Medulloblastoma: clinical presentation

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Médulloblastomes : présentation clinique

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Abstract

Medulloblastomas present generally a-specifically as a fast-evolving posterior fossa tumor. Medical literature is poor concerning clinical features of medulloblastomas and their potential significance.

In the present study, we reviewed 91 pediatric observations of medulloblastomas treated in Lille between 1997 and 2017. Clinical and epidemiological variables were collected and intercorrelated. They were also compared with anatomical and pathological findings, and outcome, with the aim of defining clinical-pathological entities. We also compared the group with 32 cases of posterior fossa ependymoma and 130 cases of cerebellar astrocytoma treated during the same period.

We found that in medulloblastomas, the M/F ratio was higher and diagnostic delay was shorter than in astrocytomas. Also, the mean age was older than in ependymomas. Intracranial hypertension was constant; we further observed that altered general status was common (16.5%) and correlated with a metastatic tumor.

We delineated two clusters: the "nodular" cluster, which associates young age, cerebello-pontine angle tumor, herniation, desmoplastic tumor, and tumor predisposition syndrome; and the "metastatic" cluster, which associates altered status, initial metastases, hydrocephalus, and diagnostic delay.

Meticulous collection of clinical data at the initial phase is integral part of the oncological evaluation, with a search for genetic and prognostic risk factors, which then permits us to define clinical pathological entities.

Key-words

Medulloblastoma – clinical presentation – tumor predisposition syndrome – outcome

Résumé

La présentation clinique des médulloblastomes est généralement aspécifique, c'est le tableau stéréotypé d'une tumeur de fosse postérieure évoluant rapidement. La littérature médicale est particulièrement pauvre concernant les caractéristiques cliniques des médulloblastomes et leur possible signification.

Dans la présenté étude, nous avons revu 91 observations de médulloblastome de l'enfant traités à Lille de 1997 à 2017. Les variables épidémiologiques et cliniques ont été colligées et corrélées entre elles et avec les constatations anatomiques, histologiques et le devenir clinique et oncologique, dans le but de définir des associations syndromiques. Nous avons comparé le groupe des médulloblastomes avec 32 cas d'épendymome de fosse postérieure et 130 astrocytomes du cervelet diagnostiqués durant la même période.

Nous avons retrouvé chez les médulloblastomes un sex-ratio plus masculin que chez les astrocytomes, un âge plus élevé que chez les épendymomes, et une durée d'évolution plus courte que pour les astrocytomes. L'hypertension intra-crânienne était constante ; par ailleurs on retrouvait fréquemment une altération de l'état général (16,5%), qui était significativement associée à une tumeur métastatique.

Nous avons identifié deux clusters de variables : le cluster "nodulaire" associant jeune âge, localisation dans l'angle ponto-cérébelleux, signes d'engagement, caractère desmoplasique, et présence d'un syndrome de prédisposition tumorale ; et le cluster "métastatique" associant AEG, métastases d'emblée, hydrocéphalie, et retard diagnostique.

Le recueil méticuleux des données cliniques à la phase initiale fait partie intégrante de l'évaluation oncologique avec recherche des facteurs de risque génétique et de pronostic clinique et oncologique, et permet de définir des entités anatomo-cliniques.

mots-clé

médulloblastome – présentation clinique – syndrome de prédisposition tumorale - devenir

Introduction

Medulloblastoma is one of the most common tumors in children. Although the diagnosis is now made earlier due to the availability of imaging, clinical diagnosis is still a problem because of often unremarkable, even a deceptive presentation, especially in infants, whose symptoms are easily overlooked in the flux of emergencies. However, diagnostic delay can have deleterious consequences, resulting in an unfavorable outcome like vision loss or herniation. Delay also occurs when the diagnosis is misled by digestive symptoms, sometimes leading to an unnecessary appendectomy, or worse, suspicion of meningitis with a harmful lumbar puncture.

Data from the literature on clinical presentation of medulloblastoma in children are scarce, even non-existent. We found it useful to review the elements of clinical diagnosis in our experience with medulloblastoma, comparing them with data on other common posterior fossa tumor types whenever available; we also found it interesting to point out diagnostic errors, which sometimes delay the diagnosis.

