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Medulloblastomas in adults: lessons from pediatrics

THESE

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Rapport de synthèse

Buts de la revue:

Les Médulloblastomes sont des tumeurs rares chez l'adulte. Le traitement habituel comprend une radiothérapie de tout l'axe cranio-spinal avec ou sans chimiothérapie. Beaucoup d'efforts sont actuellement entrepris pour mieux comprendre la biologie tumorale, afin de mieux stratifier les patients en différents groupes à risques et de les traiter en fonction. Cette revue discute les nouveaux facteurs de risques cliniques et moléculaires qui peuvent aider à optimiser le traitement des patients adultes avec des médulloblastomes.

Découvertes récentes:

Jusqu'à présent les patients étaient divisés en groupes à bas risque ou à haut risque sur la base de facteurs cliniques (âge, maladie résiduelle après chirurgie, dissémination dans le système nerveux central et l'histologie). Cette classification devrait être complétée par des facteurs pronostics moléculaires. Le profilage de l'expression des gènes a permis d'identifier six sous-groupes moléculaires de médulloblastomes. Le WNT sous-groupe montre une activation des gènes de la voie de signalisation WNT/wingless avec des mutations fréquentes du gène *CNNTB1*, une perte du chromosome 6 et une accumulation de β-catenine nucléaire. Ce sous-groupe est rencontré le plus souvent chez les enfants avec des médulloblastomes avec une histologie classique. Ils ont un bon pronostic. Une activation de la voie de signalisation du sonic hedgehog montre des mutations fréquentes des gènes *PTCH* et *SUFU*, une perte du 9q et une positivité pour GLI1 et SFRP1 et est rencontré plus fréquemment chez les enfants de moins de 3 ans et chez les adultes. Ce sous-groupe est souvent associé à une histologie de type desmoplastique. D'autre sous-groupes sont moins bien délimités et présentent des caractéristiques qui se chevauchent. Cependant une amplification MYC/MYCN, un gain du 17p et une histologie de type grandes cellules/anaplasique sont des facteurs de mauvais pronostic.

Résumé:

Des nouveaux sous-groupes moléculaires vont dorénavant aider à mieux adapter les traitements aux différents groupes de risque et permettront à développer de nouvelles thérapies ciblées. Des études prospectives et si possibles randomisées devraient être effectuées comprenant une stratification dans des sous-groupes moléculaires, afin d'identifier au mieux le meilleur traitement pour chaque groupe à risque.

Medulloblastomas in adults: prognostic factors and lessons from paediatrics

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Purpose of review

Medulloblastomas are very rare in adults. Usual treatment consists of craniospinal radiation with or without chemotherapy. Current efforts focus on a better understanding of tumour biology, stratifying patients into risk groups and adapting treatment accordingly. This review discusses clinical and new molecular risk factors that will help to optimize treatment in adult medulloblastoma patients.

Recent findings

The clinical risk stratification should be complemented with new molecular prognostic markers. Gene-expression profiling has permitted identification of four to six molecular medulloblastoma subgroups. The WNT subgroup shows overexpression of genes of the WNT/wingless signalling pathway with frequent mutations of the *CNNTB1* gene, loss of chromosome 6 and accumulation of nuclear β-catenin, and is most often seen in children with medulloblastomas of classical histology. This variant has a good prognosis. Activation of the sonic hedgehog pathway with frequent mutations of the *PTCH* and *SUFU* genes, loss of 9q, and positivity for GLI1 and SFRP1 is more frequent in children less than 3 years old and in adults, commonly associated with desmoplastic histology. Other subgroups are not so well defined and have overlapping characteristics, but *MYC/MYCN* amplification, 17q gain and, large cell/anaplastic histology are factors of poor prognosis.

Summary

New molecular subgroups will help tailor treatment and further develop new targeted therapies. Prospective and ideally randomized trials should be performed in adults, including risk stratification by molecular markers, to identify optimal treatment for each risk group.

