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Brainstem tumors: moral reflection on surgery management

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Abstract

Brainstem tumors represent about 10% to 20% of central nervous system tumors in children. Diffuse intrinsic glioma is the most frequent (80% of cases) in this group of tumors, characterized by poor prognosis and short survival. Diagnosis can be made by magnetic resonance (with spectroscopy) or by stereotactic biopsy, a controversial method that allows immunohistochemical and molecular study of the tumor. Moral reflection focuses on the indication of biopsy for vulnerable patients with a poor prognosis. Surgery is analyzed from an ethical point of view based on the best interests of the child and altruistic attitude of patient and family.

Keywords: Neoplasms. Neurosurgery. Biopsy. Bioethics. Child.

Resumo

Tumores do tronco encefálico: reflexão moral sobre conduta cirúrgica

Os tumores de tronco encefálico representam cerca de 10% a 20% dos tumores do sistema nervoso central em crianças. O glioma intrínseco difuso é o mais frequente (80% dos casos) desse grupo de tumores, caracterizados pela má evolução e por uma curta sobrevida. O diagnóstico pode ser feito por ressonância magnética (com espectroscopia) ou por biópsia estereotáxica, um método controverso, que permite o estudo imunohistoquímico e molecular do tumor. A reflexão moral se concentra na indicação de biópsia para pacientes vulneráveis e com mau prognóstico. A cirurgia é analisada do ponto de vista ético com base no melhor interesse da criança e na atitude altruísta do paciente e da família.

Palavras-chave: Neoplasias. Neurocirurgia. Biópsia. Bioética. Criança.

Resumen

Tumores de tronco encefálico: reflexión moral sobre la conducta quirúrgica

Los tumores de tronco encefálico representan alrededor del 10% al 20% de los tumores del sistema nervioso central en niños. El glioma intrínseco difuso es el más frecuente (80% de los casos) de este grupo de tumores, que se caracterizan por la mala evolución y una sobrevida corta. El diagnóstico se puede hacer por resonancia magnética (con espectroscopía) o por biopsia estereotáxica, un método controvertido, que permite el estudio inmunohistoquímico y molecular del tumor. La reflexión moral se focaliza en la indicación de biopsia para pacientes vulnerables y con mal pronóstico. Se analiza la cirugía desde el punto de vista ético, con base en el mejor interés del niño y en la actitud altruista del paciente y su familia.

Palabras clave: Neoplasias. Neurocirugía. Biopsia. Bioética. Niño.

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Bioethical dilemma

Brainstem tumors account for about 10% to 20% of central nervous system tumors in children, with 40 new cases per year in Great Britain and between 300 and 400 cases in the United States. In Argentina, in a high complexity hospital in the city of Buenos Aires, 55 cases were diagnosed from 2016 to 2019 (personal communication).

These tumors are most frequently manifested in patients aged between 6 and 9 years, but cases have been reported in children under one year of age [1,2]. These tumors are classified according to histology, location, infiltration, and pattern of progression. The most frequent types are diffuse glioma, dorsal exophytic glioma, focal tectal glioma and cervicomedular junction glioma [3].

Diffuse glioma, or diffuse intrinsic pontine glioma (DIPG), corresponds in pathological anatomy to high-grade anaplastic astrocytoma (grade III in the World Health Organization classification) or to glioblastoma multiforme (grade IV) [4,5]. Magnetic resonance imaging (MRI) can be used for diagnosis, especially MRI with spectroscopy, and, in this case, it is accepted that the information provided does not differ from the anatomopathological diagnosis [6]. Another option is stereotactic biopsy, a controversial method in the field of neurosurgery and neuro-oncology [7].

Diffuse glioma is the most frequent of brainstem tumors (80% of cases) and its rapid evolution is characterized by enormous patient deterioration, limited survival and high mortality, regardless of treatment [1,8]. Median survival is 10 months, and radiotherapy treatment can transiently improve neurological symptoms and extend survival by 6 to 9 months, no more than that [9].

The National Institutes of Health (NIH) indicate the value of magnetic resonance to define the tumor condition (diffuse or focal) and explain that having a biopsy sample allows histological diagnosis and the application of immunohistochemical, cytogenetic and molecular genetic tests, which favors a more accurate diagnosis and classification of neoplasms [10]. NIH guidelines indicate partial resection and biopsy for the diagnosis of focal tumors; for diffuse tumors, which generally did not undergo biopsy surgery, the agency now recommends stereotactic biopsy techniques (safer and innocuous) with the aim of providing tissue for molecular tumor characterization, always within the framework of clinical trials [10].