Clinical evaluation also includes the search for elements like tumor predisposition syndromes, whose numbers and scope are steeply increasing with our knowledge on genetics and molecular biology. This implies starting genetic screening in the very early diagnostic phase.

The clinicopathological correlation and the predictive value of clinical findings (age, sex, developmental achievement, general status at the time of presentation) are also topics, which remain to be studied.

Patients and methods

Because of the scarcity of clinical data in the literature, we decided to review the Lille series of medulloblastoma in children diagnosed during the 1997-2017 period, gathered in a semi-prospective fashion and recorded in a computerized database.

We studied the sex, age at diagnosis, delay between the first clinical signs, symptoms, and diagnosis, and recorded the presence or absence of the following: ataxia, developmental delay or motor regression, intracranial hypertension, herniation, altered general status, papilledema, decreased vision, oculomotor trouble, and torticollis. In cases initially misdiagnosed, we also noted the initial diagnosis.

We then studied the correlations between the above-mentioned variables, and their relationship with the presence or absence of hydrocephalus, metastases, tumoral location on the midline or the cerebello-pontine angle (CPA), the pathology (whether desmoplastic or not), and the occurrence of such outcome elements as: postoperative mutism, tumor recurrence, death by tumor progression, functional outcome (graded according to the Karnofsky (KNK) independence scale). In order to evaluate the results in medulloblastoma, we compared these with posterior fossa ependymoma and cerebellar astrocytoma diagnosed during the same period (unpublished data).

For statistical analysis, we used univariate tests with Student's-t-test for continuous variables, Chi-square and Fisher's exact tests for binary variables, and survival analysis of event-free survival (EFS) and overall survival (OS) with the Kaplan-Meier method and the log-rank test for statistical significance. For all tests, the threshold for significance was 0.05. We completed this quantitative analysis by performing a qualitative study in principal component analysis, in order to delineate clusters of variables representing meaningful clinical entities. All analyses were performed using the IBM SPSS statistics 22 software.

Results

Epidemiology

We reviewed 91 observations of medulloblastoma, 59 boys and 32 girls (M/F ratio 1.84), with a mean age of 87.8 months (3.8 months to 17.1 years, median age 90 months, 95%CI 82.7-92.8). For comparison, 130 children with astrocytoma (58 boys, 72 girls, M/F ratio 0.80) had a mean age of 97.8 months (12.1 months to 17.5 years, median age 94.1, 95%CI 92.1-101.4). Thirty-one children treated for ependymoma (15 boys and 16 girls, M/F ratio 0.93) had a mean age of 48.3 months (11 months to 14.4 years, median age 30 months, 95%CI 14.1-55.4).

A tumor predisposition syndrome was diagnosed or suspected in 13 cases of medulloblastoma (14.3%), due to family history of uncommon or early cancers, or the presence in the child of a clinical syndrome or an identified mutation. These diagnoses, often made in retrospect, were Gorlin syndrome in 4 cases (figure 1), Gardner syndrome (1 case), Fanconi syndrome (1 case), BrCa1 mutation (1 case), and several associated cancers.

Among medulloblastoma, the diagnostic delay ranged between 1 and 846 days (in the latter case, the precise onset was difficult to assess because of a debilitated terrain with language delay and a protracted course of macrocrania and vomiting). The mean diagnostic delay was 52.5 days (median 30, 95%CI 42.8-62.1). For comparison, in astrocytoma, the mean delay was 128.7 days (0-days-4.5 years, median 46.5 days, 95%CI 107.9-149.4); in ependymoma, the mean was 52.6 days (2-229 days, median 29, 95%CI 22.0-63.6).

At the time of diagnosis of medulloblastoma, intracranial hypertension was present in all cases, with papilledema in 15 (16.5%), vision loss in 5 (5.5%), oculomotor disturbance in 11 (12.1%); 4 patients presented with signs of herniation (4.4%). Cerebellar ataxia was present in 40 cases (44.0%), with motor delay or regression in 8 cases (8.8%); altered general status (weight loss, intense weariness) was observed in 15 cases (16.5%); finally, a torticollis

was noted in 11 cases (12.1%). We identified misdiagnoses in 8 cases, especially with digestive signs and symptoms interpreted initially as enteritis (3 cases), appendicitis (prompting appendectomy), reflux (prompting fibroscopy), ketonuria in one case; in 2 cases, the cervical stiffness was interpreted as spinal problem (prompting X-Rays).

