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ORIGINAL PAPER

Factors affecting diagnosis of primary pediatric central nervous system neoplasias in a developing country

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Abstract

Purpose Understand the variables that could interfere with diagnosis and prompt treatment in CNS childhood cancer in Brazil, a developing country with continental dimensions.

Methods From 2005 to 2010, we retrospectively evaluated factors, which could represent a negative influence on the time period elapsing from the onset of symptoms until the diagnosis of the central nervous system (CNS) neoplasia in children and adolescents attended in our service.

Results Two hundred seventeen records were analyzed retrospectively. Factors of the households were evaluated, and this data was related to the time period elapsing from presentation of the first symptoms until the diagnosis of CNS neoplasia. The average time elapsed from the onset of the symptoms until seeking medical assistance was 96 days, and from medical assistance to patient referral to a reference service was 33 days. The symptoms which most contributed to a shorter delay in diagnosis were changes in gait and paresis, mother's occupation, father's education level, patient gender, and living in the state of São Paulo. Besides that, variables such as male gender, mother's education level, and lower patient age were associated with an early diagnosis time.

Conclusion There is great difficulty in performing early diagnosis of CNS tumors, partly due to parent's inability to recognize signs and symptoms, and in part due to an educational deficit among healthcare professionals. Identification of measures that can minimize these causes of delay is fundamental to increasing the chance of cure and survival of these patients.

Keywords Epidemiology · Diagnosis · Primary · Pediatric · Neoplasia

Introduction

In developed and in developing countries alike the leading cause of death due to disease in those from the age of 1 to 19 is cancer [1]. In this pediatric age group, the central nervous system (CNS) neoplasias are the most frequent solid tumors, representing 8–15% of the neoplasias [2]. Only leukemia, responsible for approximately one third of the records of childhood cancer, has a higher prevalence throughout the world [3, 4]. There are many types of brain tumors, with different treatments and prognosis depending on the location, histological type, and staging [5]. The most prevalent CNS tumors among children and adolescents are pilocytic astrocytomas, brainstem gliomas, ependymomas, and medulloblastomas [6, 7]. CNS cancer in children and adolescents presents with signs and symptoms common to other diseases occurring in this age group, which contributes to the delay in diagnosis [8]. The education level of parents' impacts awareness of the importance of early signs of the disease, and awareness of health care professionals regarding interpretation of signs and symptoms, which are often similar to frequent minor childhood diseases, are vital for the early diagnosis and successful treatment of pediatric cancer [9, 10]. Socioeconomic and

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education levels of parents may have an impact upon early recognition of complaints associated with CNS tumors. Medical capacity depends, in large part, on the instruction received during their professional education.

Brazil is a country of continental dimensions and of major socioeconomic and cultural differences; this and the restricted access to specialized centers in our country also contribute to delays in diagnosis. The aim of this study was to evaluate the main clinical characteristics of CNS tumors in children and adolescents and correlate those results to the time elapsing from the onset of manifestations and definitive diagnosis in our specialized center for pediatric cancer treatment. Identification of the main variables related to delays in diagnosis could be the basis for the development of strategies to reduce this time period.

Material and methods

This study was approved by the Research Ethics Committee of the institution. Records of patients attended to at the Centro Infantil Dr. Domingos A. Boldrini with a diagnosis of central nervous system cancer were retrospectively evaluated. Children and adolescents under 18 years of age, of both genders, with a pathology diagnosis for primary central nervous system neoplasia, between the years 2005 to 2010 were included in the study. Individuals who failed to attend the follow-up at the center were excluded. Necessary information was collected from 192 records and in 25 of these, the social-demographic and economic factors could not be collected.

The variables studied herein were social economic and cultural differences, such as city of origin, profession of the mother and father, family income (minimum wage and income per capita), the number of employed first-degree relatives living in the same household, housing conditions, and level of education of the father and mother. Other aspects related to the diagnosis were also evaluated, such as initial signs and symptoms, pathology diagnosis, primary site of tumor and presence of metastasis, as well as 5-year survival, with or without the disease.

