Infratentorial congenital glioblastoma multiforme. A rare tumour with a still unknown biology

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Introduction. Congenital glioblastoma multiforme represents only 3% of congenital central nervous system tumours and an infratentorial location is unusual.

Case report. A newborn with congenital glioblastoma multiforme with no mutation in the *TP53* gene or p53 nuclear immunoreactivity that infiltrated practically the whole brainstem and also invaded supratentorial structures.

Conclusions. As far as we know, only four cases with an infratentorial location have been reported previously, three in the cerebellum and one in the brainstem. The biology of congenital glioblastoma multiforme is not well known and, unlike glioblastoma multiforme in adults and children, mutations in the *TP53* gene are uncommon. However, this is not associated with a more favourable prognosis. These observations suggest that specific biological processes underlie fetal glioblastoma multiforme development.

Key words. Brain tumor. Congenital tumor. Glioblastoma multiforme. Infant. p53. *TP53* gene.

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Introduction

Congenital tumours of the central nervous system (CNS) represent less than 2% of all cerebral tumours in paediatric patients and their incidence ranges from 1.1-3.6/100,000 newborns [1]. In 80% the origin is neuroepithelial and, although they can be present at birth, they usually develop during the first two months of life and are mainly located in the supratentorial region [2].

Congenital glioblastoma multiforme (cGBM) is a very rare high-grade astrocytoma (grade IV WHO) that accounts for 3% of all congenital CNS tumours [2]. An infratentorial location is unusual, with only a few cases located in the cerebellum and one case with origin and infiltration in the brainstem reported [3-5]. The biology of cGBM is not well known and, unlike in adults and children, the absence of p53 nuclear immunoreactivity in the tumour tissue or mutations in the *TP53* gene does not seem to be associated with a more favourable prognosis [2].

We report the case of a newborn with a large cGBM that infiltrated practically the whole brainstem and invaded the central grey nuclei of the right hemisphere as well as other supratentorial structures. The tumour did not show p53 nuclear immunoreactivity and no evidence of mutation was identified in the *TP53* gene. The low incidence of cGBM, together with the unusual location and size of the case we describe, makes this report of special interest to elucidate the largely unknown biology of this tumour.

Case report

A full term male newborn with no family history of interest was delivered by caesarean section due to cephalopelvic disproportion. The pregnancy screening was unremarkable, with the last pre-natal ultrasound performed at 32 weeks that did not show any cerebral masses or anomalies. The physical examination following birth showed significant macrocephaly (head circumference was 43.5 ± 5.86 cm), irritability and generalised hypotonia, exotropia with palpebral ptosis and right facial paralysis, as well as tongue deviation to the left and dysphagia.

The cranial ultrasound and subsequent computerised tomography (CT) studies showed a mass suggesting an intracranial tumour, with hydrocephalus and frontal porencephalic cystic lesions. Cerebral magnetic resonance imaging (MRI) confirmed these findings and demonstrated that the tumour also involved the infratentorial structures. The tumour had invaded the whole brainstem, from the medulla oblongata to the cerebellar vermis and hemispheres. It also extended in a cephalic direction, involving the right temporal and parietal lobes, the hypothalamic region, as well as the ipsilateral central grey nuclei, the pineal region and the right cavernous sinus. The

Figure 1. Magnetic resonance imaging. Sagittal T_1-weighted image (a) shows a huge midline mass with heterogeneous signal intensity that compresses normal cerebral tissue. Coronal T_1-weighted image (b) midbrain mass extending to the temporal right lobe with secondary hydrocephalus. Notice bleeding within the tumour and porencephalic cysts.