In Argentina, the Ministry of Health published an expert opinion consensus document on central nervous system tumors in children. Regarding brainstem tumors, 40% of the specialists consulted suggest stereotactic biopsy for focal tumors, and 60% suggest doing it "whenever possible" [11]. The document notes that biopsy in diffuse tumors is not necessary because it does not alter treatment, holding only research character for academic purposes. In the future, when immunohistochemistry identifies a specific target therapy, such as mutated histone, biopsy will be useful [11].

Quick-Weller and collaborators note that the value of biopsy to have a tissue sample that allows carrying out, besides the classic anatomopathological and immunohistochemical study, molecular evaluation and genome analysis, which allows better categorization of these tumors and enables individualized therapy for each patient [6]. The European Society for Medical Oncology and the American Society of Clinical Oncology also emphasize the value of molecular characterization and associate histone H3.1K27M with longer survival rates than histone H3.3K27M [12].

Given this scenario, indicating surgery for these tumors requires a deep and honest analysis, especially for diffuse tumors, either with an indication for diagnostic biopsy or with the criterion of tumor resection. Besides technical-surgical knowledge, such reflection demands a deep bioethical analysis in order to answer whether it is moral or not to submit patients to a surgical procedure, taking into account their poor prognosis.

Reflection on surgical indication

In principle, when a treatment is proposed to a patient, the initial objective is to produce a benefit or, at least, not to more harm than caused by the disease itself. In this case, decisions about surgical procedures require a careful assessment of the risks and benefits of a surgery [13].

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When analyzing these risks and benefits, technical aspects related to possible complications inherent to the surgery such as bleeding, infections, anesthetic risk and changes in respiratory and cardiac function must be considered. Regarding stereotactic biopsy of brainstem tumors, some authors mention 1% of patients with post-surgical transient neurological deficit and 0.3% mortality in children and adults [7], while others report up to 9% of complications in children [1].

In the particular case of these tumors, sampling tumor tissue serves to confirm an anatomopathological diagnosis. However, since the advent of magnetic resonance imaging, the precise location and characteristics of a tumor can be defined (focal or diffuse) to make decisions about surgery with greater certainty and even to decide on radiotherapy treatment. Moreover, immunohistochemical and molecular analysis studies can be made with the tissue sample obtained. Such studies allow a better definition of tumor diagnosis and open up possibilities for future prognosis and treatment.

Today, the only treatment option, regardless of the pathological anatomy result, is radiotherapy, and it must always be taken into account that the prognosis is poor and survival is short (especially in diffuse tumors). In an extensive meta-analysis, Hassan and collaborators [2] investigated prognostic and survival factors in children with brainstem tumors and noted that there are no differences in survival when analyzing tumor classification, different radiotherapy regimens, and the use of temozolomide (although there is a wide confidence interval in these data). The authors also mention that there is still insufficient data to draw conclusions regarding the age of patients, the duration of symptoms before diagnosis, and the finding of histone K27M mutation and PCVR1 mutation [2].

Given the above, the following question should be asked: considering the risks and the limited benefit of the procedure, is stereotactic biopsy in children justified? Is it fair to submit a child to surgery that will not bring significant benefits or improve their quality of life?

Bioethics holds a deeply rooted concept called "the best interest of the child," which can and should be applied in decision making by the clinical-surgical team. To guarantee this interest is to consider the sick – and, therefore, vulnerable – child as the central object of decisions. Above all, the patient's well-being and not adding more harm are paramount. This concept of greatest interest is described in the *Convention on the Rights of the Child*, which Argentina signed and incorporated into Law 26.061/2005, Law on the Integral Protection of the Rights of Children and Adolescents [14].

Without neglecting this premise and appealing to the responsibility of the medical-surgical team, professionals are concerned and interested in offering alternatives for children with brainstem tumors. Therefore, the study of tumor molecular and immunohistochemical markers opens ways to define therapeutic approaches and to improve the prognosis and quality of life of these patients.