Time periods between the onset of symptoms and first contact with medical service and between this contact and first consultation at our reference hospital were evaluated. First contact with healthcare service was considered the first time the patient was evaluated due to symptoms related to the final diagnosis. The time period considered to define whether there was a delay in diagnosis was the interval ranging from the onset of symptoms and the first contact with the healthcare system (time period 1) and the time period ranging from the first appointment to the final diagnosis at the reference service (time period 2).

Results obtained were analyzed globally, identifying positive predictive factors for delayed diagnosis of CNS neoplasia, followed by a descriptive statistical analysis, with presentations of tables containing the categorical variable frequencies and measurements of position and spread for numerical variables. The overall survival curve was estimated using the Kaplan-Meier method. A Chi-square test and Fisher's exact test were used to check for association or to compare proportions. A Kruskal-Wallis test was used for comparing continuous or sortable variables among three or more groups. The relation between continuous and sortable values was measured by the Spearman correlation coefficient, which varies from -1 to 1. Values near extremes indicate a negative or positive correlation. In order to identify variables discriminating time periods, a multiple linear regression analysis was used, applying a rank transformation of dependent variables due to the absence of normality. Stepwise was the criteria used to select variables.

Results

Using descriptive analysis, the median age of children at diagnosis was defined as 7.2 years (variation of 0 to 23.6 years); 57.6% were male and 42.4% female; 0.46% were Asian-descendant, 77.88% Caucasian, and 21.66% were Afro-descendant, proportionally divergent to the population distribution documented by the Brazilian Institute of Geography and Statistics (IBGE) during the same period [11]. Considering their topography, tumors were classified into cerebellar, diencephalic, brain hemisphere, brainstem or neuroaxis and, additionally, through anatomical-pathological examination or in a presumptive manner through image exams and clinical characteristics, as astrocytomas (37.95%), ependymomas (11.44%), glioblastomas (4.82%), gliomas (21.69%), and medulloblastomas (24.1%).

The analysis of demographic, socio-economic, and cultural variables revealed that 83.41% of the patients lived in the State of São Paulo; 2.76% and 1.85% of the mothers and fathers, respectively, did not know how to read and write; 33.15% and 38.27% had incomplete primary school education; 18.78% and 17.28% had complete primary school education; 10.50% and 7.41% had incomplete middle school education; 22.10% and 17.28% had complete middle school education; 3.87% and 9.88% had incomplete higher education; 8.84% and 8.02% had complete higher education; and 55.98% of the mothers were housewives. Among fathers, 4.69% were unemployed, 7.81% were bricklayers, 7.29% rural workers, and 80.21% technicians. Regarding housing conditions, 91.40% had basic sanitation. The overall household income was estimated at 3.2 times the minimum wage for a full-time employee (equivalent to US $790).

The main initial symptoms presented by patients were headaches (52.53% of the cases), vomiting (48.39%), nausea (7.37%), weight loss (6.45%), paresis (5.02%), change in gait (26.73%), learning difficulty (2.30%), and drowsiness (12.44%).