Pathological findings

Hydrocephalus was present initially in 57 cases (62.6%), metastases were found in 32 (35.2%); the tumor involved the midline in 77 cases (35.2%), the CP-angle in 6 cases (6.6%), the cerebellar hemisphere in 12 cases (13.2%). The tumor type was desmoplastic in 10 cases (11.0%).

Outcome

After a mean follow-up of 69.6 months (median 54, CI95% 63.8-75.5), 33 patients (36.5%) presented with tumor progression, and 24 (26.4%) died of tumor progression. The event-free survival at 5 years was 56.8%, unchanged at 10 years. Overall survival at 5 and 10 years was 71.5% and 64.8% respectively. At a mean age of 12.7 years (median 12, IC95% 12.0-13.3), 29 of the survivors had a KNK of 100, 13 (20.3%) had a KNK of 90, 6 (9.4%) had a KNK of 80, 12 (18/8%) had a KNK of 70, and 3 (4.7%) had a KNK of 60.

Analysis

The comparison between medulloblastoma, astrocytoma, and ependymoma as regards their epidemiology, diagnostic delay, and signs and symptoms, is summarized in table 1. We also observed significantly more boys with medulloblastoma, a younger age in ependymoma, a longer diagnostic delay with more children without intracranial hypertension in astrocytoma.

Among medulloblastoma, significant correlations are summarized in table 2. We note an association between young age and motor delay or regression ($p = 0.04$) as well as with a desmoplastic tumor ($p = 0.013$). We also found no association between altered general status and the presence of metastases ($p = 0.02$), and between herniation and tumor of the CP angle ($p = 0.021$). A context of tumor predisposition syndrome was associated with a younger age ($p = 0.046$), a location in the CP-angle ($p = 0.036$) although no correlation was found with the desmoplastic type.

Motor delay or regression was also associated with a longer diagnostic delay ($p = 0.03$), the presence of hydrocephalus ($p = 0.023$) and a lower EFS ($p = 0.047$), although no correlation was found with OS. EFS was also better when the patient presented with ataxia ($p = 0.019$), again without significant correlation with OS.

Factorial discriminant analysis permitted the construction of a model with 9 components accounting for 67.6% of variance. Figure 2 shows a tridimensional graph of the first 3 components, accounting for 30.9% of variance.

Discussion

The objective of our study is limited by its partly retrospective nature, with a non-systematic collection of data, and by its limited number of cases scattered over two decades. Nevertheless, the series is homogeneous, originating from a single institution; patients were managed in a comparable fashion and collected by a single author. Due to the limited numbers, statistical significance was often liminal, and some results are dubious (like the "protective effect" of ataxia). For these reasons, we limited our study to univariate analyses, especially since our aim was to characterize qualitatively rather than quantitatively the clinical presentation of medulloblastoma, and define clinical-pathological entities. We thus elected to study the association of variables in principal components analysis with a three-dimensional

diagram. It is worth noting that the first three components of the analysis account for only 31% of variance. Despite this, we managed to identify these components as: 1 the lesions; 2: the outcome; 3: the terrain; the result then appears to segregate meaningful clusters of variables.

Epidemiological data of medulloblastoma differ from other tumor types, with a male predominance compared with astrocytoma, and a later age compared with ependymoma. These differences do not apply on the individual level, obviously, since medulloblastomas can be diagnosed in very young infants, even in fetuses [1]. The association of young age with developmental delay or regression at the time of diagnosis has been reported earlier [2], and our results corroborate this finding. However, we did not confirm the negative impact of young age on tumor outcome reported in an ancient study [3], which could be due to advances in the management of medulloblastoma in infants. We also did not confirm the better prognosis in females reported earlier [4], which is possibly a feature of adult medulloblastoma [5].