However, one must always consider that if a patient undergoes a tumor biopsy to detect cell markers in this tissue, considering the current knowledge on the subject, it is very likely that such information will not represent any benefit for that particular child. For this reason, honest dialogue with the child's family (and, if possible, with the patient) is very important to reconcile the surgical approach and not generate false expectations about the procedure's outcome, which may help other children in the future but most likely will not help the patient. The agreement to undergo this procedure would be for altruistic reasons and would show a caring attitude towards other children who will suffer from the same disease, which can be emotionally positive for the child and family alike.

A dilemma arises regarding such altruistic attitude, which generates diverse opinions. There are those who consider that participating in clinical research is a moral duty, since good research results benefit society as a whole. From this concept, children and their parents would have moral reasons to accept a tumor biopsy for scientific purposes. Others, however, consider that such children must be protected from any invasive procedure given their serious condition and vulnerability.

Given the strong and contradictory opinions in favor and against biopsy, it is difficult to answer whether this procedure respects the best interests of the child [15]. In this case, the attitude of the neurosurgeon physician, oncologist and clinical

pediatrician who intervenes in the decisions is crucial. These professionals must be honest with the child's family and take the time to have an honest conversation, providing accurate information about the disease, its characteristics, prognosis and treatment, especially regarding the indication for surgery, which is often seen by distressed parents as a solution.

The medical team should avoid a paternalistic attitude under these circumstances. All information transmitted to the patient and family must be recorded in writing in the informed consent form, which will indicate the risks and benefits of the surgery, whether or not the procedure is part of a clinical trial, and whether the biopsy material will be preserved at the hospital for further studies.

Undoubtedly, it will be up to the medical team to decide when to intervene, based on professional criteria and on the analysis of each case. The procedure may be justified in children with reasonable clinical neurological conditions, and always with the agreement of the patient's parents or guardians, who are those who represent the minor and must fully exercise autonomy [16] in making decisions based on understanding the information received. Autonomy in children is progressive, according to their maturation and development, so these patients should receive information about the procedure to which they will be submitted to the extent of their ability to understand [17].

In this situation, as in so many others, the advancement of science and technology brings challenges, and the answer to them goes beyond solely scientific decisions, including the need to analyze the moral values at stake. Ethics can be used as a tool to reflect on these values. Science must look for new diagnostic and treatment options for the good of human beings, but always in a responsible way. In this sense, it is important to highlight the Clinical Ethics Committee as the most appropriate area for an interdisciplinary reflective analysis.

Decisions regarding children with brainstem tumors should be carefully evaluated by a surgical medical team, and not individually. In turn, the incorporation of these children in clinical trials must be evaluated by research ethics committees. This is a way to incorporate different views and opinions, always with the objective of offering the best to the patients, thinking of their interest and well-being. It is precisely the research ethics committee that must protect children who, in addition to patients, are research subjects.

Final considerations

Scientific research brings benefits to society and to future generations, and such benefits are taken into account when including children in research that will not directly benefit them, since they are the only ones who will be able to help other children in similar conditions [18]. However, even if the immense value of research should be recognized, the obligations of all persons or entities involved in a clinical trial protocol must always be considered (in the case analyzed here, neurosurgeons, pathologists, neuro-oncologists, clinical pediatricians, hospital authorities, and research ethics committees).

According to Jonas [18], technology is not neutral and can be used for both good and evil; technology generates power and therefore demands responsibility from those using it. Human good must be promoted at all times, respecting people's interests and rights, repairing injustices and alleviating suffering. The object of human obligation is humankind [18].

Brainstem tumors are a clear example where the surgical medical team must ensure respect for the autonomy of the patient and family, reconciling care practice, which has a defined goal of beneficence, with clinical research, which does not always provide a concrete benefit to the patient.

References

1. Laigle-Donadey F, Doz F, Delattre JY. Brainstem tumors. In: Grisold W, Soffietti R, editores. Handbook of clinical neurology [Internet]. Amsterdam: Elsevier; 2012 [acesso 10 fev 2021]. p. 585-605. DOI: 10.1016/B978-0-444-53502-3.00010-0