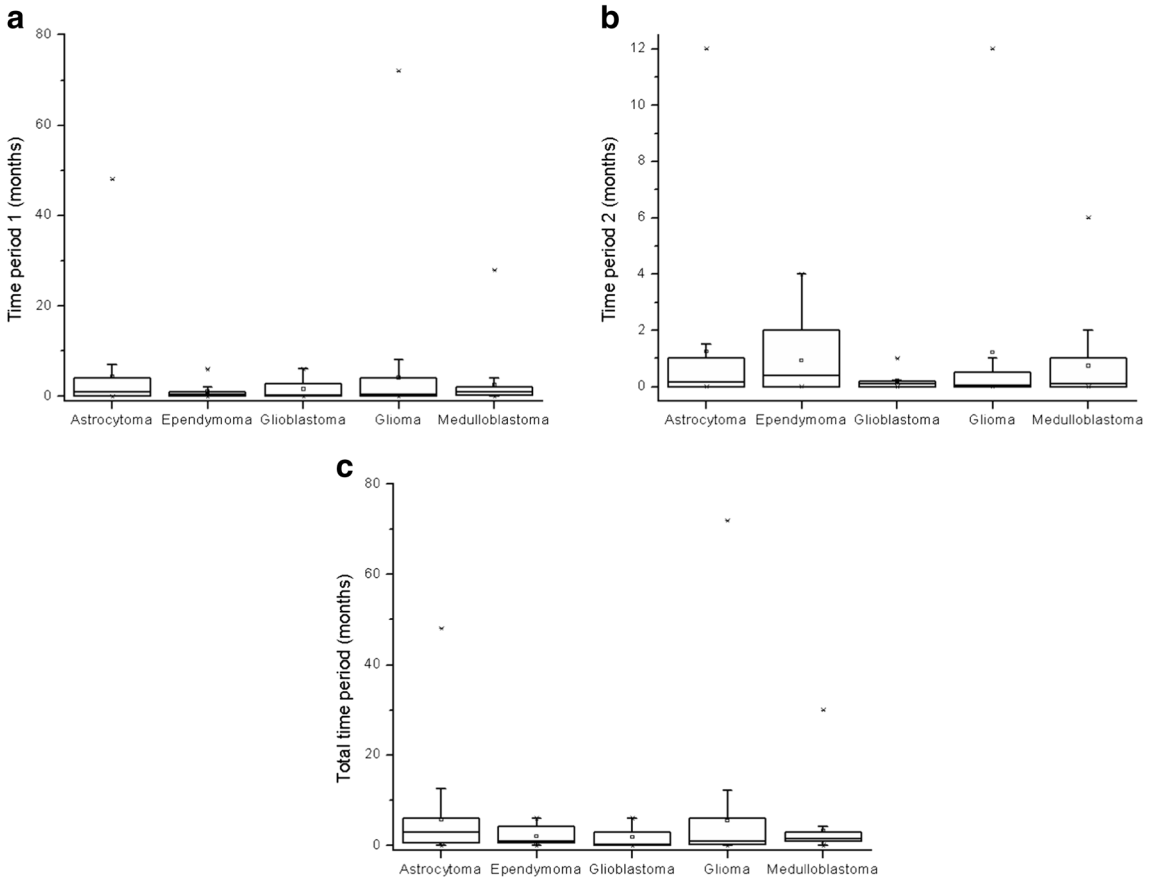

Fig. 1 Box-plot for time periods by CNS tumors types. (**a**) Time period 1: Time, in months, elapsed from the onset of symptoms and the first medical contact. No statistically significant difference between the CNS tumors ($p = 0.67^{1}$). (**b**) Time period 2: from the first medical contact to the first consultation at the reference hospital in months. No statistically significant difference between the CNS tumors ($p = 0.86^{1}$). (**c**) Total time period (*T*): sum of time periods 1 and 2, in months. No statistically significant difference between the CNS tumors ($p = 0.31^{1})^{1}$ based on Kruskal-Wallis test

The median length of time from when parents observed the made first symptom and first contact with medical service was 30 days (variation of 0 to 2.160 days). The median total time period between first symptom and diagnosis was 48 days (variation of 0 to 2.160 days). The relation of these time periods and tumor type can be observed in Fig. 1. According to the Kaplan-Meier method, analysis of disease-free overall survival for all histological types revealed a period of approximately 8.3 years (95% CI 7.56–9.14%) (Fig. 2).

Multiple analysis, using the *stepwise* process, was used to find associations which taken together would better explain the time period from first symptoms onset to first medical contact. Negative correlations for diagnosis delay were found for age and presence of basic sanitation; whereas, headaches, changes in gait, learning difficulties, and drowsiness revealed positive correlations for longer time period elapsed until diagnosis (Fig. 3).

Moreover, using the same process but now considering the time elapsed from first medical service contact to definitive diagnosis of malignant neoplasm of the central nervous system, we found a positive correlation for nausea and negative correlations for presentation of for paresis, males, residents of the State of São Paulo, and for those children whose mother's sole profession was "housewife," and whose father had higher education level (Fig. 4).

