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Pilocytic Astrocytoma: a Clinical Study in a Single Brazilian Institution

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ABSTRACT

Background: This study describes the clinical, laboratorial, and therapeutic data of patients with pilocytic astrocytomas, their predictive factors, and to propose a therapeutic strategy.

Methods: Retrospective analysis of clinical files of pediatric patients followed between 1984 and 2014 in a single institution.

Results: There were 48 patients (22 boys and 26 girls). Age at diagnosis varied from 6 months to 15.2years (mean: 6.9 years, median: 7.0 years). Median follow-up was 9.1 years (range: 6 months to 21.5 years). Twenty-five (52%) were cerebellar, 8 (17%) hemispheric, 10 (21%) hypothalamic-chiasmatic, and 5 (10%) midbrain. Twenty-eight tumors were solid-cystic, 9 solid, 4 cystic, and 7 unknown. Total gross resection was achieved in 17 (35%), partial resection in 27 (56%). Two patients had biopsy only and 2 were not operated on. Adjuvant therapy was performed in 17 patients (9 radiotherapy, 7 chemotherapy and 1 both therapies). Recurrence occurred in 14 patients, 8 of which remained stable after reoperation associated or not to adjuvant therapy. Significant factors associated with a poor outcome were gross total resection and lower age at diagnosis.

Conclusions: The epidemiological and clinical data of this cohort of patients do not differ from other geographical regions. Except the extension of resection and age at diagnosis, all other parameters analyzed failed to show prognostic significance. Although biological behaviour of residual tumors is unpredictable, most of them appear stable for many years even after a first recurrence. These tumors must be treated cautiously. Chemo and/or radiotherapy should be considered only in those cases with more than one recurrence.

Keywords: Pilocytic astrocytoma, pediatric brain tumor, epidemiology, prognostic factors, treatment.

BACKGROUND

Pilocytic astrocytoma (PA) is the most frequent brain tumor in children and adolescents [1,2]. It mostly occurs under age 20 and the preferential location is the cerebellum and hypothalamic-optic pathways [3-5]. Neurofibromatosis type 1 (NF-1) is associated with PA in 15-20% of the cases [6]. PA is considered a benign neoplasm graded I by the World Health Organization classification [7,8]. Although it is a relatively frequent brain tumor there are few large series reported in the literature and most of them concern retrospective studies of cases proceeding from several institutions [3-5,9-13]. Several aspects concerning its biology remain obscure or are matter of controversy [14-19]. The influence of clinical variables on prognosis is not well understood. Therapeutic strategies for residual tumors after surgery are not uniform [20-26]. The use of adjuvant therapy in these cases is largely controversial [27-30]. Also, it is not known whether there is a biological difference in its behaviour according to geographical areas or different ethnic populations. In a recent study, Tihan et al. [5] found some differences among patients proceeding from four Medical Centers in three distinct countries. They point out that it is important to determine whether PA from different regions is similar enough to be included in a single cohort for clinical trials.

Our purpose is to present the clinical, laboratorial, and therapeutic aspects of a cohort of Brazilian patients studied in a single institution, and to compare the findings with the most relevant series of the literature.

METHODS

We studied all patients with PA diagnosed between 1984 and 2014 at the Santa Casa of São Paulo School of Medicine. Clinical, radiological, therapeutic and follow-up data were collected. Inclusion criteria were patients under age 16 with tumors located in the brain, followed-up for at least 6 months, whose medical records contained appropriated data for pertinent analysis. Pathological diagnosis was reviewed by one of us (SR). Clinical factors which were correlated with prognosis included interval between onset of symptoms and diagnosis, age at diagnosis, gender, ethnic background, location of the tumor, image characteristics, extension of resection, and adjuvant therapy. MRI was performed one month after surgery and each 6 months in the 3 first years of follow-up and then annually. Progression was defined as an increase of the size of the residual tumor or appearance of new clinical neurological symptoms or signs related to the tumor.

Chemotherapy included carboplatin and vincristine according to the protocol proposed by Packer et al [27,28]: Carboplatin was administered at an intravenous dose of 180mg/m2 for four consecutive weeks followed by three week-rest period and then renewed for three more weeks.

