Birth Anomalies and Obstetric History as Risks for Childhood Tumors of the Central Nervous System

WHAT'S KNOWN ON THIS SUBJECT: Primary central nervous system tumors are the most common solid tumor in the pediatric population. Little is known about the causes of these tumors, although a small proportion are associated with genetic syndromes.

WHAT THIS STUDY ADDS: This study reveals that the presence of birth defects increases the incidence of childhood central nervous system tumors, as does a maternal history of late fetal losses. These findings suggest that genetic errors in development may drive the formation of central nervous system tumors in some children.

abstract

OBJECTIVE: The causes of childhood central nervous system (CNS) tumors are largely unknown. Birth characteristics have been examined as possible risk factors for childhood CNS tumors, although the studies have been underpowered and inconclusive. We hypothesized that birth anomalies and a mother's history of previous pregnancy losses, as a proxy for genetic defects, increase the risk for CNS tumors.

METHODS: From the California Cancer Registry, we identified 3733 patients aged 0 to 14 years with CNS tumors, diagnosed from 1988 through 2006 and linked to a California birth certificate. Four controls were matched to each patient. We calculated odds ratios (ORs) for the reported presence of a birth defect and for history of pregnancy losses by using logistic regression, adjusted for race, Hispanic ethnicity, maternal age, birth weight, and birth order.

RESULTS: Offspring from mothers who had ≥2 fetal losses after 20 weeks' gestation had a threefold risk for CNS tumors (OR: 3.13 [95% confidence interval (CI): 1.32–7.41]) and a 14-fold risk for high-grade glioma (OR: 14.28 [95% CI: 1.56–130.65]). Birth defects increased risk for the CNS cancers medulloblastoma (OR: 1.70 [95% CI: 1.12–2.57]), primitive neuroectodermal tumor (OR: 3.64 [95% CI: 1.54–8.56]), and germ cell tumors (OR: 6.40 [95% CI: 2.09–19.56]).

CONCLUSIONS: Multiple pregnancy losses after 20 weeks' gestation and birth defects increase the risk of a childhood CNS tumor. Previous pregnancy losses and birth defects may be surrogate markers for gene defects in developmental pathways that lead to CNS tumorigenesis. *Pediatrics* 2011;128:e652–e657

AUTHORS: Sonia Partap, MD, MS,[a] Jane MacLean, MD, MS,[a] Julie Von Behren, MPH,[b] Peggy Reynolds, PhD,[b,c] and Paul G. Fisher, MD, MHS[a,d,e,f]

Departments of [a]Neurology, [d]Pediatrics, [c]Health Research and Policy, [e]Neurosurgery, and [f]Human Biology, Stanford University, Stanford, California; and [b]Cancer Prevention Institute of California, Berkeley, California

KEY WORDS

childhood brain tumors, congenital anomalies, birth defects, central nervous system tumors

ABBREVIATIONS

CNS—central nervous system
CCR—California Cancer Registry
MB—medulloblastoma
PNET—primitive neuroectodermal tumor
GCT—germ cell tumor
LGG—low-grade glioma
HGG—high-grade glioma
OR—odds ratio
CI—confidence interval

All authors provided substantial contributions to the conception, design, data collection, analysis, and interpretation of the manuscript. The article's contents were reviewed and edited by all parties, and final approval was unanimous.

www.pediatrics.org/cgi/doi/10.1542/peds.2010-3637

doi:10.1542/peds.2010-3637

Accepted for publication May 5, 2011

Address correspondence to: Sonia Partap, MD, MS, Division of Child Neurology, Stanford University, 750 Welch Rd, Suite 317, Palo Alto, CA 94304. E-mail: spartap@stanford.edu

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: *Dr Partap's work was supported by a National Institute of Neurological Disorders and Stroke/National Institutes of Health Neurological Sciences Academic Development Award (K12 NS049648-05). This work was also supported, in part, by a Stanford Cancer Center Developmental Research Award. Dr Partap has no other financial disclosures. Dr Fisher serves/has served on editorial boards of the* Journal of Pediatrics, Journal of Neuro-Oncology, *and the* Journal of Clinical Oncology. *The other authors have indicated they have no financial relationships relevant to this article to disclose.*

Funded by the National Institutes of Health (NIH).