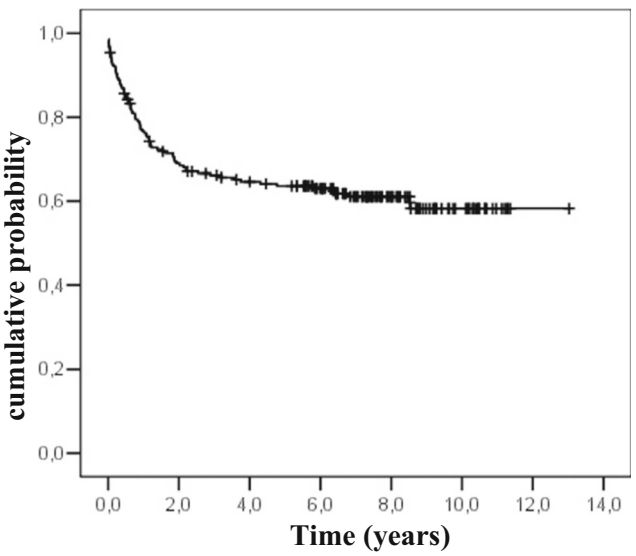

Fig. 2 Kaplan-Meier analysis revealed a disease-free survival of approximately 8.3 years (95% CI 7.56–9.14%)

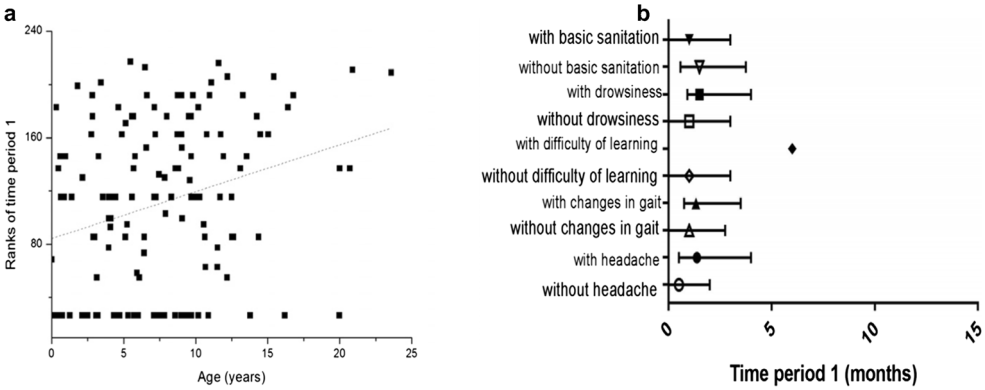

Fig. 3 Variables that discriminated the time period 1 using multiple linear regression analysis, stepwise process. In (**a**) dispersion of age ($p < 0.001$) and in (**b**) symbol = median with interquartile range, headache ($p = 0.01$); changes in gait ($p = 0.004$); learning difficulties ($p = 0.001$); drowsiness ($p = 0.03$), and basic sanitation ($p = 0.04$). Empty symbol = NO and full symbol = YES

Finally, considering the time period from first symptoms onset to final diagnosis of CNS neoplasia by using a stepwise multiple analysis of all variables available, a significant negative association was found between the increase of the time period and the age of patients, and a positive association was found with in learning difficulties (Fig. 5).

The correlation between family income and delayed diagnosis was considered insignificant in all cases. The p values associated with these different time periods and these specific variants were 0.6578, 0.3247, and 0.7771, respectively.

Discussion

Signs and symptoms associated with brain tumors in children are often common to other pathologies, which are more prevalent in this age group; hindering recognition of signs and symptoms on behalf of the parents and general practitioners or even pediatricians, and leading to delayed diagnosis. This delay has an impact on both immediate measures and prognosis of the disease [10].

Recognition of acute symptoms in the central nervous system (CNS) neoplasias is particularly difficult. Headaches are a very common symptom at all ages, with over 20% of children presenting this symptom at some point. The decision of which situations should be referred to a more rigorous investigation can be difficult [12].