Keywords

adult medulloblastomas, molecular factors, prognostic factors, treatment

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Introduction

Embryonal tumours [medulloblastomas, primitive neuroectodermal tumours (PNETs) and atypical teratoid/rhabdoid tumours] are the most frequent primary brain tumours in children between 0 and 4 years. Medulloblastomas account for 13% of all brain tumours in children from 0 to 14 years, 4% in children between 15 and 19 years and 2% in young adults between 20 and 34 years. In adults (defined as age >18 years), medulloblastoma is a very rare tumour with a slight male predominance (male–female ratio of 1.28) [1]. Five subtypes of medulloblastomas can be distinguished by histology: classical histology, desmoplastic/nodular medulloblastoma, medulloblastoma with extensive nodularity, anaplastic medulloblastoma and large cell medulloblastoma [2]. The extensive nodularity and anaplastic variants were only recently introduced in the Fourth Edition (2007) of the WHO classification [2]. The large cell and the anaplastic variants have a considerable cytological overlap, so that in studies often a combined large cell/anaplastic category with poor prognosis has been used. The medulloblastoma with extensive nodularity is closely related to the desmoplastic/nodular variant and shares a more favourable outcome [3].

Because of the typical location in the posterior fossa, patients often present with symptoms of increased intracranial pressure, hydrocephalus and/or cerebellar signs. Medulloblastomas have the particularity of early dissemination to the cranial and/or spinal subarachnoid space. In more advanced disease, extraneural metastases to the bone marrow, bone, lung (especially in children) and liver may be present.

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The standard therapy includes local surgery followed by craniospinal radiation therapy with or without chemotherapy.

Understanding prognosis and prognostic factors is crucial in order to decide on treatment strategy and intensity. Clinical prognostic factors have recently been complemented by rapidly increasing molecular knowledge.

Clinical prognostic factors

Age, extent of residual disease after surgery, dissemination within the central nervous system and histology are clinical prognostic factors; however, their relative importance and value varies between children and adults.

Children

Several hundreds of children have been included in prospective randomized trials that can now be tailored according to reliable risk factors. Extent of disease and resection status have been shown as important factors for survival. The commonly used Chang classification (Table 1) established already in 1969 distinguished tumour size and local invasiveness [4]. However, the T-stage has not been shown to be of prognostic value [5,6] and is thus often no more reported. In patients with localized disease (M0) at diagnosis, the presence of residual tumour after surgery of more than 1.5 cm^2 has been identified as an independent prognostic factor in several studies [5,7,8], even if in other studies residual tumour appeared not to influence prognosis [9–12]. Possibly, these different results are dependent on the subsequently administered local and systemic treatment and may only be important in M0 disease when less aggressive therapy is to be given.

Patients are also grouped into high and low risk, based on presence or absence of disease dissemination (M-stage) at diagnosis, with M1–M4 considered high-risk patients [5,6,11,13]. Patients with M0 disease and less than 1.5 cm^2 residual disease should be considered as low risk or standard risk. Whether microscopic M1 disease (tumour cells in cerebrospinal fluid at least 14 days after surgery) has a true prognostic value is matter of debate.

Key points

- Clinical prognostic factors such as stage and dissemination of disease (M0 vs. M1–4), extent of resection (controversial in adults) and histology should be completed by molecular prognostic factors.
- Molecular subgroups can be identified by immunohistochemistry: CTNNB1 expression for WNT subgroup, SFRP1 for SHH subgroup, KCNA1 for subgroup D and NPR3 for subgroup C, the latter existing only in children.
- SHH-activated medulloblastomas are the most frequent subtype in adults; the inhibition of SHH pathway by GDC-0449 has been suggested as a promising strategy in this subgroup.
- WNT subgroup has an excellent prognosis in children, but not in adults.

Several studies show a trend to inferior outcome without a statistically significant difference compared to M0 disease [5,10,14]. Packer *et al.* [15] proposed an intermediate-risk group for M1 patients. Incomplete staging [9,16] and major deviations from the complex standard radiotherapy protocol [16,17] were also adverse prognostic factors, whereas reducing dose of chemotherapy after occurrence of toxicity seemed not to have an impact on outcome [9].

