Congenital glioblastoma multiforme: Is it curable?

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Abstract

Congenital brain tumours are a rare occurrence, accounting for 2% of all brain tumours presenting during childhood. Less than 15% of these congenital tumours turn out to be glioblastoma mutiforme. Here described, a newborn that presented with history of poor feeding and uncontrolled seizures since birth. He was the outcome of an uneventful pregnancy and normal delivery. His routine prenatal ultrasonographic scan in the gestational period was normal. Magnetic resonance imaging scans, after birth, revealed left temporal lobe haemorrhagic tumour with heterogeneous enhancement and significant mass effect. Left temporal craniotomy and complete resection of a histological proven glioblastoma multiforme was achieved. The baby received adjuvant chemotherapy for two years. He remained neurologically intact and seizure free with no recurrence at his 6th year of life.

The author reports this rare case of congenital glioblastoma multiforme that has the longest survival period in the literature and certainly the first reported in the Arab world. The literature was reviewed and the possible factors that favour long survival are discussed. *(p70-75)*

***Keywords**: Congenital, glioblastoma, infant, brain neoplasm, brain and pathology*

Introduction

Congenital brain tumours are quite rare, representing less than 2% of all paediatric central nervous system tumours, with a reported incidence of 1.1-3.6 per million live births.[5,11,18-20] In the series reviewing such tumours, the commonest types include germ cell tumours (teratomas) up to 40-54%, followed by primitive neuroectodermal tumours (neuroblastoma, medulloblastomas and retinoblastoma) in 10-20%, and primary neuroectodermal tumours, mostly glioblastoma multiforme (GBM) in 2-15%.[5,10,19,30,31,41] Associated anomalies, like cleft palate, cardiac and genitourinary system malformations are associated in up to 14% of children with congenital brain tumours.[15,41]

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The author reports this case of distinct congenital glioblastoma mutiforme (CGBM) that was successfully treated and still surviving after a prolonged period. The literature of the reported cases of CGBM was reviewed with analysis of the possible prognostic factors that may have some influence on long-term survival.

Case Report

A newborn male of an uneventful pregnancy of a 30-year-old female, delivered on March 1, 2000 via spontaneous vaginal delivery at the 39th week of gestation. He is the third child of non-consanguineous Saudi Arabian parents with no family history of brain tumours. During the gestation period, routine foetal ultrasonographic (US) scans were normal at the 18th and 30th weeks of gestation. At birth, his Apgar score was 7 and 10, and his weight was 3.250 grams. General and neurological examinations, including routine laboratory tests, were within normal. His mother reported brief episodes of blue spells and jittering that lasted just a few seconds since the first week of his life. He presented at King Faisal Hospital & Research Center (KFSH&RC) in Jeddah a week later because of poor feeding from frequent episodes of staring spells and cyanosis associated occasionally with tonic posturing of the extremities. General physical and neurological examinations were within

