standard care of children receiving cisplatin.

In the future, we hope to be able to continue to use cisplatin in the treatment of CNS tumours, but hopefully using genetics and protective agents we will be able to minimize or even eliminate hearing loss in children with cancer. In the meantime, all survivors who have received cisplatin, high dose carboplatin, and radiation should have intermittent audiological testing so that deficits can be found early and, with appropriate interventions, the functional impact of hearing loss can be minimized.

In 2012...

HCPs need to be aware of the information seeking behaviors of families and assist them in making informed and wise choices when retrieving health related resources on the internet.

Neuro-Oncology team members are working on a project to collate information and resources for families in a format that is easily accessible and easy to read on the oncology section (www.kidsccancer.bc.ca) of the Children’s Hospital website. Hopefully this will provide support and insight for those embarking on this journey.
POST-TRAUMATIC STRESS IN CHILDHOOD BRAIN TUMOUR SURVIVORS AND THEIR FAMILIES

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Psychologist

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Psychologist

With media coverage and international research efforts, the diagnosis of Post-Traumatic Stress Disorder (PTSD) has become recognized as a valid clinical entity in public as well as clinical circles. Closer to home, the link between post-traumatic stress reactions and cancer survivorship appears as a hot topic in the past decade or more of published research. To many of us working in the field of Pediatric Oncology, especially psycho-social team members, the growing body of research dedicated to understanding the phenomenon of post-traumatic stress (PTS) in pediatric cancer survivors and their family members is perhaps not surprising. Yet at first glance, the conflicting conclusions drawn from the data can be confusing. On the one hand, there is a strong message that the majority of pediatric cancer survivors and their family members adjust well over the long term. On the other, researchers repeatedly flag PTS reactions in pediatric cancer populations. Reviewing the literature with a more discerning eye, we notice that several researchers exclude CNS-related and brain tumour survivors from their studies because this cohort stands apart. Here, we opt for the reverse: we present findings on PTS reactions as they have been documented in pediatric oncology samples that DO include survivors of CNS tumours, including the brain. Our goal is to provide information to neuro-oncology patients and their family members.

The experience of cancer (its diagnosis and treatment) is commonly accepted as traumatic as defined by the Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition (DSM-IV). There are three types of characteristic symptoms that constitute a post-traumatic stress reaction: The first is persistent re-experiencing of the traumatic event. Parents, patients, and siblings will report that they have distressing images and thoughts of treatment that just “pop into” their heads, especially when they see, hear or smell something that reminds them of treatment. Nightmares or bad dreams are also a typical example endorsed. The second is persistent avoidance of stimuli associated with the trauma and numbing of emotional reactions. For cancer patients and their families who often do not have the option of avoiding triggering stimuli, such as medical procedures, treatments, and settings, this symptom may manifest through isolation from family members or friends and restriction of emotion (e.g. not feeling much if at all). The third is increased anxiety or arousal that may present as hyper vigilance, sleep difficulties, irritability, feeling jumpy, being easily startled, or having trouble concentrating. PTS reactions, much like those of war and accident victims, can begin at any point in the cancer journey - soon after diagnosis, during treatment, or even years after the end of treatment.

PRESENCE OF PTS

A consistent research finding is that a considerable proportion of pediatric cancer survivors and their family members experience at least sub-clinical levels of PTS at some point in their cancer journey (Taieb, Moro, Baubet, Revah-Levy, & Flament, 2003). That is, although a diagnosis of PTSD is not usual during or after treatment, the endorsement of some PTS symptoms is. For example, in an American sample of pediatric cancer patients and their families, 99% of the participating families had at least one family member endorse re-experiencing symptoms (Kazak, Alderfer, Rourke, Simms, Streisand, & Grossman, 2004). Similarly, in an Israeli sample of survivors of childhood cancer, only 16% of participants reported an absence of PTS symptoms; the large majority endorsed moderate or severe PTS reactions (DeKeyser Ganz, Raz, Gothelf, Yaniv, & Buchval, 2010).