Vincristine was used at a dose of 1.5mg/m2/week for 10 weeks concurrent with carboplatin. The maintenance regimen consisted of four doses of carboplatin at 175mg/m2/week and vincristine at 1.5mg/m2/week administered weekly for the first three weeks of each four-week cycle. There was 2-week rest between each maintenance cycle. . The regimen was continued for 12 cycles. Radiation therapy was delivered in conformational fractioned scheme (range dose: 40.5-54 Gy), in approximately 1,8 Gy daily, during five weeks.

Statistical analysis included Mann-Whitney and Kruskal-Wallis tests was performed with SPSS (Statistical Package for the Social Science), version 13.0. For analysis of progression free survival (PFS) and overall survival (OS), the Kaplan-Meier method was performed. The study was approved by the institutional Ethics Committee.

RESULTS

Epidemiological and clinical data

The cohort was composed of 64 cases. During analysis, 16 cases were excluded because they did not fulfil the inclusions criteria: 7 were followed-up for less than six months, 7 died between 5 and 40 days after surgery for causes unrelated to the tumor (meningitis and herniation because dysfunction of ventricular shunt), the medical records were insufficient in one case, and there was one case diagnosed as pilomyxoid astrocytoma after the pathological revision. Of the remaining 48 patients, 22 (46%) were boys and 26 (54%) girls; 35 (73%) were white, 8 (17%) brown, and 5(10%) black. Age at diagnosis varied from 6 months to 15.2 years (mean: 6.9 years, median: 7.0 years). The interval between onset of symptoms and diagnosis varied from 0.2 to 180 months (mean: 12.7 months, median: 3 months). The clinical symptoms were headache (56%), ataxia (39%), papilledema (37%), vomiting (23%), motor deficits (19%), seizures (10%), visual disturbances (8%), and alterations of behaviour (7%). Only one patient had NF-1.

As to the location, 25 (52%) were cerebellar, 8 (17%) were hemispheric, 10 (21%) were hypothalamic-chiasmatic, and 5 (10%) were in the midbrain. Radiological findings showed that 28 tumors were solid-cystic, 9 were solid, 4 were purely cystic, and in 7 these data were unknown. All patients but 2 were operated on. Two tumors were only biopsied. Total gross resection (TGR) was achieved in 17 cases (35%), partial resection (PR) in 27 (56%). Median time of follow-up was 9.1 years (mean: 8.9 years, range: 6 months to 21.5 years). Two patients died (one biopsied and one with PR), four patients were discharged after 10 years without tumor recurrence (all them with GTR) and 42 patients (one biopsied, two not operated, 26 with RP and 13 with GTR) were followed clinically and radiologically. Tumor recurrence occurred in 14 patients (29%). Adjuvant therapy was performed in 17 patients (7 chemotherapy, 9 radiation therapy and 1 both therapies).

Outcome

The GTR group (n=17): The median time of follow-up for this group was 7.9 years (mean: 9 years, range: 1.2 to 21.3 years). There was only one recurrence 8 years after surgery. The tumor reappeared in the same local and new surgery was performed and the resection was partial. This patient was submitted to radiation therapy and remained stable for another 13 years.

The PR group (n=27): The median follow-up time for this group was 9.6 years (mean: 8.7 years, range: 6 months and 20.9 years). Seventeen patients are free from progression (median time of follow-up: 8.8 years, mean: 7.5 years, range: 6 months to 13.2 years). From these, 7 had adjuvant therapy. Recurrence occurred in 10 cases between 7 months and 7.5 years (median:1.8 years and mean: 2.6 years) after surgery. All patients were re-operated on (2 with GTR, 7 PR, one died during the procedure). Both patients with GTR remained free from disease (follow-up: 2.9 and 11.5 years, respectively). One with PR is free from disease (follow-up: 6.4 years). In the remaining 6 patients, tumor recurred and they were submitted to adjuvant therapy remaining free from disease (follow up: 2 years to 15.1 years; median: 6.1 years and mean: 6.5 years).