With ~2880 new cases annually in patients aged 15 years in the United States, primary central nervous system (CNS) tumors are the most common solid tumor of childhood and second only to leukemia in incidence of pediatric cancers.[1] Few causes of neuraxis tumors in children are known, aside from ionizing radiation and rare genetic syndromes.[2] Genetic predisposition has long been implicated as a cause of CNS tumors in all ages. Although syndromes such as tuberous sclerosis, neurofibromatosis type 1 and 2, and von Hippel-Lindau are recognized initiators of CNS neoplasms, such disorders account for only a small minority of CNS tumors.[3] Other known genetic links are lacking.

We hypothesized that children born with congenital anomalies and mothers with a history of pregnancy losses would have an increased risk of having a child with a CNS neoplasm. Maternal miscarriages and abortions may be a proxy for a predisposition, because fetal chromosomal aberrations are present in ~50% of aborted fetus samples in the first trimester.[4] Couples with ≥2 miscarriages are more likely to be genetic carriers of translocations and inversions, suggesting that future offspring may harbor a genetic anomaly and future cancer risk.[5] Indeed, children born with birth defects, often associated with genetic abnormalities, are at a two- to threefold increased risk of pediatric cancer.[6–8] As with all epidemiologic studies for rare disorders, a large population base is essential to overcome sample size limitations. Therefore, we used the California Cancer Registry (CCR), which records all cases of cancer diagnosed in California and reported by state law, to study the risks of congenital anomalies and prior fetal losses for a childhood CNS tumor.

METHODS

CNS tumors were ascertained for all children diagnosed younger than age 15 years between 1988 and 2006 through California's population-based surveillance system, the CCR. Cases were classified by using the *International Classification of Childhood Cancer, Third Edition*[9] and sorted into the categories medulloblastoma (MB), other primitive neuroectodermal tumor (PNET), ependymoma, and intracranial/intraspinal germ cell tumor (GCT). We classified pineoblastomas as PNET. Rather than using "astrocytomas" as a group classification, these tumors were sorted into 2 categories: low-grade glioma (LGG) and high-grade glioma (HGG). The LGG and HGG groups were created to reflect clinically relevant biological differences in childhood gliomas. We thus grouped pilocytic astrocytomas, astrocytomas not otherwise specified, and other grade I and II gliomas from the World Health Organization grading system into the LGG category. We grouped malignant gliomas, anaplastic astrocytomas, and other grade III and IV gliomas into the HGG category.

A linkage of all identified cases to their respective California birth certificates, from the California Office of Vital Records' birth certificate database, was then performed, using probabilistic record linkage software from the Centers for Disease Control and Prevention (Link Plus).[10]

Control subjects were also selected from the California Office of Vital Records' birth certificate database. Each case patient was matched with 4 control subjects by exact date of birth and gender. All controls were cross-referenced with the vital records' death certificate database to exclude those control subjects who had died before the patient's diagnosis. Any such controls were replaced with a new control subject. Variables obtained from California birth certificates included self-reported race, Hispanic ethnicity, gender, birth weight, gestational age, singleton or multiple birth, maternal and paternal age, maternal pregnancy history (including number of pregnancies, live births, prior pregnancy losses, and time since last live birth), prenatal care, method of delivery (vaginal or cesarean delivery), complications during pregnancy and delivery, and birth defects. Prior pregnancy losses were subdivided into 3 categories: none, 1, or ≥2. Fetal gestational age at the time of loss was also recorded as either ≤20 or >20 weeks' gestation. Birth defects were coded under "abnormal condition and clinical procedures relating to the newborn." Birth certificates were completed at the time of birth by the delivering providers (eg, obstetricians, midwives). We excluded abnormal birth conditions that were not congenital defects, such as fetal alcohol syndrome, birth injury, meconium aspiration, seizures, ICU admission, and assisted ventilation. The gestational age of the prior pregnancy losses and the birth defect information were not available for the birth years 1973 and 1977 (74 patients and 296 control subjects).

To calculate odds ratios (ORs) and 95% confidence intervals (CIs), conditional logistic regression was used with univariate and then multivariate models. All analyses were completed by using SAS 9.0 (SAS Institute, Inc, Cary, NC). The study protocol was reviewed and approved by the institutional review boards of Stanford University, Cancer Prevention Institute of California, California Office of Vital Records, and California State Committee for Protection of Human Subjects.

