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Abstract

Purpose: In addition to the four histopathologically defined entities of medulloblastoma (MB), four distinct genetically defined subgroups have been included in the WHO classification of 2016**.** The smallest subgroup is the medulloblastoma with activated wingless pathway (WNT-MB). The goal of this study was to identify a typical MR-morphology in a larger number of pediatric patients with WNT-MB.

Methods: 38 WNT-MB cases were obtained from the database of the German pediatric brain tumor (HIT) - trials. Pediatric patients with histological subtyping and molecular confirmation of WNT-activation and adequate imaging data were included. Images were rated by standardized imaging criteria and a modified laterality score (LS).

Results: 36/38 presented with classic histology. 28/38 (73.7%) were primary midline tumors but with a lateral tendency in 39.3%. One extensively eccentric midline tumor was rated by the LS as off-midline position. Five tumors were found in the cerebellopontine angle, three in the deep white matter and two in a cerebellar hemisphere. Leptomeningeal dissemination was rare. In 60.5% intratumoral blood degradation products were found and 26.3% showed cysts with blood contents. T2-signal intensity was low. Contrast enhancement was moderate to strong predominantly in 76-100% of tumor volume.

Conclusion: This is the largest pediatric WNT-MB cohort systematically examined for MRI characteristics thus far. According to our observations WNT-MBs are not preferentially off-midline tumors as postulated in previous studies with smaller WNT-MB cohorts. Dense intratumoral blood degradation products and cysts with blood contents are frequently found and might help to differentiate WNT-MB from other MB-subtypes.

Introduction

According to the revised WHO classification of tumors of the CNS of 2016[1] medulloblastoma (MB) is not considered a single tumor entity but represents several entities with different cell of origin, location, biology, (epi)genetic alterations, histology and clinical behavior. According to the concept of an integrated diagnosis in the WHO classification of 2016, medulloblastoma entities are defined by both, histological and molecular/genetic features, allowing a precise assignment of patients for risk-adapted stratification in current therapeutic studies and the comparison to results of study cohorts in the past. All medulloblastoma entities correspond to WHO grade IV. For definition of the histological diagnosis, the tumors should be assigned to one of the four entities: classic (CMB), desmoplastic nodular (DNMB), extensive nodular (MBEN), or large cell/anaplastic (LC/A-MB) medulloblastoma. Large cell MB (LCMB) and anaplastic MB (AMB) were separated histologically entities before 2016.[2] In addition to these histologically entities, four genetically defined subgroups have been introduced by the WHO classification of 2016[1]. Two subgroups are defined by their genetic pathway, wingless activated (WNT) and sonic hedgehog activated (SHH) MB, the latter with or without accompanying *TP53* mutation. The non-WNT/non-SHH subgroup is provisionally subclassified into group 3 and 4 medulloblastoma which seem to be overlapping variants. WNT-MB are characterized by activating mutations of *CTNNB1*[3,4], which encodes a central component of the WNT pathway or, alternatively, by inactivating mutations of *APC*[3,5], *AXIN1*[6,7] or *AXIN2*[8] leading to nuclear accumulation of β-catenin. Accounting for approximately 10 %[9,10] of all MB, WNT-MB form a small but distinct MB entity. In children, they show a significantly better progression-free survival and overall survival compared to other subgroups.[4,9,10,11] In patients with WNT-MB younger than 16 years at diagnosis a progression-free survival

of 100% over 5 years has been observed.[11] Current therapy studies, such as the SIOP-PNET5 medulloblastoma trial, have implemented upfront genetic evaluation so that low-risk WNT-MB patients are eligible for radiotherapy reduction aimed at reducing late effects, with the therapy increasingly being adapted to the specific risk profile of each patient. Additionally, radiological imaging signatures have become apparent for certain brain tumors and their underlying genetic profile. The term “radiomics” is increasingly applied to describe the association between imaging phenotype and tumor genotype. Radiomics knowledge can become clinically meaningful, e.g. it offers surgeons a better preoperative procedure planning according to the presumed relapse risk of the tumor. Besides standard imaging characteristics, radiological studies have mainly focused on correlations of tumor position and genetic information. A first radiological subgroup analysis showed a preferential tumor location for WNT-MB in the cerebellopontine-angle (CPA) and for SHH-MB in the cerebellar hemisphere.[12] More recent studies yielded contradictory results with regards to tumor localization.[13] However, in these previous studies, the maximum sample size of WNT-MB reached 16 patients[14]. The goal of the present study was to analyze structural MRI features according to defined MRI criteria in a uniquely large number of genetically determined WNT-MB (n=38) in children within the framework of the German pediatric brain tumor (HIT) - trials and the National Reference Center for Neuroradiology.