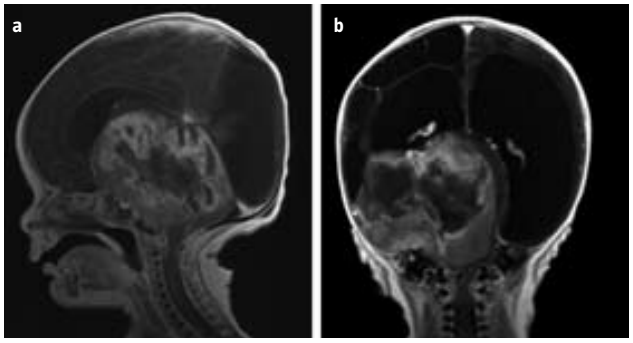
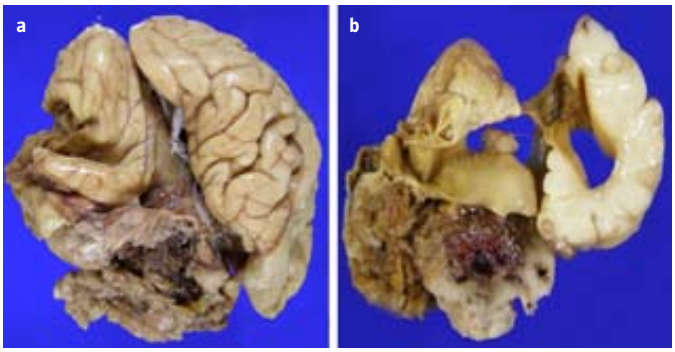


Figure 2. a) Tumour mass with extensive necrotic areas with massive involvement of the brainstem; b) The large tumour extended to the right cerebral hemisphere, reaching the wall of the ipsilateral lateral ventricle. Presence of secondary bilateral hydrocephalus.



tumour mass had heterogeneous characteristics with solid, necrotic cystic and haemorrhagic areas (Fig. 1). Given the size and the location of the tumour, the patient was transferred to palliative care and died at the age of 6 days.

A selective autopsy was carried out on the central nervous system. Macroscopically, a large tumour mass with a friable appearance and extensive necrohaemorrhagic areas and cystic degeneration was observed. The tumour had infiltrated the brainstem, with massive destruction of the mesencephalon, pons and the superior part of the medulla (Fig. 2a). It had also spread to the supratentorial region, infiltrating right cerebral hemisphere structures: thalamus, parietal and temporal lobes. The tumour reached the ventricular wall and caused secondary dilation of both lateral ventricles (Fig. 2b).

The histological study showed a densely cellular glial tumour, characterised by a proliferation of astrocytic cells with pronounced atypical cytology. Cells had large and irregular nuclei and eosinophilic cytoplasm. Several images of apoptosis and some mitosis were identified. The tumour was accompanied by microvascular proliferation (Fig. 3a) with images of vascular thrombosis and bleeding, as well as extensive areas of ischaemic necrosis and pseudopalisading cells (Fig. 3b). Areas with a fusiform pattern, corresponding to areas of meningeal infiltration, were identified. An immunohistochemical panel that was positive for glial fibrillary acidic protein and negative for synaptophysin was carried out. The INI-1 stain was positive in the tumour cell nuclei and the proliferative index measured using the ki67 antigen was elevated. No p53 positive immunohistochemical staining was observed and the histone H3 staining (trimethyl K27) showed an absence of tumour cell nuclear expression, which suggests the potential presence of a mutation. The remaining tissue showed changes compatible with cystic encephalomalacia and hydrocephalus by obstruction to normal CSF flow. All these findings were consistent with the diagnosis of GBM (Grade IV WHO). The analysis of the *TP53* gene (exons 1 to 11 and flanking intronic regions) performed using automated sequencing (Sanger method) did not identify any mutation in the fragments analysed.