Children younger than 3 years of age have often a more aggressive disease and a poor outcome. They may already present with more advanced and disseminated disease, allowing less often for complete resection and, because of the concern of treatment-induced neurotoxicity, receive less or no radiotherapy [18]. In two multicenter protocols by the German Paediatric Cancer Society (HIT-SKK'87 and HIT-SKK'92), male sex and classical histology were associated with adverse outcome [19], whereas desmoplastic and extensive nodularity histology have an excellent prognosis.

Adults

Controlled trials have never been performed in adults because of the rarity of the disease, and most data stem from retrospective analyses or prospective series collected

Table 1 Chang classification

T1	Tumour less than 3 cm in diameter and limited to the midline position in the vermis, the roof of the fourth ventricle, and less frequently to the cerebellar hemispheres
T2	Tumour more than 3 cm in diameter, further invading one adjacent structure or partially filling the fourth ventricle
T3a	Tumour further invading two adjacent structures or completely filling the fourth ventricle with extension into the aqueduct of Silvius, foramen of Magendie, or foramen of Luschka, thus producing marked hydrocephalus
T3b	Tumour arising from the floor of the fourth ventricle or brainstem and filling the fourth ventricle
T4	Tumour further spreading through the aqueduct of Silvius to involve the third ventricle or midbrain, or tumour extending to the upper cervical spinal cord
M0	No evidence of gross subarachnoid or hematogenous metastases
M1	Microscopic tumour cells in cerebrospinal fluid
M2	Gross nodular seeding demonstrated in cerebellar, cerebral, subarachnoid space or in the third or in the lateral ventricles
M3	Gross nodular seeding in spinal subarachnoid space
M4	Extraneural metastasis

over a long observation period of up to 20–30 years. Diagnostic tools, treatment techniques and therapeutic choices will have evolved over this time, adding to the heterogeneity [20–24].

An influence of age on prognosis in adults is not well established. In the Surveillance, Epidemiology, and End Results (SEER) database evaluating 454 adult patients with medulloblastoma, age of 18–20 years has been found to be a favourable prognostic factor in comparison to age older than 20 years [20]. A similar finding was reported by Herrlinger *et al.* [21], who found age less than 25 years is a strong prognostic factor for longer relapse-free survival. In contrast, Menon *et al.* [25] compared the outcome of 18 adults and 79 children treated at a single institution and reported that adults fared better than children. Other studies did not find differences in outcome solely based on age [22,26].

In most studies sex did not have any prognostic value [20,24–27], except for one study which showed that women fare better than men, similarly to observations in children [22].

The extent of disease and resection status have repeatedly been shown as important factors for survival [20,22,28,29,30•,31]. A retrospective analysis on 253 patients demonstrated a significant correlation of survival with metastasis, postsurgical performance status, brainstem involvement, involvement of the fourth ventricle, as well as radiation dose delivered to the spine and to the posterior cerebral fossa [30•]. Brainstem involvement and fourth ventricle invasion have been identified to predict poorer outcome [21,25,30•,32,33] and were often correlated with extent of surgery [25,27,30•]. Gross total resection could only be identified in three studies as a prognostic factor [23,27,28]. However, before the widespread availability of MRI, T-stage and resection status were subjectively determined by the surgeon only.

Histological subtype has been reported to affect outcome. In adults, desmoplastic histology is observed in 15–40% [20,22–24,32], whereas large cell/anaplastic histology is very rare [20]. Carrie *et al.* [32] showed a significant improvement of event-free survival for desmoplastic histology, and Herrlinger *et al.* [21] a trend for improved relapse-free survival.

