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CORRESPONDENCE

Pediatric atypical choroid plexus papilloma reconsidered: increased mitotic activity is prognostic only in older children

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Choroid plexus tumors are intraventricular tumors that represent 3 % of central nervous system tumors in children and adolescents [5], but 10–20 % of brain tumors occurring throughout the first year of life [6]. According to the World Health Organization (WHO) classification, choroid plexus tumors can be divided into choroid plexus papillomas (CPP, WHO grade I), atypical choroid plexus papillomas (aCPP, WHO grade II) and choroid plexus carcinomas (CPC, WHO grade III) [6]. While CPC show histopathological signs of malignancy and distinct molecular features [4, 7, 8], CPP are benign papillary neoplasms closely resembling non-neoplastic choroid plexus. The observation that increased mitotic activity (≥2 mitoses/10 high power fields) was associated with a higher probability of recurrence in CPP affecting children and adults [2] resulted in the current WHO definition of aCPP, i.e., CPP with increased mitotic activity [3]. In a subsequent pediatric cohort, aCPP did not have significantly worse progression-free survival when compared with CPP [9]. In the latter series, however, patients harboring atypical CPP were younger than in the first study [2], raising the possibility that increased mitotic activity might not have an adverse prognostic effect in younger children. Indeed, two recent studies suggested that CPP and aCPP in younger children show not only similar molecular profiles, but also comparable outcome [1, 4]. These results are questioning the concept of aCPP, but might well be related to an age-dependent effect. We thus aimed to investigate the prognostic value of increased mitotic activity in pediatric CPP and aCPP according to age.

The 149 patients analyzed in this study had been registered in the choroid plexus tumor registry of the International Society of Pediatric Oncology (CPT-SIOP). Informed consent had been obtained from patients or legal guardians in accordance with national laws and with the local guidelines of the participating centers. Formalin-fixed paraffin-embedded tumor samples from all patients were reviewed neuropathologically according to 2007 WHO criteria by senior neuropathologists (W.P., T.P., M.H.). Comparison of patient characteristics was done by Chi square test or Mann–Whitney *U* test. Progression-free survival was examined by Kaplan–Meier analysis and the Log-rank test using IBM SPSS 22 software (release 22.0). $P < 0.05$ was considered statistically significant.

As shown in Table 1, median age of the 77 boys and 72 girls was 18 months. The majority of tumors were located supratentorially (119/149, 80 %). The neuropathological diagnosis was CPP in 76 cases, while increased mitotic

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Table 1 Patient characteristics

	All cases ($N = 149$)	Choroid plexus papilloma (WHO grade I) ($N = 76$)	Atypical choroid plexus papilloma (WHO grade II) ($N = 73$)	
Sex (male/female)	77/72	39/37	38/35	n.s.
Age (months) (median, interquartile range)	18 (6–74)	35 (11–121)	8 (4–27)	$P < 0.001$
Young age (<3 years)	95 (64 %)	39 (51 %)	56 (78 %)	$P < 0.01$
Supratentorial location	119 (80 %)	55 (72 %)	64 (88 %)	$P < 0.05$
Gross total resection	120 (81 %)	59 (78 %)	61 (84 %)	n.s.
Chemotherapy	30 (20 %)	8 (11 %)	22 (30 %)	$P < 0.01$
Radiotherapy	8 (5 %)	2 (3 %)	6 (8 %)	n.s.