In one of the few studies of parents of childhood brain tumour survivors, 44% of parents endorsed severe levels of PTS following treatment (Fuemmeler, Mullins, & Marx, 2001). Similarly, Bruce, Gumley, Isham, Fearon & Phipps (2011) reported that over one-third of their British sample of childhood brain tumour survivors and 29% of their parents reported severe levels of PTS.

PREVALENCE OF PTSD

Across samples, current cancer-related rates of PTSD have ranged from almost 5% to 21% in childhood cancer survivors and 6% to 25% in their parents. Lifetime prevalence of PTSD has been estimated to range between 20% to 35% in childhood cancer survivors and between 27% to 54% in their parents (see Bruce, 2006, for a review). In general, rates of PTSD in adult survivors of childhood cancer are on par with those in the general population. In parents, however, rates of PTSD are significantly higher than in the general population, and higher in comparison to parents with children with other chronic, serious illnesses such as diabetes (Fuemmeler, Bernard, Mullins, Van Pelt, Carpenter, & Parkhurst, 2005).

Comparing the experiences of family members indicates that they are different. For example, Kazak et al. (2004) reported very low overlap of current or lifetime PTSD and of PTS symptomatology among adolescent survivors, mothers, and fathers. Similarly, Landolt, Vollrath, Ribi, Gnehm, & Sennhauser (2003) found no association between parent and child PTS, although they did find mother and father levels of PTS to be significantly correlated. Conversely, in a study on the benefits of childhood cancer survivorship, children’s benefit finding was not correlated to parent’s ratings of post-traumatic growth (Michel, Taylor, Absolom, & Eiser, 2009). These findings caution us against assuming that one family member’s experience is representative of others, and they highlight the importance of assessing parents and youth independently.

RISK FACTORS FOR BRAIN TUMOUR SURVIVORS AND THEIR FAMILIES

What are the risk factors that distinguish those individuals who develop a full blown PTSD from the majority who do not? This question has yet not been well addressed in brain tumour survivors and their families. Again, the existing literature in pediatric oncology yields mixed results often related to methodology or sample considerations. Here, we identify the most robust findings across studies.

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As noted earlier, PTS symptoms can present at any time. The data indeed shows that the amount of time passed since a person is diagnosed is not a predictor of past or current PTSD (Bruce, 2005). This finding suggests that symptoms do not necessarily go away with time and that the proverb "time heals all wounds" does not fit with respect to PTS symptoms. Objective quantifiers of treatment based on medical data such as treatment intensity, severity, duration, and diagnostic prognosis have also been found to be weak predictors of PTS and PTSD (Bruce, 2005). Rather, it is the participant’s subjective appraisal (i.e. the perception or recollection of the patient, parent or sibling) of cancer treatment that has repeatedly been shown to predict cancer-related PTS and PTSD (Taieb, Moro, Baubet, Revah-Levy & Flament, 2003). Other individual perceptions, including those of cancer threat (i.e. the sense that their cancer can return), low social support (e.g. few friends), and poor family functioning (e.g. low communication, high chaos) have been associated with higher PTS symptoms and a greater likelihood of being diagnosed with PTSD (Bruce, 2005).

Certain characteristics present before and after cancer diagnosis has also been found to be reliably associated with level of PTS symptoms endorsed afterward. These include female gender, past experience of stressful life events, and emotion-focused coping (i.e. avoidance, distancing oneself from the situation, controlling one’s emotions; Bruce, 2005). Physical late-effects (e.g. growth failure, cardiac impairment, and functional outcome) have also been associated with higher levels of PTS symptoms in childhood cancer and their parents (Landolt et al., 2003). Phipps and his colleagues (2009) indicate that personality factors, particularly an anxious disposition, are a strong determinant of PTS. For practitioners, it is important to keep these factors in mind so that you can follow up on these families who may be more likely to be struggling.