Until now, only one prospective trial in adults has been performed using clinical risk stratification. Initial results on 36 patients were reported in 2003 and updated with a longer follow-up in 2007 and expanded to 95 patients in 2010 [29,33,34••]. Thirty low-risk patients (T1, T2, T3a, M0, with a residual disease $<1.5\,cm^2$) were treated with craniospinal irradiation alone (36 Gy + boost of 18.8 Gy on tumour bed), whereas 65 patients with high-risk disease (T3b–T4, or postoperative residual tumour, or M positive) received platinum-based chemotherapy (cisplatin 25 mg/m^2/daily day 1–4, etoposide 40 mg/ m^2/daily day 1–4, cyclophosphamide 1000 mg/m^2 on day 4, every 4 weeks) before and after radiotherapy. Survival at 5 and 10 years were statistically different in low-risk (92 and 65%) and high-risk patients (58 and 45%) and was significantly influenced by the M status (47 and 29% in M0 and M positive, respectively). Residual disease had no prognostic value [34••]. Late relapses after 5 years were common in all risk groups and particularly important in the low-risk group. In the 36 patients published in 2003, there was a statistically significant difference in the outcome between low-risk and high-risk patients [29]. Interestingly, with long-term follow-up this difference disappeared because of late relapses in low-risk patients, suggesting that in low-risk patients chemotherapy may be of value and should be further investigated [33].

Clinical differences between adults and children

Overall, clinical prognostic factors appear comparable between adults and children, and patients can be separated into lower and higher risk for relapse. The more limited availability of solid data in adults however requires caution in interpretation and conclusions. Histological subtype is age-dependent, with desmoplastic histology being more frequent in adults [35]. Lateral localization and hemisphere involvement is also more frequently observed [22,27,30•].

Comparing overall survival between children and adults, there seems to be no difference [29,36]. However, late relapses are rare in children, but common in adults 5 and even 10 years after treatment. Up to 20% of patients relapse after 5 years [22,27]. Extracranial metastases are fewer in adults than in children and if present are more often to the bone and lung, whereas in children the site is preferentially to the liver [35].

Molecular prognostic factors

Accurate tumour classification and improved outcome prediction independent of clinical factors by gene-expression profiling was already shown almost a decade ago [37,38]. In recent years, progress in biology and molecular analyses allows for better understanding of tumourigenesis and identification of distinct molecular subtypes that should ultimately allow for tailored treatment strategies.

Children

Numerous putative molecular factors have been identified almost exclusively in children. Prognostic markers that have been validated in larger cohorts are nucleopositivity for β-catenin [39] and TrkC overexpression [38,40,41], both indicating a more favourable prognosis,

and *ErB2* overexpression [42,43], isolated 17p loss [42,44] or 17q gain [45] and *MYCC/MYCN* amplification [40,44, 46,47], associated with a worse survival. Recently, upregulation of the *LASP1* gene located on chromosome 17q has been associated with metastatic dissemination and poor outcome; in-vitro experiments suggest a role of LASP1 for cell adhesion, proliferation and migration [48].

Nuclear accumulation of β-catenin, which is encoded by the *CNNTB1* gene, activated by the WNT/Wingless pathway (WNT), has been found in 27 of 109 (25%) of children treated within the PNET3 trial of the International Society for Paediatric Oncology (SIOP)/United Kingdom Children's Cancer Study Group (UKCCSG). β-Catenin nucleopositive medulloblastomas showed a significantly better overall survival than children with tumours that showed membranous/cytoplasmic immunoreactivity or no immunoreactivity [39]. The same study showed also that there is a good correlation with mutations in *CTNNB1* that were found exclusively in patients with positive nuclear β-catenin immunoreactivity.

Later, Ellison *et al.* [49] demonstrated retrospectively the utility and feasibility of integrating molecular predictors in daily practice on 207 paraffin-embedded samples from the SIOP PNET3 trial. Nuclear immunoreactivity of β-catenin, *CTNBB1* mutation and monosomy 6 as surrogates for Wnt pathway activation were associated with excellent prognosis, whereas MYC amplification was indicative of a very poor outcome. In their model of risk stratification, low-risk is defined as absence of metastases at diagnosis, classic histology and β-catenin nucleopositivity; high-risk patients had either metastatic disease, either large cell/anaplastic histology or MYC amplification [49,50]. Samples from the prospective randomized multicenter trial HIT'91 were analysed for DNA amplification of c-myc and N-myc, and mRNA expression of c-myc and trkC. c-myc and trkC were identified as independent prognostic factors [40]. Combination of these two risk factors permitted description of three risk groups. High trkC (>1× human cerebellum) and low c-myc (≤1× human cerebellum) identified eight children with favourable prognosis and 100% event-free survival (EFS) at 7 years; two of these children were metastatic at diagnosis. Low trkC and high c-myc were found in the poor prognosis group of 15 children; EFS was 33% at 7 years. Ten of these fifteen children were metastatic at diagnosis. The remaining 78 patients had an intermediate prognosis with an EFS of 65% at 7 years. Molecular markers were superior to clinical factors in outcome prediction [40].