Material and Method

Study Cohort

Cases were retrospectively collected from the database of the National Reference Center for Neuroradiology (Department for Neuroradiology, Wuerzburg University Hospital) of the German brain tumor (HIT) - trials, conducted in German-speaking countries of Europe. All patients were registered to the HIT-2000 trial (NCT00303810) (including the German PNET 4-cohort [NCT01351870]), the HIT-2000 interim registry (NCT02238899), the I-HIT-MED registry (NCT02417324) or SIOP-PNET 5 MB trial (NCT02066220). Each patient or legal guardian signed an informed consent declaration allowing the scientific evaluation of biological and imaging data when entering the study. All cases were centrally reviewed at the National Brain Tumor Reference Center of the German Society of Neuropathology and Neuroanatomy (DGNN) (Institute of Neuropathology, Bonn University). Patients were eligible if they had a) histopathological and genetic classification data and b) preoperative cranial and spinal imaging data. Images on X-ray films and examinations with strong movement artefacts were excluded.

Molecular Analysis

Histological diagnosis was made at inclusion into the trial according to the WHO classification valid at the time of inclusion. Patients were diagnosed by a combination of histological examination by immunohistochemistry (IHC) and Sanger sequencing of exon 3 of *CTNNB1.*[15,16] In case of negative *CTNNB1*-mutation, *APC, AXIN1* and *AXIN2* sequence was assessed additionally.[11] Neuropathological evaluation and *CTNNB1* mutational analysis were supplemented by 450k DNA methylation microarray (Illumina) if applicable.[17,18] Where tissue was too scarce for analysis by methylation

microarray, subgroup was assigned using the mass spectrometry-minimal methylation classifier (MS-MIMIC) assay in addition to IHC and *CTNNB1* mutational analysis.[11,19] Where initial workup did not include prospective assessment of WNT-activation, this was done during retrospective workup as previously described.[11,17] Patients were considered to have WNT-MB if molecular analysis confirmed a mutation in *CTNNB1* or *APC* and/or assignment to the WNT-subgroup by methylation profiling or MS-MIMIC.

Imaging analysis

All MRI datasets were assessed in consensus by two neuroradiologists dedicated to pediatric brain tumor imaging (M. W.-M. and A. S.).

Multicenter data acquisition resulted in nonuniform MRI protocols, sequence technique, parameters and field strength. Local standardized diagnostic parameters were supplemented and used for the imaging assessment. The primary tumor location was determined as: cerebellar hemisphere, deep white matter, CPA, cerebellar vermis or fourth ventricle (figure 1). Deep white matter, cerebellar hemisphere and CPA were rated as primary lateral position. When the CPA was involved, the status of the fourth ventricle and the foramen of Magendie were recorded additionally. Fourth ventricle and cerebellar vermis were defined as primary midline positions. Additionally, laterality of primary midline tumors was assessed according to a modification of the laterality score (LS) by Patay et al[14]. Primary position in the fourth ventricle or the cerebellar vermis were rated as midline (LS-0). Fourth ventricle or cerebellar vermis plus bilateral recess extension were rated as LS-0 as well. Midline tumors were rated as moderately lateralized in case of tumor extension into only unilateral recess or bilateral recesses plus one CPA (LS-1). Extension into only the unilateral recess and further into the