Searching for a tumor predisposition syndrome is part of the initial evaluation, because it can affect the management and outcome [2]. The best known is Gorlin syndrome related to a mutation of the PTCH1 gene, associating periodontal cysts, facial dysmorphia, skeletal anomalies, and could be linked with a better outcome [6]; it should be noted, however, that the diagnosis is often made several years in retrospect, which leaves space for a selection bias. In addition, Gorlin syndrome predisposes to radiation-induced tumors like meningioma and glioma [7], which can influence treatment choices. It is associated with a nodular or desmoplastic tumor, which is linked to the Sonic Hedgehog group (SHH), and has a somewhat better prognosis [8]. However, desmoplastic histopathology does not always coincide with the molecular biology, and the prognosis of tumors of the SHH group could in fact be less favorable [9]. Gardner syndrome is caused by a mutation of the APC

(Adenomatous Polyposis Coli) gene and is suspected because of family antecedents of intestinal tumors. Rubinstein-Taybi syndrome, caused by different mutations, is remarkable for its dysmorphic appearance. Unexpectedly, we found a hypothalamic hamartoma in one of our otherwise non-syndromic patients, and also in the sister of another patient. This association, to our knowledge, has not been reported in literature and we think it is likely fortuitous.

Misdiagnoses can delay the management of the patient and result in loss of chance. They are common in medulloblastoma, and not just in infants. Digestive symptoms are very common and easily overlooked, especially during epidemics, especially since genuine enteritis can be associated with intracranial hypertension, for example when a child returns to the emergency room contaminated with enteritis from a previous visit. In addition, ketonuria is an "easy" diagnosis, which should be no more than provisional until the presentation becomes clearer. Even more dangerous is when the misdiagnosis of meningitis leads to potentially fatal spinal puncture (not found for medulloblastoma in our series). This underlines the need for imaging before lumbar puncture in emergency. More deceptive is a torticollis, which can mislead the diagnosis toward a spinal problem (figure 3), causing delays all the more damaging because it indicates a pre-herniation state; this is an opportunity to repeat that spine stiffness is a clinical equivalent for pain in child who will never complain.

Among the clinical presentations, intracranial hypertension is striking by being frequent in medulloblastoma, even in the absence of hydrocephalus, especially because this is not the case for astrocytoma. This is likely explained by the difference between these two tumors regarding growth speed. Therefore, when a posterior fossa tumor is diagnosed, the absence of intracranial hypertension indicates an astrocytoma, especially when the diagnostic delay is long. Intracranial hypertension often has a severe and lasting impact on vision, which bears special significance considering that platinum-based chemotherapy and irradiation can

also impact hearing. Altered general status was found on admission in 16.5% of children with medulloblastoma, and an indication of possible metastases, features quite different from astrocytoma, and a strong argument in favor of medulloblastoma.

Overall, clusters of variables emerge as coherent and meaningful ensembles. The first, which we could name "nodular", regroups the following variables: young age, motor regression, desmoplastic tumor, tumor predisposition, location in the CP angle, and herniation; the second, which we could mention “metastatic”, regroups the following variables: altered status, metastases, hydrocephalus, vision loss, and diagnostic delay. The diagnostic value of these profiles however still remain to be validated.

Conclusions

Clinical presentation of medulloblastoma is generally nonspecific; it is the stereotyped presentation of a tumor of the posterior fossa progressing rapidly. Although some features are more common in medulloblastoma than in other tumors of the posterior fossa, these differences do not allow guessing in advance which type of tumor will be found.

This diagnosis may appear easy in retrospect; however, it is often a difficult one for the general practitioner or the pediatrician in the emergency room. Faced with a non-verbal child often with no neurological presentation, the association of vomiting with an altered status, a motor regression, a torticollis, a child appearing “too quiet”, are all features that should arouse attention. In spite of the advances and availability of seriated imaging, clinical evaluation remains the cornerstone of diagnosis. The perspicacity of the clinician is tested by apparently nondescript symptoms, but with persistence and by seeing the patient again, until the situation becomes clear enough to go to the imaging stage, which will finally produce the unfortunate diagnosis.