By gene-expression profiling, four molecular subtypes were first described by Thompson *et al.* [51]. Specific mutations of genes associated with the Wnt (*CTNNB1*) or the sonic hedgehog pathway (*PTCH*; *SUFU*) were subsequently identified and may allow for easier implementation of molecular markers in daily clinical practice. Cho *et al.* [52••] described six molecular subgroups when analysing 194 medulloblastoma samples by gene-expression profiling. On the basis of these data and clinical factors, they then proposed a nomogram indicating the relative prognostic value of a number of chromosomal aberrations or gene mutations [53]. Similarly, Northcott *et al.* [54••] reported on unsupervised gene-expression profiling of 103 primary medulloblastoma cases. They found four distinct subgroups of nonoverlapping gene signatures. Subsequent analysis by immunohistochemistry for DKK1 (Wnt pathway), SFRP1 (sonic hedgehog), NPR3 (natrionatriuretic peptide receptor) and KCNA1 (potassium voltage-gated channel) allowed classification of tumour samples reliably into each molecular subgroup. All these studies (Table 2) consistently report an excellent and distinct outcome for patients with Wnt pathway activation, a good prognosis when hedgehog is activated and a poor outcome with cMYC activation. The Wnt activation is also frequently associated with monosomy 6 [54••] and classical histology, and was observed in all (paediatric) age groups. The SHH subgroup is characterized by 9q loss and PTCH1 mutation, and desmoplastic histology, and most often occurs in children younger than 3 years and in adolescents and adults [51,52••, 54••,55].

Adults

All of the discussed studies analysed mainly samples from paediatric medulloblastomas. Two recent studies specifically focussed on adults. The first analysed 34 medulloblastoma samples by comparative genomic hybridization [56•]. DNA copy number aberrations correlating with outcome were subsequently validated in a large independent dataset of both adult and paediatric patients. In adults, both type and frequency of genetic aberrations were distinct from paediatric samples. Furthermore, the negative prognostic value of *CDK6* amplification, 10q loss and 17q gain were stronger than any of the known clinical prognostic factors. The authors propose to classify the patients based on their cytogenetic profile: high-risk group of both 10q loss and 17q gain (estimated 5-year survival 0%); intermediate risk group of either 10q loss or 17q gain (estimated 5-year survival 44%); and finally a low-risk group with neither 10q loss nor 17q gain (5-year survival 92%). Prospective validation is warranted.

In a second study by the same group of investigators, gene-expression profiles of 28 adult medulloblastomas were analysed by unsupervised hierarchical clustering [57••]. Three different molecular subgroups were identified: Wnt/wingless pathway activated genes (WNT), sonic hedgehog activated genes (SHH) and non-WNT/SHH tumours that show a great concordance with the genetic profile of the previously described Northcott