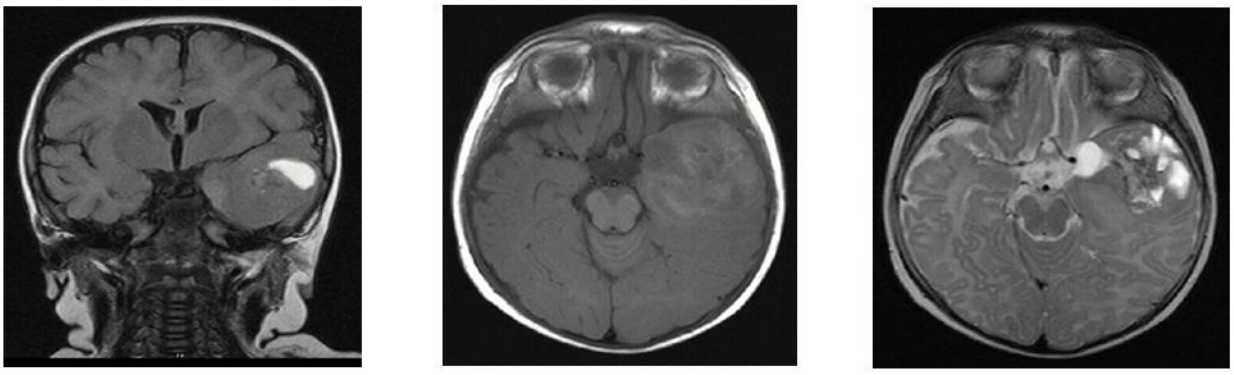


Figure 1a and b - Preoperative T1-weighted MRI scans demonstrating a 40 mm × 45 mm × 40 mm left haemorrhagic temporal tumour with heterogeneous enhancement. (**c**) Heterogeneous intensity on T2-wieghted image showing haemorrhagic components

normal at the 2nd week of age. The head circumference was on the 90th percentile and the anterior fontanel was 2 × 2 cm and soft. Routine laboratory screening on admission were within normal limits. Magnetic resonance imaging (MRI) scan demonstrated a 40 mm × 45 mm × 40 mm left haemorrhagic temporal lobe tumour, with areas of heterogeneous enhancement and significant mass effect (Fig. 1). There was no extra-temporal extension and the mesial structures of the temporal lobe were not involved. The seizures were difficult to control prior to surgery with several anti-epileptic medication trials (phenobarbitone, phenytoin, lamotrigine, and topiramate).

At surgery, a relatively soft and vascular tumour with areas of necrosis and dural invasion was encountered. Left temporal lobectomy, sparing the amygdale and the hippocampus, with complete resection of the tumour was achieved.

Histopathological examination with haematoxylin-eosin staining revealed the presence of polymorphic astrocytic tumour cells, hypervascularity, tumour cell mitosis, microvascular proliferation and pseudo-palisading necrosis consistent with glioblastoma mutiforme (Fig. 2a). Immunohistochemical studies were negative for synaptophysin, NSE, and cyto-keratin, but positive for GFAP, S-100 protein, and vimentin, with significant p53 over expression (Figs. 2b and c). Postoperative MRI scan performed within 24 hours revealed no residual tumour. The baby recovered well from surgery with good control of his seizures on lamotrogine and topiramate. He received postoperative adjuvant chemotherapy consisting of etoposide, vincristine, cisplatin and cyclophosphamide for two years. At six years, he remained seizure free with normal neurological development and good performance in school. There was no tumour recurrence on the last annual follow-up MRI scans (Figs. 3a and b).

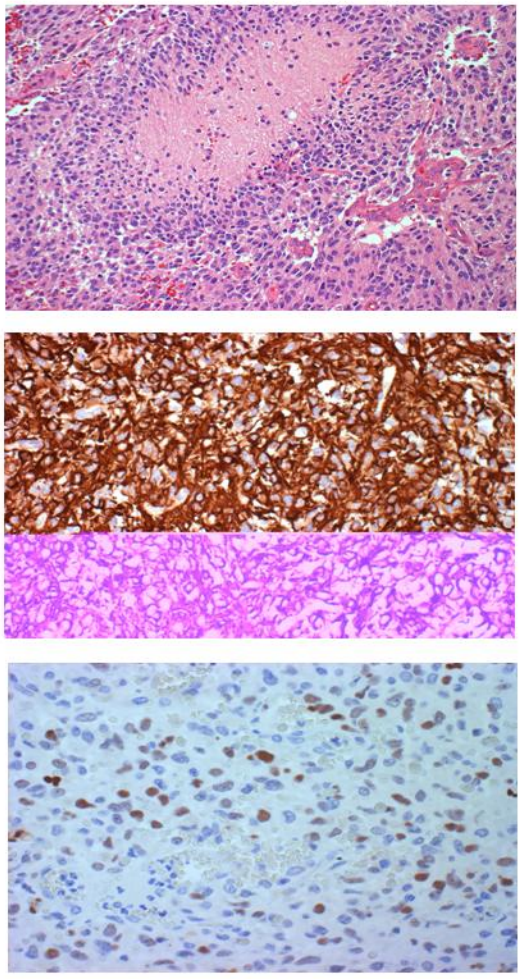
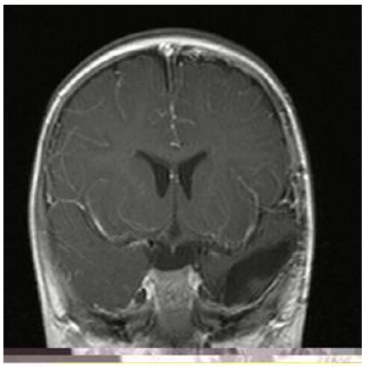