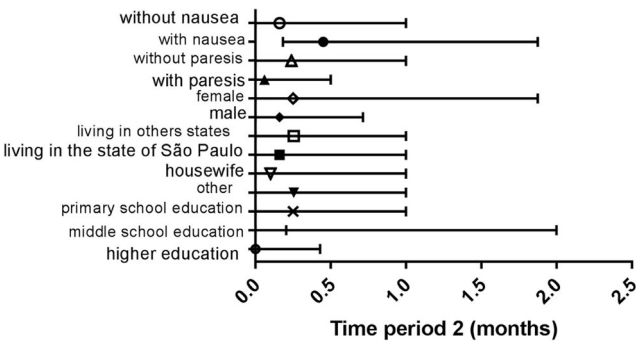

Fig. 4 Variables that discriminated the time period 2 using multiple linear regression analysis, stepwise process. Symbol = median with interquartile range, nausea ($p = 0.001$); paresis ($p = 0.03$); gender ($p = 0.04$); living in the state of São Paulo ($p = 0.003$); profession of mother ($p = 0.001$), and education level of father ($p = 0.01$). Empty symbol = NO and full symbol = YES

Previous studies [13, 14] revealed that symptoms may present years before the diagnosis, and the mean time period until brain tumor diagnosis in children is estimated between 20 and 28 weeks, less in case of posterior fossa tumors, 3 to 14 weeks [10, 15–19]. Imprecise signs and symptoms influence pediatrician/general practitioner delayed diagnosis in most cases. Isolated symptoms such as headaches are rarely related to tumors. A study carried out by Berlaer et al. evaluated 117 children under the age of 16 years who had arrived at the emergency room complaining of headaches, 33 were submitted to brain computed tomography due to the presence of "warning signs." No cases of brain tumor were identified [20]. Chu et al., in a retrospective study which revised medical records of children with CNS tumors, showed that these children usually presented nonspecific symptoms which led to a delayed diagnosis. Symptoms onset occurred 2 years before diagnosis, and patients had sought primary and secondary medical assistance before diagnosis was reached [14].

As pioneers in studies of this kind in our country, we identified that among the most frequent symptoms, only fever, vomiting, and lower age presented a positive statistical correlation with time period for seeking medical attention. Other symptoms related to CNS tumors were not determinant in the motivation for seeking medical attention, corroborating the observation that CNS tumor symptoms are often taken for symptoms of diseases common to the pediatric age group and do not cause major preoccupation in parents. We observed that the mean time period between the onset of symptoms and seeking medical care was 96 days (3.2 months), highlighting the difficulty in recognizing signs and symptoms of CNS tumors by the parents.

Signs such as gait changes and paresis, in addition to higher father education levels, being male, and living in the state of São Paulo had positive statistical associations with a shorter time period in seeking medical care and being referred to an oncological service. More localized and specific signs, as shown in our study, are usually tardy, and the waiting time

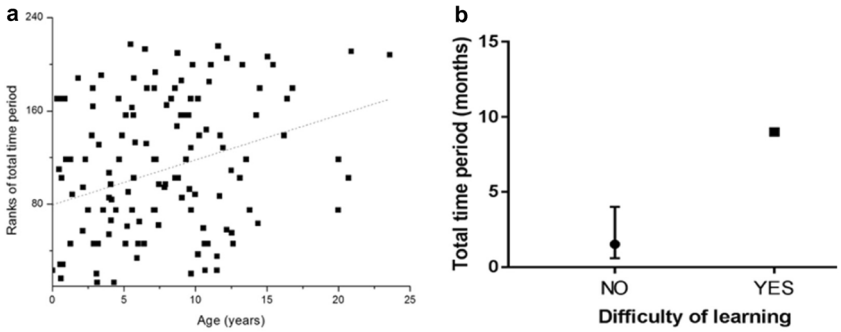

Fig. 5 Variables that discriminated the total time period using multiple linear regression analysis, stepwise process. In (**a**), dispersion of age ($p < 0.01$). In (**b**) symbol = median with interquartile range, learning difficulties ($p = 0.008$)

for these signs or symptoms of increased intracranial pressure signs determine the delayed diagnosis. The time elapsed to refer patients to a primary or secondary medical service in pediatric oncology was 33 days (1.1 months), highlighting the difficulty for physicians to suspect CNS tumors.