RESULTS

CNS Tumor Subtypes

A total of 4560 newly diagnosed CNS tumors were identified in children

TABLE 1 CNS Tumor Types in Case Patients

Tumor Type	*n* (%)
LGG (WHO I, II)	1380 (37.0)
HGG (WHO III, IV)	757 (20.3)
Embryonal tumors	
MB	516 (13.8)
PNET	402 (10.8)
Ependymoma	292 (7.8)
GCT	187 (5.0)
Choroid plexus	75 (2.0)
Craniopharyngioma	18 (0.5)
Other	106 (2.8)

WHO indicates World Health Organization.

younger than age 15 years between 1988 and 2006. Among the patients identified in the CCR, 3733 were linked to a California birth certificate, for an overall 82% linkage rate. However, among children known by the CCR to have been born in California, the linkage rate was 92%. A total of 14 932 controls were selected, individually matched 4:1 to patients.

Gliomas comprised the majority of cases, with 2137 subjects; 1380 cases were classified as LGG and 757 as HGG (Table 1). There were 889 embryonal tumors (516 MB, 402 PNET [29 of these were pineoblastomas]) and 292 ependymomas. GCTs, choroid plexus tumors, and craniopharyngiomas constituted 7.5% of the cases collectively (187, 75, and 18, respectively).

History of Pregnancy Losses

Among the cases, 3083 mothers reported no prior fetal losses, 467 (8%) listed 1 loss, and 163 (4.4%) listed ≥2 losses. Only 11 cases had missing data. In the control group, 12 378 mothers had no recorded losses, 1844 (8.1%) had 1 previous loss, 655 (4.4%) had ≥2 losses, and 55 were unknown. When stratified according to any loss or number of prior losses regardless of the gestational age of the loss, there was no relationship to risk of CNS tumor (1 loss, OR: 1.04; ≥2 losses, OR: 1.00) nor by tumor subtype.

When further categorized by gestational age of the fetal loss, the number of pregnancy losses ≤20 weeks' gestation was not found to be a risk factor for CNS tumors in general or specific tumor subtypes in either univariate (1 loss, OR: 1.04 [95% CI: 0.93–1.16]; ≥2 losses, OR: 1.00 [95% CI: 0.84–1.19]) or multivariate analyses (Table 2). However, ≥2 prior fetal losses after 20 weeks' gestation did show an increased risk for a CNS tumor (OR: 2.50 [95% CI: 1.13–5.51]), with a 16-fold risk of HGG (OR: 16.00 [95% CI: 1.79–143.15]) (Table 3). Multivariate analysis revealed a consistent threefold increased risk for CNS tumors overall (OR: 3.13 [95% CI: 1.32–7.41]) and 14-fold (OR: 14.28 [95% CI: 1.56–130.65]) for HGG, but this finding was based on only 10 cases with 4 HGG cases. Univariate analysis revealed that a fetal loss >20 weeks' gestation seemed to be protective for LGG (OR: 0.49 [95% CI: 0.25–0.98]); 36 cases were in that cohort with 9 LGG cases. The numbers of cases in the MB, PNET, and ependymoma groups were too small for analysis.

Presence of Birth Defects

The presence of a birth defect was recorded in 45 (1.2%) patients and 90 (0.6%) controls. The odds of developing an MB, PNET, and GCT were elevated in patients with birth defects (Table 4). Patients with birth defects were then stratified according to age. Infants with a reported birth defect who were diagnosed when younger than 2 years of age had a significantly elevated risk for CNS tumors (OR: 1.70 [95% CI: 1.12–2.57]) and among children diagnosed with a CNS neoplasm at younger than 1

TABLE 2 Univariate and Multivariate Analysis of Prior Pregnancy Losses: Risk for Childhood CNS Tumors for Any Gestational Age and at ≤20 Weeks' Gestation