Figure 2a - Glial neoplasm displays marked endothelial proliferation, high mitotic rate and pseudopalisading necrosis (H&E × 200), (**b**) marked staining to GFAP (**c**) and p53 over expression



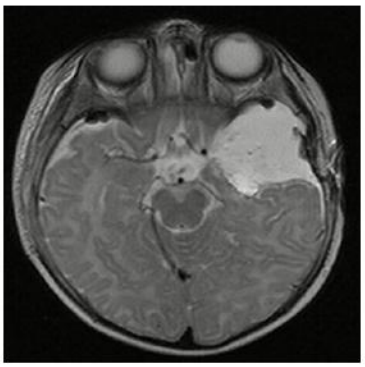


Figure 3a - Postoperative enhanced T1-weighted (**b**) T2-weighted MRI scans demonstrating no residual tumour at the 5th year of age

Discussion

Arnstein, et al defined a brain tumour to be congenital, when it presents within 60 days after birth.[3] Since then, a variety of definitions of "congenital" have been proposed. Solitare and Krigman defined congenital tumour as: 1) definitely congenital - present or producing symptoms at birth; 2) probably congenital - present or producing symptoms within the first week of life; and 3) possible congenital - present or producing symptoms within the first month of life.[37] Nine years later, Jellinger and Sunder-Plassmann proposed an alternate classification as follows: 1) definitely congenital - producing symptoms at birth or within the first 2 weeks of life; 2) probably congenital - producing symptoms in the first year of life; and 3) possibly congenital - producing symptoms beyond the first year of life.[20]

Since the first report by Holt in 1917 of CGBM in a seven-week-old male, the Medline literature search revealed a total number of 36 cases plus this case. The demographics of five cases; four in Buetow, et al and one in Halperin, reports were insufficient to be added to the summarisation in Table 1.[5,15]

The geographic distribution of the reported cases revealed that the majority of the published cases were from European and American countries and presumed to be of Caucasian origin. Eight cases reported from Asian countries were three cases from Japan, two from Korean, one from China, one from India, and this case being reported from Saudi Arabia.[6,18,21,23,28,35,36,39]

There has been a male predominance of 2:1, similar to that seen in adult GBM. Of the 25 reported cases, where previous pregnancy data was mentioned, the mean age of the mothers was 26 years (range of 17-43 years). Most of the infants were first pregnancies (10/25) followed by second pregnancies (7/25), third pregnancies (4/25), a single fifth pregnancy and a single sixth pregnancy.[6,27,28,35,42] Family history of congenital brain tumours was reported in only one infant where a cousin was born with a brain tumour.[42] The majority (27 cases) of these tumours have been located in the supratentorial region (Table 1), except four were located in the posterior fossa.[18,33,39,40] In the reported cases with documented prenatal US examination the tumour was detected in the third trimester.[1,6,9,13,14,16,22,23,26-28,35] In these reports, the descriptions were that of an echogenic lesion with brain shift and contralateral or bilateral hydrocephalus with or without haemorrhage.