**SUMMARY**

The jury may not be out regarding whether the experience of PTS symptoms and PTSD among survivors of childhood cancer and their families is a widespread late effect. When we focus our own investigation in the field of PTS and Pediatric Oncology on those studies that include brain tumour survivors, we find enough evidence indicating that clinicians should be mindful of the potential presence of PTS in their families. Although the majority of brain tumour survivors and their parents will not meet the criteria for PTSD, the available data suggests that a subset of patients and perhaps an even larger subset of parents will experience PTS symptoms at some point in their cancer journey. Even subclinical levels of PTS can be distressing and disruptive to family members, particularly if they are not aware of how commonly these reactions are reported.

In our interactions with survivors of childhood brain tumours and their family members it may be helpful to remember some of the main findings reported here. Symptoms can have their onset at any point on the journey, from diagnosis to many years post-treatment. It is the patients’ and parents’ perception of their experiences that is most telling of whether they are at risk, and not objective characteristics (e.g. prognosis, treatment duration and intensity). Certain factors present prior to the cancer diagnosis appear to increase risk for individuals.

Physicians, nurses and allied health care providers in the community are in a valuable position to assess whether children and/or parents may need additional support to process their experiences and manage their PTS symptoms. Referrals to mental health professionals including psychologists, counselors or social workers should be considered. In our experience, parents and survivors feel validated when we draw on the phenomenon of PTS. By accepting their symptoms as legitimate and not "crazy", survivors and parents find renewed hope and motivation to work on returning to a better level of emotional and social functioning.

**REFERENCES**


The Provincial Pediatric Oncology/Hematology Network

The Network is an interdisciplinary organization whose goal is to ensure appropriate diagnosis, management, follow-up, and end-of-life care for pediatric patients with malignancies and blood disorders.

The Network supports community hospitals and practitioners, and develops partnerships with other health care facilities to enable seamless and integrated care for patients and families on treatment and off treatment.

It will further develop and enhance the research programs of basic, translational, and clinical research to better childhood cancer control and improve outcomes for these patients and their families.

For More Information

To learn more about the Provincial Pediatric Oncology/Hematology Network, or to submit articles or stories to this newsletter, please contact:

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CARE OF THE ADOLESCENT WITH CANCER

Too Young, Too Old, Where Do I Fit In?

Thursday, May 10, 2012 - Evening session
Friday, May 11, 2012 - Full day session
Chan Centre for Family Health Education, BC Children’s Hospital, Vancouver, BC

The Division of Oncology/Hematology/BMT, Department of Pediatrics, University of British Columbia presents a multidisciplinary conference on Care of the Adolescent with Cancer. This conference will include discussions on ethical considerations, strategies and interventions to improve the care for this population through the trajectory of illness and survivorship. We will hear from health care professionals with expertise in this field and learn from the adolescents themselves.

Preliminary Agenda:

- Post Traumatic Stress Disorder in Adolescents with Chronic Illness
- Adolescent Brain Development
- Ethics and Decision-Making in Adolescent Care
- Sexuality and Fertility Preservation
- “Does the Journey Ever End…Through Our Eyes” – adolescents’ and parents’ perspective on recovery and challenges of survivorship
- “Let Me Help You Help Me Better” – adolescents’ insights on how to improve care to adolescents
- “A Funny Thing Happened to Me on the Way to Chemotherapy” – Dr. Dan Shapiro

More information to follow in the coming months at www.kidscancer.bc.ca

CME accreditation to be confirmed.

15TH INTERNATIONAL SYMPOSIUM ON PEDIATRIC NEURO-ONCOLOGY (ISPNO)

June 24-27, 2012
Sheraton Centre Hotel, Toronto, ON

ISPNO has become the premier event in the paediatric neuro-oncology community. This symposium is a special meeting at which new information and results can be shared and new collaborations can be established for health care professionals involved in the care of children and adolescents with central nervous system tumours. The program will feature plenary and poster sessions, as well as an Education Day and a Family day.

For more information visit the ISPNO 2012 website (http://www.ispno2012.com/home)