Two patients underwent biopsy only and were submitted to chemotherapy. In one, progression occurred after 1.6 years. New chemotherapy was performed and death occurred due to meningeal gliomatosis after 36 months. In the other, there was no response and the patient was eventually submitted to a partial resection after four years, being lost the follow up after surgery.

Two patients were followed-up without pathological diagnosis. One patient, whose tumor was located in the midbrain, is followed-up for 2.2 years and the tumor remains stable. In the other, the tumor located in the hypothalamic-chiasmatic region, was detected at age of 8 months. He was submitted to chemotherapy. The tumor shrunk and remained stable for 4.4 years when it was observed a growth of its size. New chemotherapy was performed, the tumor shrunk again and remains stable in the last 13 years. This patient is currently 22 year-old.

Analysis of prognostic factors for outcome

The factors analysed included: age at diagnosis, sex, ethnic background, interval between onset of the symptoms and diagnosis, location, extension of resection, imaging characteristics, and adjuvant therapy. From these, GTR showed a statistical significance for OS and PFS ($p<0.05$) (Fig. 1). Also, age at diagnosis had an influence on tumor recurrence, which was more frequent in younger patients (4.9 years) the older ones (7.7 years) ($p<0.05$) (Fig. 2).

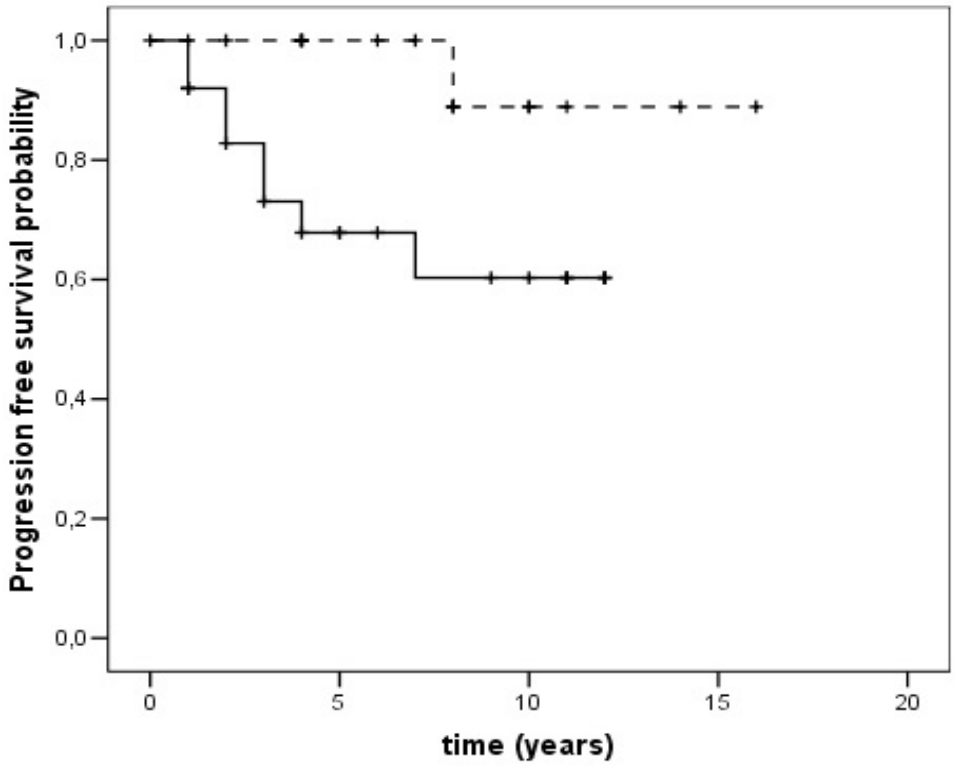
DISCUSSION

The epidemiological and clinical findings in this series do not differ from those found in large series from different countries [4,9,10,12,13]. Two-thirds of the cases occur between 0 and eight years of age and 20% of patients was younger than 36 months at time of the surgery. Sex preponderance varies widely [3,4,10]. In the present series females accounted for 54% of the cases (1:1.2). Cerebellar tumors were the most frequent (52%). There was no preponderance as to the ethnic background. From these findings, it seems that there are no essential differences in the properties of PA in different geographic regions of the globe; an issue recently raised by Tihan and co-workers [5].