Interestingly, in 11 reports, including this case, the routine prenatal US examination done between 8-30 weeks of gestation was reported as normal.[1,9,13,14,16,22,23,26,27,38] Theoretically, one can speculate that CGBM may actually start after 30 weeks of gestation and for reasons related to its biological behaviour, it rapidly grows and presents with increased intracranial pressure later or after birth. The recent advances in the quality of foetal MRI in delineating CGBM were reported in 4 cases.[6,14,16,22,27] The tumour was described to be of a heterogeneous intensity in all MRI sequences, probably because of associated haemorrhage.

The clinical presentation in the reported cases born alive was due to the increased intracranial pressure from the tumour mass or the associated hydrocephalus or intratumoural haemorrhage (Table 1). Spontaneous intratumoral haemorrhage was the most important factor associated with rapid clinical deterioration.[9,23] Seizures were reported in three cases, and were difficult to control medically in this present case.[25,36,38]

The histopathological examination in the majority of reported CGBM cases has not been well described and only a diagnosis of GBM is given.[1,13,17,26,33,36,39] In the remaining, the descriptions are identical to those seen in findings reported for adult GBM.[16,18,21-25,27,29,32,38,42] The infiltrative growth of CGBM was described in

Table 1 - Summary of the reported cases of congenital glioblastoma multiforme in the literature

Author (year)	Case No.	Age (at diagnosis) / Sex	Clinical presentation	Location	Treatment	Survival
Holt (1917)	1	2 weeks / M	Macrocephaly	Cerebral hemisphere	None	7 weeks
Amolsch (1935)	2	At birth / NA	NA	Thalamus	None	Stillbirth
Thiele & Dimmick (1951)	3	At birth / NA	Macrocephaly (Hydrocephalus)	Diencephalon	None	7 weeks
Scarez (1954)	4	1 month / M	Vomiting (Hydrocephalus)	Cerebellum	None	9 months
Marsh (1956)	5	At birth / NA	Vomiting (Hydrocephalus)	Temporal lobe	Subtotal resection	2 months
Takaku (1978)	6	At birth / M	Facial weakness, hydrocephalus	Cerebello-pontine angle	None	3 weeks
Sabet (1982)	7	At birth / F	Hydrops foetalis, hydrocephalus	Cerebral hemisphere	None	1.5 hours
Riboni (1985)	8	33 gestation weeks / M	Hydrops foetalis	Cerebral hemisphere	None	20 minutes
Alvarez (1987)	9	33 gestation weeks / M	Macrocephaly	Cerebral hemisphere	None	24 hours
	10	31 gestation weeks / F	NA	Cerebral hemisphere	Subtotal resection	Alive at 5 years
Itoh (1987)	11	At birth / M	Facial weakness, hydrocephalus	Cerebellum	None	43 days
Geraghty (1989)	12	33 gestation weeks / F	Hydrocephalus	Cerebral hemisphere	None	Stillbirth
Jung (1990)	13	At birth / M	Hydrocephalus	Cerebral hemisphere	None	3 days
McConachie (1991)	14	33 gestation weeks / NA	Macrocephaly	Cerebral hemisphere	None	Stillbirth
Singhal (1994)	15	23 days / NA	Vomiting, seizures	Parietal lobe	Subtotal resection + radiotherapy	Alive at 18 months
Heckle (1995)	16	31 gestation weeks / M	Macrocephaly (Hydrocephalus, ICH)	Cerebral hemisphere	None	NA
Mazzone (1995)	17	13 days / M	Vomiting, seizures	Cerebral hemisphere	None	1 day
Doren (1997)	18	29 gestation weeks / M	Macrocephaly (ICH)	Both cerebral hemispheres	None	Stillbirth
Guilbaud (1997)	19	36 gestation weeks / M	Macrocephaly	Both cerebral hemispheres	None	Stillbirth
Sylvestre (1998)	20	33 gestation weeks / M	Macrocephaly, seizures	Cerebral hemisphere	Transcranial biopsy, VPS	2 months
Kamitomo (1998)	21	33 gestation weeks / M	Macrocephaly (ICH)	Cerebral hemisphere	None	41 days
Lee (1999)	22	39 gestation weeks / M	Macrocephaly	Cerebral hemisphere	None	1 day
Winter (2001)	23	3.5 months / F	Vomiting, lethargy, hydrocephalus	Lateral ventricle	Resection + VPS + chemotherapy	Alive at 5 years
	24	At birth / M	Macrocephaly	Fronto-temporal region	Subtotal resection	Alive at 2.5 years
	25	30 gestation weeks / M	Hydrops foetalis, ICH	Cerebral hemisphere	None	1 hour
Morof (2001)	26	37 gestation weeks / NA	Macrocephaly (ICH)	Both cerebral hemispheres	None	5 hours
Schindelmann (2002)	27	37 gestation weeks / M	Macrocephaly Hydrocephalus, ICH	Cerebral hemisphere	Subtotal resection	NA
Nakayama (2002)	28	33 gestation weeks / M	Macrocephaly Hydrocephalus, ICH	Parieto-temporal region	None	10 hours
Shimamura (2003)	29	4 days / F	Fever, Macrocephaly	Parieto-temporal region	Subtotal resection + chemotherapy + radiation	27 months
Chuang (2003)	30	33 gestation weeks / M	Skew ocular deviation	Cerebral hemisphere	None	2 hours
Baessa	31	7 days / M	Seizures	Temporal lobe	Resection + chemotherapy	Alive at 6 years