	All Cases	LGG	HGG	MB	PNET	GCT	Ependymoma
Losses, *n*	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Prior pregnancy loss at any gestational age							
Univariate							
1 prior loss	1.04 (0.93–1.16)	0.98 (0.82–1.18)	1.12 (0.88–1.42)	0.97 (0.71–1.31)	1.24 (0.91–1.69)	0.84 (0.52–1.37)	1.25 (0.87–1.80)
≥2 prior losses	1.00 (0.84–1.19)	0.81 (0.60–1.11)	1.33 (0.93–1.90)	0.93 (0.57–1.51)	0.98 (0.56–1.71)	0.75 (0.31–1.82)	1.56 (0.91–2.68)
Multivariate[a]							
1 prior loss	1.03 (0.92–1.15)	1.00 (0.83–1.20)	1.04 (0.84–1.33)	1.07 (0.78–1.47)	1.17 (0.84–1.61)	0.79 (0.47–1.33)	1.21 (0.82–1.78)
≥2 prior losses	1.01 (0.84–1.22)	0.78 (0.56–1.08)	1.22 (0.84–1.77)	0.98 (0.59–1.62)	0.91 (0.51–1.62)	0.78 (0.28–2.16)	1.60 (0.90–2.83)
Prior pregnancy loss at ≤20 wk' gestation							
Univariate							
1 prior loss	1.04 (0.94–1.17)	1.00 (0.83–1.20)	1.12 (0.88–1.42)	1.02 (0.75–1.40)	1.13 (0.82–1.56)	0.89 (0.55–1.44)	1.23 (0.85–1.80)
≥2 prior losses	0.98 (0.81–1.18)	0.84 (0.60–1.16)	1.14 (0.78–1.68)	0.96 (0.59–1.55)	1.01 (0.57–1.81)	0.64 (0.25–1.68)	1.65 (0.96–2.84)
Multivariate[a]							
1 prior loss	1.04 (0.92–1.16)	1.02 (0.84–1.23)	1.03 (0.80–1.33)	1.14 (0.83–1.58)	1.05 (0.75–1.47)	0.82 (0.49–1.39)	1.20 (0.81–1.79)
≥2 prior losses	0.94 (0.77–1.13)	0.75 (0.53–1.06)	1.07 (0.72–1.60)	1.00 (0.61–1.65)	0.99 (0.55–1.79)	0.79 (0.29–2.18)	1.59 (0.88–2.85)

Unadjusted and adjusted OR (95% CI).

[a] Adjusted for birth weight, birth order, race, Hispanic ethnicity, and maternal age.

TABLE 3 Univariate and Multivariate Analysis of Prior Pregnancy Losses After 20 Weeks' Gestation and Risk for Childhood CNS Tumors

	All Cases	LGG	HGG	MB	PNET	GCT	Ependymoma
No losses	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Univariate							
1 prior loss	0.72 (0.50–1.03)	0.49[a] (0.25–0.98)	1.08 (0.53–2.20)	Samples too small for analysis			
≥2 prior losses	2.50[a] (1.13–5.51)	1.60 (0.50–5.10)	16.00[a] (1.79–143.15)				
Multivariate[b]							
1 prior loss	0.80 (0.55–1.16)	0.55 (0.27–1.12)	1.03 (0.50–2.11)	Samples too small for analysis			
≥2 prior losses	3.13[a] (1.32–7.41)	2.96 (0.86–10.20)	14.28[a] (1.56–130.65)				

Unadjusted and adjusted OR (95% CI).

[a] $P < .05$.

[b] Adjusted for birth weight, birth order, race, Hispanic ethnicity, and maternal age.

TABLE 4 Univariate and Multivariate Analysis for Presence of Birth Defects and Risk of Childhood CNS Tumors

Presence of Birth Defect	All Cases	LGG	HGG	MB	PNET	GCT	Ependymoma
No	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Yes							
Univariate	2.00[a] (1.40–2.86)	0.85 (0.38–1.92)	1.11 (0.41–2.99)	3.00[a] (1.26–7.12)	3.64[a] (1.54–8.56)	6.40[a] (2.09–19.56)	1.00 (0.11–8.95)
Multivariate[b]	1.82[a] (1.25–2.65)	0.71 (0.29–1.72)	0.64 (0.19–2.24)	3.19[a] (1.29–7.87)	2.97[a] (1.21–7.28)	7.20[a] (2.10–24.63)	1.17 (0.13–10.61)

Unadjusted and adjusted OR (95% CI).

[a] $P < .05$.

[b] Adjusted for birth weight, birth order, race, Hispanic ethnicity, and maternal age.

year of age, those with a congenital defect noted at birth had an almost threefold increased risk (OR: 2.91 [95% CI: 1.68–5.05]).

DISCUSSION

In this large, population-based case-control study, we found a significant risk of CNS tumors in offspring whose mothers had already lost ≥2 fetuses after 20 weeks' gestation and among children with congenital birth defects. Furthermore, the risk of developing MB, PNET, and GCT—tumors that tend to arise in the midline of the brain—was elevated in children with birth defects noted just after birth. These findings all point to an underlying genetic predisposition for childhood CNS tumors, especially those in the very young or those located in the midline brain. Gene defects in developmental pathways for neurogenesis may be important in childhood CNS tumors. Indeed, the finding of CNS tumors in association with late fetal loss might point to developmental pathway aberrations rather than nonchromosomal changes, as one would expect chromosomal changes to cluster with early fetal loss.