Pending further studies on the clinical presentation of medulloblastoma, our study is an attempt to apply to the field of neuro-oncology an clinical-anatomical method and define syndromic associations. In our opinion, in spite of the advances in imaging, this method still has lessons to teach us.

Conflicts of interest:
We have no conflicts of interest

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Figures and tables

figure 1

14- year-old patient with Gorlin syndrome caused by PTCH mutation. She was operated on age 13 months for desmoplastic medulloblastoma, and showed a characteristic phenotype with basocellular neurofibromatosis, which required surgery for an ulcerated cervical baso-cellular hamartoma.

figure 2

Three-dimensional diagram showing the three main components regrouping clinical variables (age, sex, predisposing syndrome,), anatomical findings (tumor location, metastases, hydrocephalus), and outcome (Karnofsky score, tumor progression), accounting for 30.9% of variance. We noted a cluster (yellow ring) including the variables "engagement" (herniation), "phaco" (predisposing syndrome), "APC" (CP-angle location) and "desmo"(desmoplastic tumor). Another cluster (red ring) regroups the variables "delay"(diagnostic delay), metastases at diagnosis, and "AEG" (altered status). Note also the proximity between the variables "ataxia" and the variable "KNK" (Karnofsky score), reflecting the better clinical outcome associated with initial ataxia.

figure 3

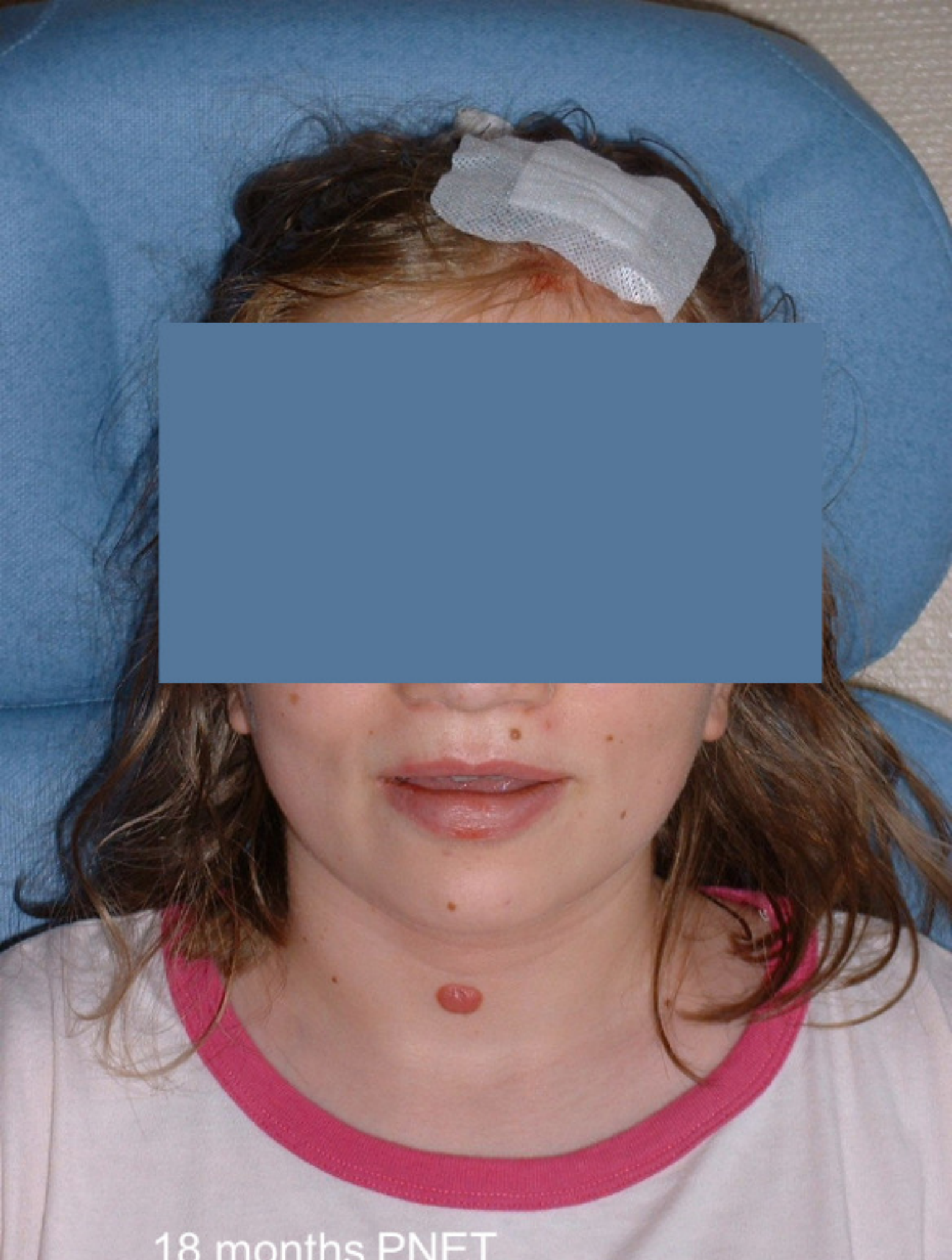
Torticollis revealing a tumor in the cerebellopontine angle in a 17-month old toddler.