only four reports.[24,27,32,40,42] Winters, et al recently reviewed the immunohistochemical study of his three reported cases and found that positive staining glial fibrillary acidic protein (GFAP) would be associated with a better differentiated tumour and a better prognosis.[42] This was challenged by the poor outcome among other patients reported with GFAP-postive results.[6,23,25,38] It should be noted that since poorly differentiated tumours can express GFAP, the presence of GFAP does not predict biologic behaviour in all tumours. The immunohistochemical findings in this present case, as well as Winters, et al confirmed two of the three cases who had long survival demonstrated p53 over expression.[42] To the contrary of some reports that demonstrated a worse prognosis with p53 protein over expression in paediatric and adult GBM, the author believes, as well as Winters and colleagues, that p53 over expression may be of a good prognostic value and that CGBM may, in fact, have a different biological behaviour.

Like adult GBM, the prognosis in the reported CGBM cases in the literature has been considered poor. In the non-treated 22 cases, the patients have presented stillbirth or died shortly thereafter (Table 1). Consequently, CGBM has been viewed as an aggressive tumour with a poor prognosis and, in six cases; treatment has been withheld based upon this perception.[17,18,33,38-40] Of the eight treated CGBM cases, including the present case, surgical resection was complete in three and those received chemotherapy with the longest tumour free survival (Table 1). Radiotherapy was administered for two cases in the first 24 months, which did not seem to alter their outcome.[35,36] On the other hand, the two cases who had long-term survival received neither adjuvant chemotherapy nor radiation therapy.[1,42]

The average survival for treated CGBM in the literature was 36 months (range 2-72 months). The prolonged survival among treated cases reported in the literature argues against the invariably fatal outcome of these congenital tumours.[1,36,42] While representing only a few patients, this survival is better than the 10 month mean survival seen in treated adults and may support the decision of the neonatologists and paediatric neurosurgeons and oncologists for surgical intervention. The outcome of the limited number of CGBM cases reported in the literature may suggest they not only have a different biology from adult tumours but also from other paediatric GBM.

Further molecular studies and reports of the outcomes of treatment of these tumours will resolve the question whether the prognosis of CGBM is better than that of similar tumours arising in adults.

The author concludes from analysis of the current data that the factors associated with good prognosis and possible cure in CGBM are complete resection of the tumour and adjuvant chemotherapy for a localised well-differentiated tumour that demonstrates positive staining for GFAP with p53 over expression.