2. Hassan H, Pinches A, Picton SV, Phillips R. Survival rates and prognostic predictors of high grade brain stem gliomas in childhood: a systematic review and meta-analysis. J Neurooncol [Internet]. 2017 [acesso 10 fev 2021];135:13-20. DOI: 10.1007/s11060-017-2546-1
3. Guillamo JS, Doz F, Delattre JY. Brain stem gliomas. Curr Opin Neurol [Internet]. 2001 [acesso 10 fev 2021];14(6):711-5. DOI: 10.1097/00019052-200112000-00006
4. Lin TF, Prados M. Brainstem gliomas. In: Gupta N, Banerjee A, Haas-Kogan DA, editores. Pediatric CNS tumors. 3ª ed. Berlin: Springer; 2017. p. 49-65.
5. Saratsis AM, Nazarian J, Magge SN. Brainstem gliomas. In: Keating R, Goodrich JT, Packer R, editores. Tumors of the pediatric central nervous system. 2ª ed. New York: Thieme; 2013. p. 347-53.
6. Quick-Weller J, Tritt S, Behmanesh B, Mittelbronn M, Spyrantis A, Dinc C *et al*. Biopsies of pediatric brainstem lesions display low morbidity but strong impact on further treatment decisions. J Clin Neurosci [Internet]. 2017 [acesso 10 fev 2021];44:254-9. DOI: 10.1016/j.jocn.2017.06.028
7. Leach PA, Listlin EJ, Coope DJ, Thorne JA, Kamaly-Asl ID, The Royal Manchester Children's Hospital Clinical Neuroscience Group. Diffuse brainstem gliomas in children: should we or shouldn't we biopsy? Br J Neurosurg [Internet]. 2008 [acesso 10 fev 2020];22(5):619-24. DOI: 10.1080/02688690802366198
8. Souza P, Hinojosa J, Muñoz MJ, Esparza J, Muñoz A. Gliomas del tronco encefálico. Neurocirugía [Internet]. 2004 [acesso 10 fev 2020];15(1):56-66. DOI: 10.1016/S1130-1473(04)70502-3
9. Maxwell R, Luksik AS, Garzon-Muvdi T, Yang W, Huang J, Bettegowda C *et al*. Population-based study determining predictors of cancer-specific mortality and survival in pediatric high-grade brainstem glioma. World Neurosurg [Internet]. 2018 [acesso 10 fev 2020];119:1006-15. DOI: 10.1016/j.wneu.2018.08.044
10. National Cancer Institute. Childhood brain stem glioma treatment (PDQ®): health professional version [Internet]. 2020 [acesso 10 fev 2020]. Disponível: https://bit.ly/37Hr9B1
11. Fischman M, Ismael J, Pesce P, Rufach D. Tumores pediátricos del sistema nervioso central [Internet]. Buenos Aires: Ministerio de Salud; 2015 [acesso 10 fev 2020]. Disponível: https://bit.ly/3iLTQ69
12. Hoffman L, Veldhuijzen van Zanten SEM, Colditz N, Baugh J, Chaney B, Hoffmann M *et al*. Clinical, radiologic, pathologic, and molecular characteristics of long-term survivors of diffuse intrinsic pontine glioma (DIPG): a collaborative report from the International and European Society for Pediatric Oncology DIPG registries. J Clin Oncol [Internet]. 2018 [acesso 10 fev 2020];36(19):1963-72. DOI: 10.1200/JCO.2017.75.9308
13. Luna F. Planteos clásicos y teoría de los principios. In: Luna F, Salles A. Bioética: nuevas reflexiones sobre debates clásicos. Buenos Aires: Fondo de Cultura Económica; 2008. p. 23-78
14. Argentina. Ley nº 26.061. Protección integral de los derechos de niñas, niños y adolescentes [Internet]. Buenos Aires: Ministerio de Justicia y Derechos Humanos de la Nación; 2014 [acesso 10 fev 2020]. Disponível: https://bit.ly/3iNKLtQ
15. Wilkinson R, Harris J. Razões morais e legais para o altruísmo no caso de biópsia do tronco cerebral em glioma difuso. Br J Neurosurg [Internet]. 2008 [acesso 10 fev 2020];22(5):617-18. DOI: 10.1080/02688690802482896
16. Beauchamp T, Childress J. Principios de ética biomédica. 4ª ed. Barcelona: Masson; 1999.
17. Ciruzzi MS. La competencia bioética en el menor de edad. In: Ciruzzi MS. La autonomia del paciente pediátrico: ¿mito, utopía o realidad? Buenos Aires: Cathedra Jurídica; 2011. p. 37-77.
18. Jonas H. Técnica, medicina y ética: la práctica del principio de responsabilidad. Barcelona: Paidós; 1997.

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