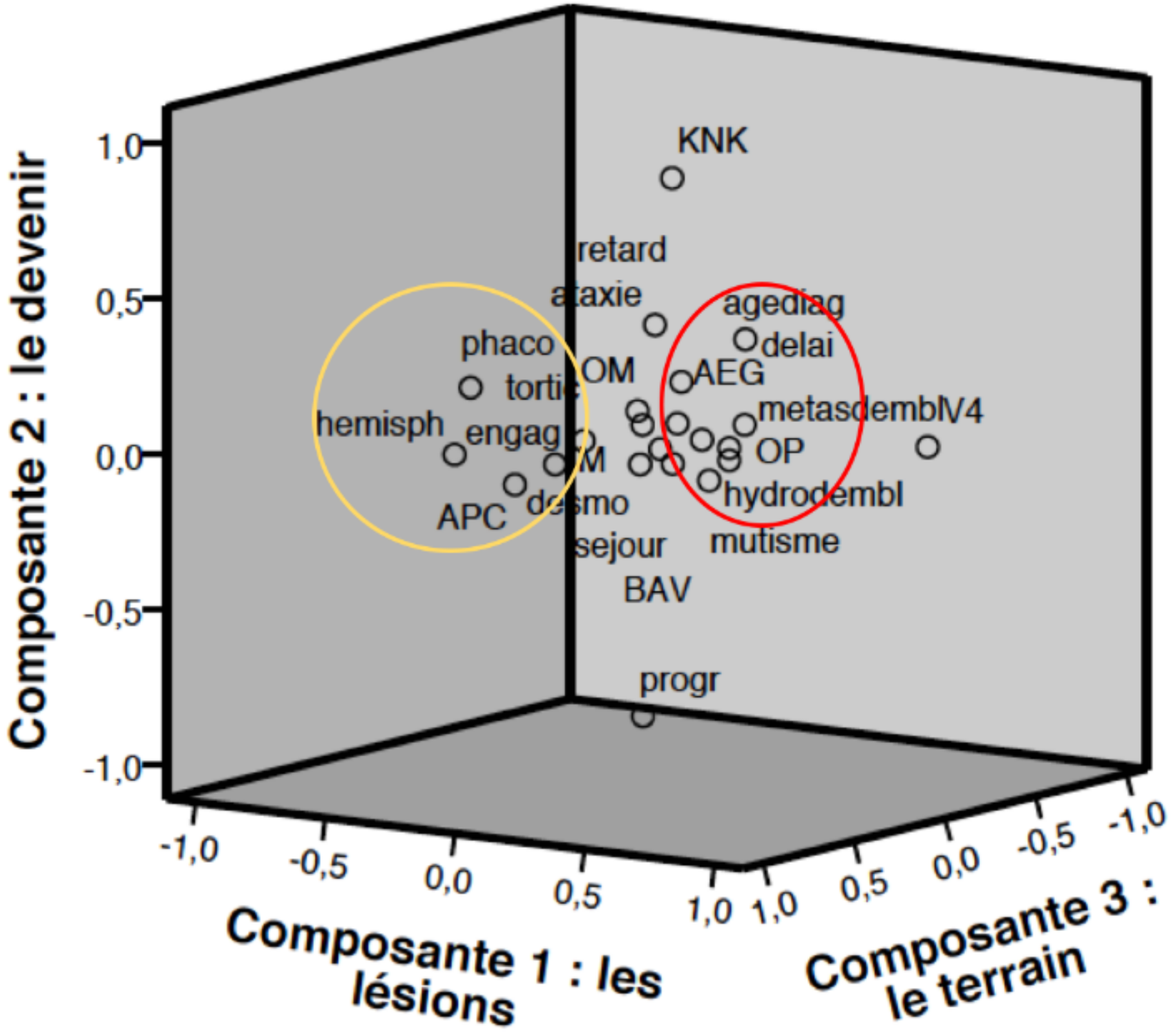
Table 1

Comparison of variables age, sex-ratio and diagnostic delay between medulloblastoma, posterior fossa ependymomas, and cerebellar astrocytoma. M: Male; F: female; CI: confidence interval; ICP: intracranial pressure; * statistically significant $p < 0.05$; ** highly statistically significant $p < 0.01$.

Table 2

Different features and correlation between clinical variables. Age was correlated with other clinical variables (diagnostic delay, tumor predisposition syndrome); other variables are correlated with anatomic (hydrocephalus or metastases at onset), or histopathological findings (desmoplastic tumor), showing clustering of variables making clinical-pathological entities. Note that motor delay or regression is associated with better EFS, although without impact on OS. Unexpectedly, ataxia was associated with better EFS, although without impact on either OS or functional outcome. No significant correlation was found between other variables (including age and sex) and oncological and functional outcome. M: male; F: female; CI: confidence interval; EFS: Event-free survival.


18 months PNET


Composante 2 : le devenir
1,0
0,5
0,0
-0,5
-1,0
KNK
retard
ataxie
agediag
delai
phaco
OM
AEG
metasdemblV4
hemisph
engag
OP
hydrodembl
APC
desmo
sejour
mutisme
BAV
progr
-1,0
-0,5
0,0
0,5