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References

1. Alvarez M, Chitkara U, Lynch L, Mehalek KE, Heller D, Berkowitz RL: Prenatal diagnosis of fetal brain tumors. Fetal Ther 1987, 2(4): 203-208
2. Arnolsch AL: The interpretation of histologic findings in encephalitis congenital. Am J Clin Pathol 1935, 5: 371-383
3. Arnstein LH, Bolderey E, Naffaiger HC: A case report and survey of brain tumors during neonatal period. J Neurosurg 1951, 8: 315-319
4. Brem S, Cotran R, Folkman J: Tumor angiogenesis: quantitative method for histologic grading. J Natl Cancer Inst 1972, 48: 347-356
5. Buetow PC, Smirniotopoulos JG, Done S: Congenital brain tumors: A review of 45 cases. Am J Roentgenol 1990, 155(3): 587-593
6. Chuang YM, Guo WY, Ho DM, Wong TT, Hung JH, Chen SJ, Sheu MH, Chang CY: Skew ocular deviation: A catastrophic sign on MRI of fetal glioblastoma. Childs Nerv Syst 2003, 19(5-6): 371-375
7. Chung SK, Wang KC, Nam DH, Cho BK: Brain tumors in the first year of life: A single institute study. J Korean Med Sci 1998, 13: 65-70
8. D'Addario V, Pinto V, Meo F, Resta M: The specificity of ultrasound in the detection of fetal intracranial tumors. J Perinat Med 1998, 26(6): 480-485
9. Doren M, Tercanli S, Gullotta F, Holzgreve W: Prenatal diagnosis of a highly undifferentiated brain tumor: A case report and review of the literature. Prenat Diagn 1997, 17(10): 967-971
10. Fort DW, Rushing EJ: Congenital central nervous system tumors. J Child Neurol 1997, 12: 157-164
11. Fraumeni JF, Miller RW: Cancer death in newborn. Am J Dis Child 1969, 117: 186-189
12. Fuste FG, Snyder DE, Price A: Congenital spongioblastoma of the pons. Am J Clin Pathol 1967, 47(6): 790-796
13. Geraghy AV, Knott PD, Hanna HM: Prenatal diagnosis of fetal glioblastoma multiforme. Prenat Diagn 1989, 9: 613-616
14. Guibaud L, Champion F, Buenerd A, Pelizzari M, Bourgeois J, Pracos JP: Fetal intraventricular glioblastoma: Ultrasonographic, magnetic resonance imaging and pathologic findings. J Ultrasound Med 1997, 16: 285-288
15. Halperin EC: Neonatal neoplasms. Int J Radiat Oncol Biol Phys 2000, 47(1): 171-178
16. Heckel S, Favre R, Gasser B, Christmann D: Prenatal diagnosis of a congenital astrocytoma: A case report and literature review. Ultrasound Obstet Gynecol 1995, 5(1): 63-66
17. Holt LE: Glioblastoma in an infant of seven weeks, resembling hydrocephalus. Am J Dis Child 1917, 14: 219-221
18. Itoh Y, Kowada M, Mineura K, Kojima H: Congenital glioblastoma of the cerebellum with cytofluorometric deoxyriboneucleic acid analysis. Surg Neurol 1987, 27(2): 163-167
19. Janisch W, Haas JF, Schreiber D, Gerlach H: Primary central