Tumor recurrence was more common in younger children. In our study ten patients were younger than 36 months at the time of surgery and 7 had tumor recurrence. Probably, this finding is due the fact that in most of the cases the resection was not total. These results were encountered in other reports [5,13].

As it seems now a common sense, the extent of resection is the main positive predictive factor [3,4,9,12]. Wisoff *et al.* analysed prospectively, for five years, a cohort of 518 children with low grade gliomas (76% PA). The progression free

Figure 1: PFS and extent of resection.



GTR dotted lines
PR full lines

Figure 2: Relationship between age at diagnosis and recurrence.

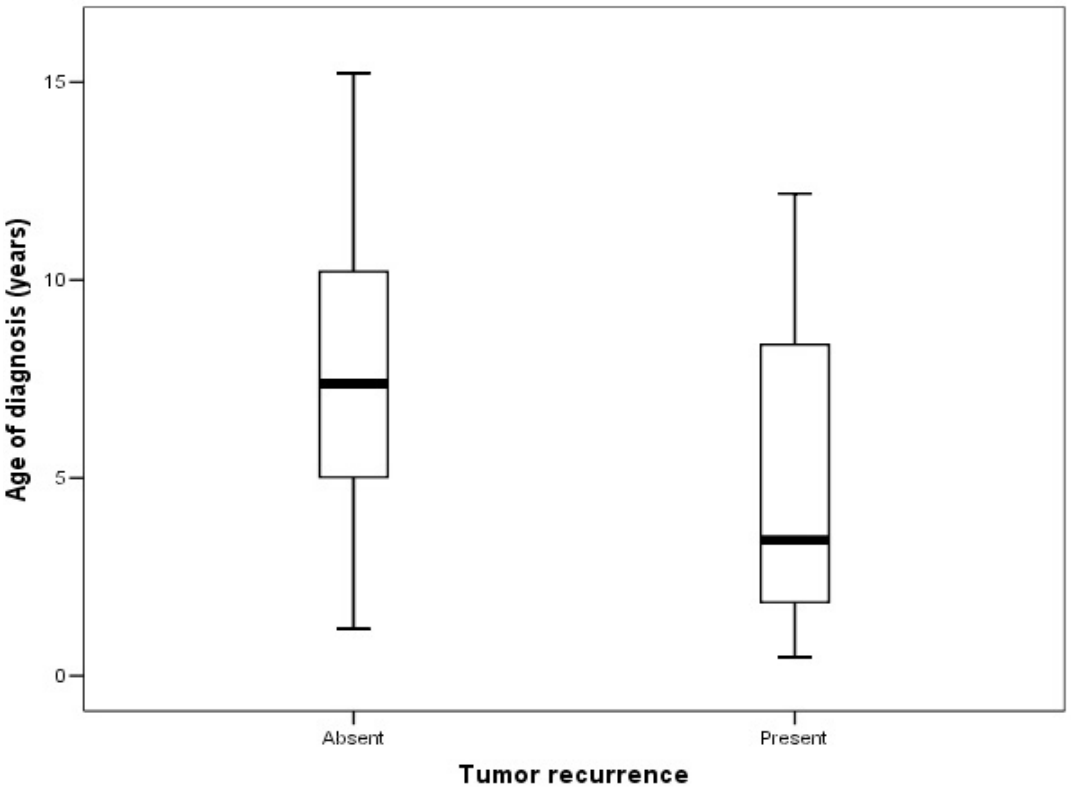
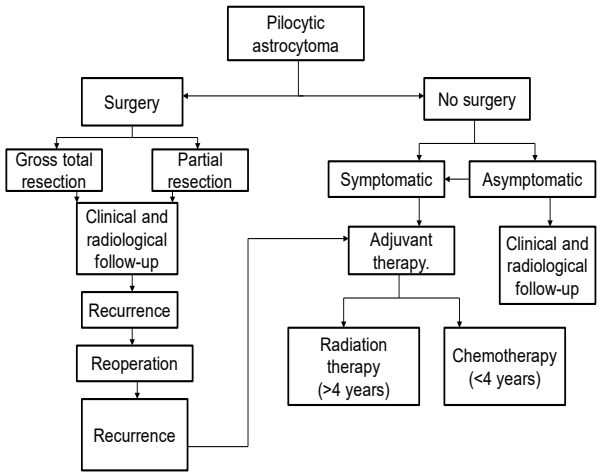