1,0
Composante 1 : les lésions
Composante 3 : le terrain

	medulloblastoma (91)	ependymoma (32)	cerebellar astrocytoma (130)
mean age (months)	87.8 (CI95% 83-93)	48.0 (CI95% 14-55)*	97.0 (CI95% 92-101)
M/F ratio	1.84*	0.8	0.94
diagnostic delay (days)	53 (CI95% 43-62)	51 (CI95% 22-62)	129 (CI95% 108-149)*
raised ICP	91 (100%)	28 (90%)	109 (84%)**
papilledema	15 (16.5%)	4 (13%)	33 (25%)
vision loss	5 (5.5%)	0	8 (6%)
oculomotor	11 (12%)	4 (13%)	21 (16%)
ataxia	40 (44%)	15 (48%)	64 (49%)
delay/regression	8 (9%)	2 (6.5%)	5 (4%)
altered status	15 (16.5%)**	2 (6.5%)	5 (4%)
torticollis	11 (12%)	6 (19%)	15 (11.5%)
particularity	altered status 15 (16.5%) : metastases 11/15	mixed nerves 2 (6.5%)	fortuitous 7 (5%)

variable	result	correlation
M/F	1.84	NS
mean age (months)	87.8 (CI95% 83-93)	delay (p = 0.04): present when younger desmoplasia (p = 0.013): present when younger
diagnostic delay (days)	53 (CI95% 43-62)	developmental delay (p = 0.03): present when diagnostic delay
delay/regression	8 (9%)	hydro (p = 0.023) recurrence: EFS lower (p = 0.047); OS non significant
ataxia	40 (44%)	EFS (0.019): higher when present; OS non significant
altered status	15 (16.5%)	metastases upon diagnosis (p = 0.02)
tumor predisposition syndrome	13 (14%)	younger (p = 0.046) location CP Angle (p = 0.036)
herniation	4 (4.4%)	location CP Angle (p = 0.021)