nervous system tumors in stillborns and infants: Epidemiological considerations. J Neuro-Oncol 1984, 2: 113-116
20. Jellinger K, Sunder Plassmann M: Congenital intracranial tumors. Neuropaediatrie 1973, 4: 46-63
21. Jung WH, Choi S, Oh KK, Chi JG: Congenital glioblastoma multiforme: Report of an autopsy case. J Korean Med Sci 1990, 5(4): 225-231
22. Kamitomo M, Sameshima H, Uetsuhara K, Tomosugi T, Matsuda Y, Ibara S, Sueyoshi K: Fetal glioblastoma: Rapid growth during the third trimester. Fetal Diagn Ther 1998, 13(6): 339-342
23. Lee DY, Kim YM, Yoo SJ, Cho BK, Chi JG, Kim IO, Wang KC: Congenital glioblastoma diagnosied by fetal sonography. Childs Nerv Syst 1999, 15(4): 197-201
24. March JS: Supratentorial glioblastoma mutiforme in infancy: Report of three cases occurring before the age of one. Bull Los Angeles Neurol Soc 1956, 21: 30-36
25. Mazzone D, Magro G, Lucenti A, Grasso S: Report of a case of congenital glioblastoma multiforme: An immunohistochemical study. Childs Nerv Syst 1995, 11(5): 311-313
26. McConachie NS, Twining P, Lamb MP: Antenatal diagnosis of congenital glioblastoma: Case report. Clin Radiol 1991, 44(2): 121-122
27. Morof DF, Levine D, Stringer KF, Grable I, Folkerth R: Congenital glioblastoma multiforme: Prenatal diagnosis on the basis of sonography and magnetic resonance imaging. J Ultrasound Med 2001, 20(12): 1369-1375
28. Nakayama K, Nakamura Y: Localization of congenital glioblastomas in the Japanese: A case report and review of the literature. Childs Nerv Syst 2002, 3: 149-152
29. Riboni G, De Simoni M, Leopardi O, Molla R: Ultrasound appearance of a glioblastoma in a 33-week fetus in utero. J Clin Ultrasound 1985, 13: 345-346
30. Rickert CH, Probst-Cousin S, Gullotta F: Primary intracranial neoplasms of infancy and early childhood. Child's Nerv Syst 1997, 13: 507-513
31. Richert CH: Neuropathology and prognosis of fetal brain tumors. Acta Neuropathol (Berl) 1999, 98: 567-576
32. Sabet LM: Congenital glioblastoma mutiforme associated with congestive heart failure. Arch Pathol Lab Med 1982, 106(1): 31-34
33. Sacrez R, Juiff JG, Friederich E: Tumeurs cerebrales du nourrisson. Arch Fr Pediatr 1954, 11: 261-263
34. Schindelmann S, Sandner G, Harbeck N, Debus G: Prenatal manifestation of a congenital glioblastoma: Case report. Z Geburtshilfe Neonatol 2002, 206(1): 19-21
35. Shimamura N, Asano K, Ogane K, Yagihashi A, Ohkuma H, Suzuki S: A case of definitely congenital glioblastoma manifested by intratumoral hemorhage. Childs Nerv Syst 2003, 19(10-11): 778-781
36. Singhal RM, Jain M, Tanwar RK, Raman NV: Congenital glioblastoma. Indian J Pediatr 1994, 61(6): 733-736
37. Solitare GB, Krigman MR: Congenital intracranial neoplasm: A case report and review of the literature. J Neuropathol Exp Neurol 1964, 23: 280-292
38. Sylvestre G, Sherer DM: Prenatal sonographic findings associated with malignant astrocytoma following normal early third-trimester ultrasonography. Am J Perinatol 1998, 15(10): 581-584
39. Takaku A, Kodsama N, Ohara H, Hori S: Brain tumors in newborn babies. Child's Brain 1978, 4: 365-375
40. Thiele RI, Dimmick ML: Intracranial malignant neoplasm with onset before birth. J Pediatr 1951, 39: 611-615
41. Wakai S, Arai T, Nagai M: Congenital brain tumors. Surg Neurol 1984, 21: 597-609
42. Winters JL, Wilson D, Davis DG: Congenital glioblastoma multiforme: A report of three cases and a review of the literature. J Neurol Sci 2001, 188: 13-19

GENTLE REMINDER

Astrocytic tumours

1993 WHO Classification (Cytologic variants)	WHO Grade
Group 1 (Diffuse)	
Astrocytoma (fibrillary, protoplasmic, gemistocytic)	II
Anaplastic astrocytoma	III
Glioblastoma mutiforme (giant cell, gliosarcoma)	IV
Group 2	
Pilocytic astrocytoma	I†
Pleomorphic xanthoastrocytoma	II†
Subependymal giant cell astrocytoma	I