n.s. not significant

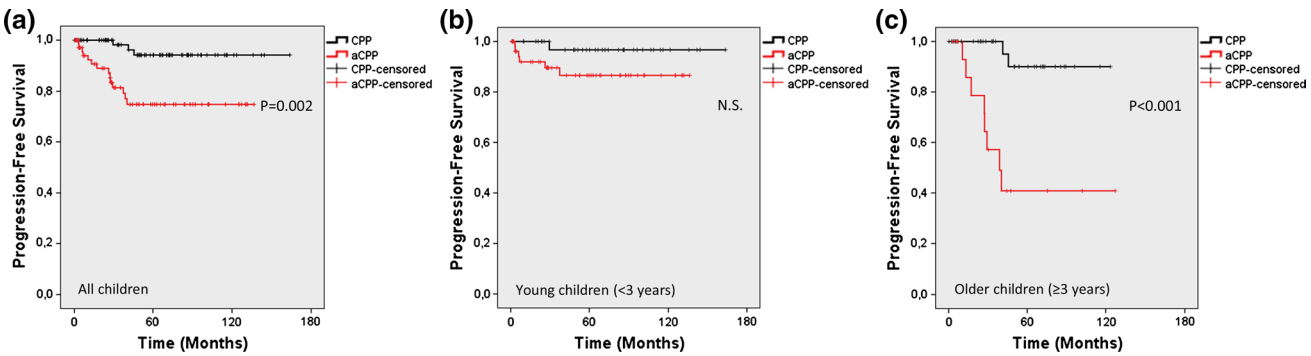

Fig. 1 Prognostic role of increased mitotic activity in pediatric choroid plexus papillomas. Kaplan–Meier estimates of progression-free survival in choroid plexus papillomas (CPP) as compared to atypical choroid plexus papillomas (aCPP), i.e., CPP with increased mitotic activity, examined (**a**) in all patients irrespective of age ($N = 149$), (**b**) in younger children (<3 years, $N = 95$) as well as (**c**) older children (≥3 years, $N = 54$). Note absent significant difference in younger children, but highly significant prognostic role of increased mitotic activity in children ≥3 years (Log-rank test $P < 0.001$)

activity resulted in a diagnosis of aCPP in 73 cases. Patients harboring aCPP were found to be younger ($P < 0.001$), and more often had supratentorial tumors ($P < 0.05$). Detailed follow-up information was available for all 149 patients. Irrespective of histopathological diagnosis, most patients experienced long-term survival and only three patients (2 %) succumbed to disease. In the whole cohort, progression-free survival accounted for 143 (133–152) months [mean (95 % confidence intervals)]. However, as shown in Fig. 1a, patients with aCPP had shorter progression-free survival as compared to patients with CPP [108 (95–121) months vs. 156 (148–164) months, $P = 0.002$]. To examine possible age dependency, the prognostic effect of increased mitotic activity was examined in younger children (<3 years) as compared to older children (≥3 years). The third birthday represents a clinically important mark, because radiation therapy is rarely considered in children younger than 3 years. Indeed, radiotherapy was more frequently administered in older children with aCPP (4/17 vs. 2/56; $P < 0.01$), but choroid plexus tumors of both age groups did not differ with regard to other treatment modalities (Supplementary Table 1). Interestingly, the diagnosis of aCPP was not associated with shorter progression-free survival in younger children (<3 years, Fig. 1b), whereas the prognostic effect of increased mitotic activity was highly significant in older children (≥3 years, Fig. 1c) [67 (40–94) months vs. 115 (105–126) months, $P < 0.001$]. Multivariate Cox regression analysis taking into account sex, age, tumor location, WHO grade, gross total resection as well as radio- and chemotherapy status confirmed that WHO grade and age were significantly associated with progression-free survival (Supplementary Table 2).

Taken together, these data convincingly demonstrate that in addition to WHO grade, younger age is an important predictor of progression-free survival. Our series thus might help to explain the discrepancy between results obtained in previous pediatric series [1, 4] as compared to older patient collectives [2]. The majority of aCPP occur in children younger than three years. Our data clearly support a conservative "watch and wait" approach following gross total resection in this age group. On the other hand, the data prompt careful follow-up examinations in children

older than 3 years harboring aCPP, because of the higher risk of recurrence associated with increased mitotic activity in older children. Increased mitotic activity is well recognized as a prognostic marker in a variety of central nervous system tumors, but an age-dependent prognostic effect of increased mitotic activity has not yet been reported. Underlying biological factors explaining this effect in aCPP remain uncertain. It is tempting to speculate that it could be related to a milieu favoring proliferative activity in the choroid plexus throughout the first years of life. The fact that treatment was not more aggressive in younger children with aCPP makes clinical confounders unlikely. In the light of our findings, a better characterization of aCPP in older children is warranted and will hopefully shed light on molecular mechanisms involved in the more aggressive biological behavior of these tumors. This also holds true for CPP and aCPP in adults, which are typically located in the fourth ventricle and whose genetic and epigenetic features are even less well characterized.

In conclusion, increased mitotic activity is associated with a higher probability of recurrence in pediatric CPP. Our finding that the prognostic role of increased mitotic activity is mainly restricted to older children argues against providing more intense therapy in aCPP as compared to CPP in children younger than 3 years.

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