Discussion

cGBM is a primary (*de novo*) CNS tumour as it does not originate in a low grade precursor. Less than 60 cases have been published and it is considered to be one of the rarest congenital CNS tumours [3,5-8]. This tumour is more common in males (ratio of 2:1) and, of the cases reported in the literature, less than half were detected prenatally, probably due to their rapid growth [7]. In our patient, an ultrasound at 32 weeks did not show any increase in the biparietal diameter or any changes suggesting intracranial pathology. As a result, the tumour was not detected until birth, when the pronounced macrocephaly, the sutural diastasis and the brainstem dysfunction strongly pointed towards the problem. Although the cranial ultrasound and the CT examinations detected the tumour, only the MRI showed the ex-

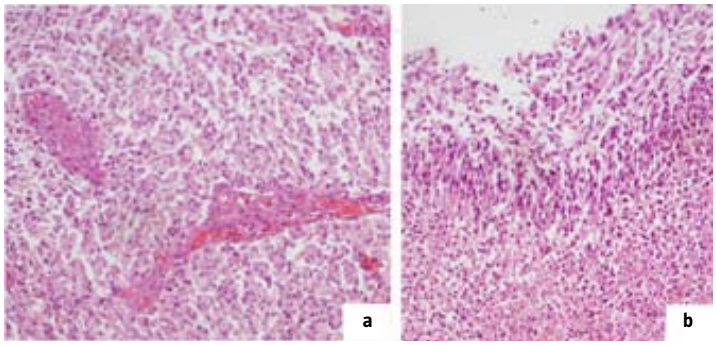
act extension in the infratentorial area. In our patient, the presence of a heterogeneous intracranial mass, with solid, cystic and necrotic areas, suggested a tumour with very rapid growth. Due to its frequency the differential diagnosis included PNET, an atypical teratoid/rhabdoid tumour or a high grade astrocytoma [9], but it was the post-mortem histological examination that established the diagnosis of cGBM.

While primary intracranial tumours in childhood and adolescence are predominantly infratentorial, congenital primary intracranial tumours, including cGBM, are predominantly supratentorial [5,10]. In the case reported, there was extensive infiltration of the brainstem, where the tumour seemed to have originated and spread to the diencephalon and the right temporal lobe. As far as we know, only three neonatal cases of cGBM originated in the cerebellum have been previously reported [1,4,5]. Hou et al reported a cGBM with an origin in the cerebellopontine angle in a neonate with hydrocephalus, right facial paralysis and dysphagia [1]. The infiltration of the brainstem in our patient was more extensive and it is surprising that the clinical expression of brainstem dysfunction was predominantly located on the right, as illustrated by the signs of right common oculomotor nerve, facial and hypoglossal paralysis.

cGBMs with a supratentorial location seem to have a better prognosis than GBM in other ages and partial or complete resection of the tumour, together with chemotherapy, improves the prognosis, with survival of more than 2 years reported [2,6,11]. Nevertheless, even with treatment, mortality is high, in part due to the high bleeding tendency and associated intracranial haemorrhage. About 40% die at birth or during the first week of life and 60% before the age of 2 months [1]. In our patient, the surgical approach, even considering a partial resection, was dismissed due to the risk of bleeding associated but mainly due to the size of the tumour and the structures that had been infiltrated.

The biology underlying cGBMs seem to differ from both paediatric and adult GBMs, which seems to give them a better prognosis and implies that they have different molecular pathways of tumorigenesis [2,5,8]. GBM tumours both in adults and in children, the presence of *TP53* mutation and nuclear staining of the p53 protein are associated with a worse prognosis, independent of other factors such as the clinical features or the histopathological findings [8,11,12]. The biological and genetic examination of these tumours can help determine the tumour's response to chemotherapy treatment. In paediatric GBM, the expression of the p53 protein varies according to the location of the tumour; it is present in 62% of tumours located in the cerebral hemispheres, and in 75% and 30% of those located in the diencephalon and brainstem, respectively [12]. Mutations in the *TP53* gene are rare in children under the age of 3 years; even when they are absent, some cGBMs show p53 nuclear immunoreactivity, without this leading to lower survival [5]. It is not known whether p53 expression can differ according to the location of the cGBM. The patient we report did not have any mutations in the TP53 gene or p53 nuclear immunoreactivity. The biology of cGBM largely remains unknown, but this case provides additional information regarding the limitations of these prognostic indicators in cGBM which do not seem to be useful. The absence of p53 immunohistochemical staining or *TP53* mutation does not seem to be associated with a lower level of severity or patient survival. This supports the hypothesis that cGMB tumours that occur in this period of life have a different biology.