Figure 3: Algorithm of treatment protocol



survival was 94% and 61% after GTR and PR, respectively. These patients had no adjuvant therapy [31]. In the present study, no tumor recurrence was observed in all patients but one who had GTR. In one case, the tumor recurred 8 years after surgery. This poses the issue of when a patient with GTR may be considered cured and for how long he or she must be followed-up.

Nowadays, the major issue concerning PA is related to the management of patients with residual tumor after surgery or of those whose tumor cannot be operated on. This issue comes from the fact that the biological behaviour of PA is unpredictable. Some tumors with or without adjuvant therapy may remain quiescent for decades whereas others show a more aggressive behaviour with several recurrences or dissemination in spite of adjuvant therapy.

The vast majority of PA seem to be very indolent in their biological behaviour. There were only two deaths (4%) due to tumor progression. Recurrence occurred in 14 patients (1 GTR, 10 PR, 2 biopsies and 1 not operated). From these, the tumor remained stable after reoperation associated or not to adjuvant therapy in eight patients, three of which were followed-up for more than 10 years, without recurrences. Only in 4 patients there was more than one tumor recurrence (two recurrences in 3 patients and three in one). Six patients experienced recurrence between 4 and 8 years after treatment whereas in the remaining 8, recurrences occurred within the two first years.

The interval between treatment and recurrence is unpredictable. For these reasons, at the current stage of our knowledge about the biology of PA, we think that these tumors should be treated very cautiously.

Total resection should be performed whenever possible. When operation is not possible for whatever reason or in cases with residual tumors after partial resections, a "wait and see" strategy with a careful clinical and radiological follow-up should be the rule. In case of recurrence, a new surgery should be performed. In case of new progression, chemotherapy in children below age 4 or 5 should be performed. For older children, radiation therapy may be considered in spite of the absence of evidence in the literature of the superiority of this method. In the present series, there were no statistical differences between both methods regarding PFS. It is worth of mentioning that five out seven of our patients submitted to chemotherapy experienced a sustained reduction of the tumor volume. The algorithm for therapeutic strategies recommended by the authors based on the data of this cohort is shown in figure 3.

The ideal method of treatment of PA will be attained only when their biology is fully understood or at least when predictors factors for PFS are uncovered. The epidemiological and clinical data so far analysed–and the present study is an example- failed to clarify this issue. Also, the studies focused on the neuropathology of PA have failed in demonstrating any undeniable predictor morphological feature [3-5,14-16].

In the last few years many studies on the molecular genetics of these tumors have emerged. The mitogen-activated protein kinase (MAPK) pathway has a central role in the tumorigenesis of PA [18]. The tandem duplication of chromosome 7q34 with gene fusion *KIAA1549: BRAF* was found in 55% of PAs without NF1 [32,33]. There are 5 known subtypes fusion, detected by PCR method: *KIAA1549*-exon-16/*BRAF*-exon-9, KIAA1549-exon-15/*BRAF*-exon-9, KIAA*1549*-exon-16/*BRAF*-exon11, KIAA*1549*- exon-18/*BRAF*-exon-10 and KIAA*1549*-exon-19/*BRAF*-exon-9[33]. Although these molecular studies open an important path towards the discovery of drugs targeted against PAs, they have, up to know, as the clinical ones, failed in finding any predictor factor [5,13,19,31-33].

Competing interests

The authors have declared that no competing interest exists.

Author contributions

Both authors contributed equally to this work.

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