Table 2 Molecular medulloblastoma subtypes

Gene expression	WNT pathway [51,52••,54••,55]	SHH pathway [51,52••,54••,55]	Neuronal differentiation [52••,55]	Neuronal and photoreceptor differentiation [52••,55]	Photoreceptor differentiation [52••,55]
Genetic alterations	Monosomy 6 [52••,54••,55]	Loss of chromosome 9q [54••,55]	Isochromosome 17q	Loss of chromosome 8 and 17p [55]	myc amplification [52••,54••]
			Loss of chromosome 8 and 17p [55], myc amplification [54••]		PTEN, 10q loss for c5 [52••]
Gene mutation	CTNNB1 [51,55]	PTCH1 [51,55], SUFU [51]	SUFU [51]		
RT-PCR	MAF1, DKK,WIF [51]	PTCH2, GLI1 [51]	PTCH2, GLI [51]		
Immunohistochemistry	CTNNB1 [51], β-catenin [51], DKK1 [54••]	GLI1 [51], SFRP1 [51,54••,57••]	GLI1, SFRP1 [51] KCNA1 [54••,57••]		NPR3 [54••]
Histological subtype	Classic [55]	Desmoplastic [52••,55,57••]	Mainly classic [55]	Mainly classic [55]	Mainly classic [55]
					High frequency of LCA [52••,54••]
Age distribution	Older children [54••,55]	Children <3 years and adults [52••,54••,55]	Children [54••,55]	Children [55]	Younger children [54••,55]
Sex distribution		Female predominance [54••]	Male predominance [54••,57••]	Male predominance [54••]	Male predominance [52••,54••]
Outcome	Good [51,55]				Poor [54••,55]
Thompson subgroup [51]	B	D	C	A	E
Kool subgroups [55]	A	B	C	D	E
Northcott subgroup [54••]	A	B	D		C
Cho subgroup [52••]	C6	C3	C2	C4	C1 + C5
Remke/adults [57••]	WNT	SHH	D		

subgroup D [54••,57••] (Table 2). Genetic loss on 6q, a hallmark of the prognostically favourable WNT tumours, was also identified in three early progressing patients without WNT activation. Adult WNT and subgroup D tumours have worse prognosis than in children.

These three distinct molecular subsets were confirmed by immunostaining in an independent cohort of 103 adult medulloblastomas; each sample stained exclusively only for one of the three markers and none stained for NPR3 (subtype C) [57••]. SSH subtype had a prevalence of 60% (SFRP1), subtype D 25% (KCNA1) and WNT subtype (CTNNB1) 15%. Adult WNT and subgroup D tumours have worse prognosis than their paediatric counterparts [57••].

Molecular differences between children and adults

Adult medulloblastomas have a different genetic profile from those in children. It is probable that clinical differences seen between children and adults are a consequence of a distinct distribution of the different molecular subtypes over age. The SHH subtype has a higher incidence in adults, which can explain the clinical differences as the higher incidence of hemispheric localization in adults and the predominant desmoplastic histology [35,57••].

Medulloblastoma was thought to arise from stem cells in the cerebellum, a developmental process that requires maturation, differentiation and migration. Recent work suggests that the subtype of Wnt pathway activated medulloblastoma may arise outside the cerebellum from cells of the dorsal brainstem and may thus explain in part the distinct natural history and prognosis [58].

Conclusion

Molecular characterization allows nowadays accurate and reproducible identification of different subtypes of medulloblastoma, with improved prognostic value in children and adults. Therapeutic decisions and definition of treatment were until recently solely based on clinical factors. In paediatric low-risk patients, current strategies aim at reducing treatment intensity in order to lower acute and late toxicity. When chemotherapy has been added to radiation therapy, the dose of the craniospinal irradiation could safely be reduced in low-risk patients [16,59], whereas treatment intensification and high-dose chemotherapy added to radiotherapy suggests improved outcome in children with high-risk disease [9]. Centre expertise and quality of radiotherapy have been shown to be of significant prognostic value, thus treatment should be delivered or planning reviewed by a reference centre.

New trials should aim at validating these molecular signatures, and risk-adapted classification should allow

optimization of treatment and improvement in outcome with current or future treatment strategies [60]. In adults, a distinct risk stratification should be further developed and validated [57••]. For the WNT subtype with a more favourable outcome, treatment intensity may possibly be reduced. On the other hand, cMYC-amplified tumours should receive more intensified treatment even when not metastatic. Recognition of the importance of the hedgehog pathway has already led to investigation of specifically targeted therapies. A recent report on a 26-year-old patient with a refractory medulloblastoma being treated with the hedgehog pathway inhibitor GDC-0449 showed impressive tumour regression and improvements of symptoms [61••]. This agent is now being further investigated and three trials are open for accrual in adults and children.

Molecular characterization may also allow better classification of the rare and ill-defined PNETs. In adult medulloblastomas, there is an urgent need for prospective and possibly randomized trials. Investigations need to include tissue collection in order to characterize molecular profiles and develop adapted treatment strategies.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 660–661).

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