With more than half of miscarriages having evidence of chromosomal aberrations,[4] this finding suggests that a genetic defect could be the cause. Previous studies of fetal loss and brain tumors with smaller samples have had mixed results.[11–15] A case-control study of 157 childhood CNS tumors revealed a higher risk for astrocytoma with prior fetal loss (OR: 1.9); however, the data were not adjusted for birth weight.[14] Adjusting findings for birth weight is imperative, because birth weight has been independently associated with CNS tumor risk.[16,17] In 1970, Choi et al[15] reported 157 cases and controls matched on race, gender, geographic area of residence, and age groups and found that mothers who had abortions had a higher incidence of brain tumors in future offspring than in controls. Moreover, these mothers also had a higher incidence of multiple abortions. Their study, like ours, did not specify if losses were elective or spontaneous. However, because of our unique cohort, not only could we assess CNS tumor risk and prior pregnancy losses, but we also had the power to stratify gestational age of loss and tumor subtypes, unlike prior studies. Understanding why HGG might be associated with prior pregnancy losses is not clear but could be related to the concept that congenital HGG might be a distinct entity.[18] In regard to our finding that a single fetal loss after 20 weeks' gestation was associated with lower future risk of LGG, we raise the possibility that a mechanism such as epigenetic change could be at play. An epigenetic change of variable magnitude in DNA, activated by the environment or intrinsically, might at times be incompatible with life yet at other times protective against tumorigenesis. The protective relationship between fetal loss and future LGG could also be spurious or due to chance.

We also found an increased risk of having a midline cerebral tumor (MB or GCT) in patients with a recognized congenital defect at birth, particularly for GCT. Adjusting for race in GCT cases

was essential because the incidence is higher in Asian populations[19]; multivariate analysis only strengthened the relationship. Profound risk for childhood CNS tumors was seen in younger children after age stratification, which reinforces conclusions discovered in other cohort studies.[3,6–8,20] In a Canadian cohort of 90 400 children, there was a sixfold cancer risk in the first year of life if anomalies were present. Children with birth defects had a twofold relative risk for developing leukemia, CNS tumors, and neuroblastoma.[7] A Scandinavian study of 5.2 million children linked birth records with cancer registries and observed an overall cancer risk in children with birth defects, with highest risk in those with trisomy 21, CNS malformations, and multiple congenital defects. Studies have shown that embryos with homeobox genes mutations have abnormal skeletal and segmental development that then manifest as congenital anomalies. These mutations may also predispose children to malignancies.[21] During the first year of life, cancer risk was four- to fivefold higher in those with defects. Patients with oral clefts had a higher incidence of CNS tumors but not other tumors,[20] again suggesting midline defects and midcerebral neoplasms to be genetically linked. This association is seen in Pai syndrome, a rare genetic syndrome with midline cleft defect and midline cerebral lipomas.[22] Similarly, MB and GCT arise almost exclusively in the midline cerebellum and pineal/suprasellar regions, respectively. Our findings are consistent with the Scandinavian and Canadian studies reporting an increased risk of cancer in the first year of life, and point specifically to midline CNS tumors.

Our study has several limitations. We were restricted to information collected on birth certificates. We did not have a method of assessing the accuracy of the data on prior pregnancy losses. In addition, there was no indication if fetal losses were spontaneous or elective. However, elective abortions are rarely performed after 20 weeks and only accounted for 1.3% of all abortions in the United States reported to the Centers of Disease Control and Prevention in 2005.[23] Many of the risk estimates, although significant, were only moderately precise, because of the small case numbers in the analyses according to tumor subtypes. Birth certificate data on the presence of birth defects are often incomplete and exclude our ability to capture congenital anomalies found after hospital discharge. Data reported on birth certificates may not be completed by individuals with the best training to detect defects.

CONCLUSIONS

Our population-based case-control study is the largest of its kind and shows a convergence of risk factors relating to pregnancy and birth defects, suggesting the possibility of underlying defects in developmental pathways. Our findings suggest a need for future studies on developmental genetic defects that predispose children to brain tumors. In addition to genetics, other factors such as environmental exposures, hormonal exposures in utero, or gene-environment interactions could also be involved in the etiology of these rare tumors.