Figure 3. a) High-grade glial proliferation with presence of microvascular proliferation (H/E 400×); b) Evidence of extensive areas of necrosis with pseudopalisading cells (H/E 400×).



References

1. Hou LC, Bababeygy SR, Sarkissian V, Fisher PG, Vogel H, Barnes P, et al. Congenital glioblastoma multiforme: case report and review of the literature. Pediatr Neurosurg 2008; 44: 304-12.
2. Macy ME, Birks DK, Barton VN, Chan MH, Donson AM, Kleninschmidt-DeMasters BK, et al. Clinical and molecular characteristics of congenital glioblastoma. Neuro Oncol 2012; 14: 931-41.
3. Brat DJ, Sehata BM, Castellano-Sánchez A, Hawkins C, Yost RB, Greco C, et al. Congenital glioblastoma: a clinicophatologic and genetic analysis. Brain Pathol 2007; 17: 276-81.
4. Seker A, Ozek MM. Congenital glioblastoma multiforme. Case report and review of the literature. J Neurosurg 2006; 105 (Suppl 6): S473-9.

5. 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: 13-9.
6. Isaacs HI. Perinatal brain tumors: a review of 250 cases. Pediatr Neurol 2002; 27: 249-61.
7. Severino M, Schwartz ES, Thurnher MM, Rydland J, Nikas I, Rossi A. Congenital tumors of the central nervous system. Neuroradiology 2010; 52: 531-48.
8. Pollack IF, Finkelstein SD, Woods J, Burnham J, Holmes EJ, Hamilton RL, et al. Expression of p53 and prognosis in children with malignant gliomas. N Engl J Med 2002; 346: 420-7.
9. Donmez FY, Aslan H, Coban G, Ozen O, Agildere M. Multimodal MR imaging findings of a congenital glioblastoma multiforme. Childs Nerv Syst 2012; 28: 1831-3.
10. Manoranjan B, Provias JP. Congenital brain tumors: diagnostic pitfalls and therapeutic interventions. J Child Neurol 2011; 26: 599-614.
11. Boukas A, Panaretos P, Cowie C, Nicholson C, Jenkins A. Congenital glioblastoma multiforme: complete resection with long-term survival and a novel technique of contralateral cystoventriculostomy. Pediatr Neurosurg 2012; 48: 327-30.
12. Ganigi PM, Santosh V, Anandh B, Chandramouli BA, Sastry Kolluri VR. Expression of p53, EGFR, pRb and bcl-2 proteins in pediatric glioblastoma multiforme: a study of 54 patients. Pediatr Neurosurg 2005; 41: 292-9.

Glioblastoma multiforme congénito infratentorial. Un tumor excepcional con una biología aún desconocida

Introducción. El glioblastoma multiforme congénito representa sólo el 3% de los tumores congénitos del sistema nervioso central, y su ubicación infratentorial es excepcional.

Caso clínico. Recién nacido con un glioblastoma multiforme congénito sin mutación en el gen *TP53* ni inmunorreactividad nuclear p53, que infiltraba prácticamente todo el tronco cerebral e invadía también estructuras supratentoriales.

Conclusiones. Hasta donde sabemos, sólo se han referido previamente cuatro casos de localización infratentorial, tres en el cerebelo y uno en el tronco del encéfalo. La biología del glioblastoma multiforme congénito no se conoce bien y, a diferencia del glioblastoma multiforme en la edad adulta, las mutaciones en el gen *TP53* son poco frecuentes, sin que eso parezca implicar un mejor pronóstico. Estas observaciones sugieren que el glioblastoma multiforme con origen en la vida fetal tiene una biología diferente del que se presenta en otras etapas de la vida.

Palabras clave. Gen *TP53.* Glioblastoma multiforme. Neonato. p53. Tumor cerebral. Tumor congénito.