Analyzing the time elapsed from first symptom or sign onset related to CNS tumor and the diagnosis in a reference oncology center was approximately 126 days (4.2 months). A positive association was verified with variables such as male gender, mother's education level (middle school), and lower age. More specific signs and symptoms, such as headaches, loss of sphincter control, and learning difficulties correlated negatively to this time period, which may be the result of patients having been first referred to other specialists such as orthopedists and ophthalmologists among others due to these signs and symptoms, leading to delayed diagnosis. These findings support the finding that parents and doctors have difficulty in suspecting CNS tumors based on determined signs and symptoms. These data are discrepant with data collected in developed countries. According to Dobrovoljac et al., the median pre-diagnostic symptomatic interval was 60 days with a parental delay of 14 days, correlated significantly with patients' age and tumor histology, but not with gender, year of diagnosis, or tumor location (supratentorial hemispheric, supratentorial midline, infratentorial) [10]. Still, Lohmann et al. in another study, showed that headache, vomiting, and lethargy were the most frequent symptoms, being the delay of pre-admission dependent on the degree of tumor, as well as the location with delay of non-solitary diagnosis of 1 week [21].

Furthermore, a relationship between histological type and delayed diagnosis has also been reported. Our data revealed a longer time until low grade malignancy tumors were diagnosed, justified by the fact that high-grade tumors, such as glioblastomas and medulloblastomas, present a more rapid progression of signs and symptoms contributing to the earlier diagnosis.

With the intent of aiding pediatricians and other doctors in the early recognition of brain tumors in children, several guidelines have been developed, with a list of the most important symptoms for each age group [22, 23], such as in the case of focal neurological deficits and macrocephaly in children under the age of four and headaches and visual symptoms in children over 4 years of age. Early diagnosis of CNS tumors can be reached when parents and healthcare professionals are aware of signs and symptoms such as headaches, nausea/vomiting, visual symptoms (particularly visual disturbances in preschoolers under the age of 4 years), motor and sensorial signs and symptoms, changes in growth and development, behavioral changes, diabetes insipidus, seizures, and altered stage of consciousness. All doctors involved in care of children and adolescents, in primary or secondary care, must be fully aware of the possibility of brain tumors in any child with neurological symptoms and consider the need for image exams in case of warning signs and symptoms or persistent or progressive ones, particularly those associated with sudden changes of behavior or learning.

The reality we are faced with is the great difficulty encountered in performing early diagnosis of CNS tumors, partly due to parents inability to recognize signs and symptoms of these tumors, partially due to an education deficiency among healthcare professionals leading to difficulty in recognizing these signs and symptoms, and also due to the difficulty of carrying out image exams and referrals to reference centers. Clarification handbooks have already been developed for parents and families [24].

With current universal internet access, an alternative would be to develop telemedicine platforms with participation of specialized professionals, linked to oncology reference centers, who could aid professionals in primary and secondary assistance to identify possible CNS tumors and facilitate the referral of previously screened cases to these reference centers.

Conclusion

CNS tumors in children initially usually present vague clinical signs and symptoms, and the difficulty encountered by parents and doctors to connect these signs and symptoms to the severe condition contributes to a delayed diagnosis, contrary to what is seen in developed countries where diagnosis time is shorter. Implementation of strategies to develop awareness of parents and healthcare professionals is of major importance to reduce the time elapsed until detection of these tumors. Education brochures for parents and guidelines for healthcare professional have been developed and should be broadly disseminated.

Diagnostic resources should be expanded, and strategies to facilitate referral to reference centers should be discussed. In developing countries such as ours (Brazil), the implementation of a telemedicine program sponsored by oncology reference centers could facilitate access of primary and secondary healthcare professionals for discussion of suspicious cases, which could be then referred to these centers.

Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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