REFERENCES

1. Central Brain Tumor Registry of the United States. CBTRUS statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2004–2006. In: Central Brain Tumor Registry of the United States. Available at: www.cbtrus.org. Accessed July 21, 2011
2. Baldwin RT, Preston-Martin S. Epidemiology of brain tumors in childhood: a review. *Toxicol Appl Pharmacol*. 2004;199(2):118–131
3. Narod SA, Stiller C, Lenoir GM. An estimate of the heritable fraction of childhood cancer. *Br J Cancer*. 1991;63(6):993–999
4. Goddijn M, Leschot NJ. Genetic aspects of miscarriage. *Baillieres Best Pract Res Clin Obstet Gynaecol*. 2000;14(5):855–865
5. De Braekeleer M, Dao TN. Cytogenetic studies in couples experiencing repeated pregnancy losses. *Hum Reprod*. 1990;5(5):519–528
6. Merks JH, Ozgen HM, Koster J, Zwinderman AH, Caron HN, Hennekam RC. Prevalence and patterns of morphological abnormalities in patients with childhood cancer. *JAMA*. 2008;299(1):61–69
7. Agha MM, Williams JI, Marrett L, To T, Zipursky A, Dodds L. Congenital abnormalities and childhood cancer. *Cancer*. 2005;103(9):1939–1948
8. Rankin J, Silf KA, Pearce MS, Parker L, Ward Platt M. Congenital anomaly and childhood cancer: a population-based, record linkage study. *Pediatr Blood Cancer*. 2008;51(5):608–612
9. Kramárová E, Stiller CA. The international classification of childhood cancer. *Int J Cancer*. 1996;68(6):759–765
10. Buehler JW, Prager K, Hogue CJ. The role of linked birth and infant death certificates in maternal and child health epidemiology in the United States. *Am J Prev Med*. 2000;19(1 suppl):3–11
11. Fear NT, Roman E, Ansell P, Bull D. Malignant neoplasms of the brain during childhood: the role of prenatal and neonatal factors (United Kingdom). *Cancer Causes Control*. 2001;12(5):443–449
12. Schüz J, Kaletsch U, Kaatsch P, Meinert R, Michaelis J. Risk factors for pediatric tumors of the central nervous system: results from a German population-based case-control study. *Med Pediatr Oncol*. 2001;36(2):274–282
13. Schüz J, Kaatsch P, Kaletsch U, Meinert R, Michaelis J. Association of childhood cancer with factors related to pregnancy and birth. *Int J Epidemiol*. 1999;28(4):631–639
14. Emerson JC, Malone KE, Daling JR, Starzyk P. Childhood brain tumor risk in relation to birth characteristics. *J Clin Epidemiol*. 1991;44(11):1159–1166
15. Choi NW, Schuman LM, Gullen WH. Epidemiology of primary central nervous system neoplasms. II. Case-control study. *Am J Epidemiol*. 1970;91(5):467–485
16. Von Behren J, Reynolds P. Birth charac-

teristics and brain cancers in young children. *Int J Epidemiol*. 2003;32(2):248–256

17. MacLean J, Partap S, Reynolds P, Von Behren J, Fisher PG. Birth weight and order as risk factors for childhood central nervous system tumors. *J Pediatr*. 2010;157(3):450–455
18. Hou LC, Bababeygy SR, Sarkissian V, et al. Congenital glioblastoma multiforme: case report and review of the literature. *Pediatr Neurosurg*. 2008;44(4):304–312
19. Goodwin TL, Sainani K, Fisher PG. Incidence patterns of central nervous system germ cell tumors: a SEER study. *J Pediatr Hematol Oncol*. 2009;31(8):541–544
20. Bjørge T, Cnattingius S, Lie RT, Tretli S, Engeland A. Cancer risk in children with birth defects and in their families: a population based cohort study of 5.2 million children from Norway to Sweden. *Cancer Epidemiol Biomarkers Prev*. 2008;17(3):500–506
21. Anbazhagan R, Raman V. Homeobox genes: molecular link between congenital anomalies and cancer. *Eur J Cancer*. 1997;33(4):635–637
22. Savasta S, Chiapedi S, Perrini S, Tognato E, Corsano L, Chiara A. Pai syndrome: a further report of a case with bifid nose, lipoma, and agenesis of the corpus callosum. *Childs Nerv Syst*. 2008;24(6):773–776
23. Gamble SB, Strauss LT, Parker WY, Cook DA, Zane SB, Hamdan S. Abortion surveillance: United States, 2005. *MMWR Surveill Summ*. 2008;57(13):1–32