ipsilateral CPA was rated as heavily lateralized and off-midline (L-2). The tumor volume is calculated using the (approximation of the ellipsoid volume) formula A x B x C ½ where A, B, and C are the maximum dimension in the standard anteroposterior, craniocaudal and transverse planes. The largest diameter of the perifocal edema was measured in centimeters. Signal intensity and homogeneity of the tumor were assessed in comparison to grey matter on T2WI and T1WI without contrast enhancement. Intensity and percentage of enhancing volume after gadolinium application were estimated. The contrast enhancing area of the tumor mass is mainly diffuse wherefore the rating was subjective in approximate percentages (0 - 25%, 26 - 50%, 51 - 75%, 76 - 100%). Hydrocephalus was rated as slight, moderate and severe (slight meaning only visible dilatation of the ventricles, moderate showing CSF pressure caps and severe showing pressure caps with compression of the sulci at the vertex). Fluid of intratumoral cysts was compared to the signal of CSF and defined as: as bright as CSF, brighter than CSF, presence of blood degradation products like met-hemoglobin or hemosiderin. Presence of blood degradation products like methemoglobin and hemosiderin in solid tumor mass was rated as: no blood degradation products, blood degradation products in less than 50 % of the tumor volume and blood degradation products in more than 50 % of the tumor mass. Leptomeningeal dissemination was assessed only by MRI according to the Chang classification.[20] Cranial dissemination was rated as M2, spinal dissemination as M3 and cranial plus spinal dissemination as M2+3.

Results

In 38 of 75 patients with WNT-MB, adequate image datasets of preoperative cranial MRI and pre- or postoperative spinal MRI were available for analysis. In this MRI cohort, age ranged from 5 to 21.6 years (median 12.8 ± 4.6 years) and a female predominance (1.71:1; female:male-ratio) was found. According to traditional histopathological criteria, most WNT-MB cases of this cohort were CMB (36/38; 94.7%), further 2 LC/A-MB (one AMB and one LCMB [2.6% each], diagnosed before 2016). Thirty-four tumors were diagnosed by a combination of immunohistochemistry (IHC) and Sanger sequencing of exon 3 of *CTNNB1,* each with a detectable mutation of *CTNNB1.* In fifteen of these patients, 450k methylation microarray was supplemented and classified all tumors as WNT. There were two cases without Sanger sequencing; one was categorized as WNT-activated by MS-MIMIC assay and the other one by 450k methylation microarray. In one tumor, *CTNNB1* mutational analysis was negative but was classified as WNT subgroup by 450k methylation microarray analysis and additionally a copy-neutral loss of heterozygosity within chromosome arm 5q (*APC)* and a R213* mutation in the *APC* gene were identified. One patient was diagnosed as WNT-MB based on tissue of tumor recurrence; here, *CTNNB1* mutation and WNT-activation in 450k methylation microarray were detectable.

An overview of the MRI features is shown in table 1 and primary tumor localization and extension are presented in table 2. Twenty-eight tumors were primarily located in the midline position. Fourteen of 25 (56%) WNT-MB in the fourth ventricle and 2 of 3 in the cerebellar vermis were midline tumors without lateral tendency (LS-0). Eleven of 28 (39.3%) WNT-MB showed extension into one recess only or into both recesses with further extension into only one CPA (LS-1). Only one WNT-MB located in the fourth ventricle, extended into a unilateral recess and further the ipsilateral CPA (LS-2). In

summary, 74% of all WNT-MB showed primarily a midline position but only 42% represented “pure” midline tumors, with nearly half of the midline tumors showing a lateral tendency (39.3%). Only one (3.6%) primarily midline-located WNT-MB was rated as off-midline according to our LS score because of its strong eccentric position. Five of 38 (13%) WNT-MB were positioned in the cerebellopontine angle, 2 of 38 (5%) in the cerebellar hemisphere and 3 of 38 (8%) in the deep white matter. These positions were rated as off-midline. One CPA tumor showed some extension into the fourth ventricle. In both cerebellar hemispheric tumors, the ipsilateral recess was involved. One tumor with its epicenter in the deep white matter expanded into the fourth ventricle and one into the ipsilateral recess.

Most WNT-MB were moderately (39.5%) to very sharply (42.1%) delineated. Eighteen of 38 (47.4%) WNT-MB contained cysts. In ten of 18 (55.6%) partly cystic tumors, the cysts contained blood degradation products, visible as blood-fluid levels (figure 2). The cyst contents were brighter than cerebrospinal fluid in 27.8% and similar to cerebrospinal fluid in 16.7%. Twenty-three patients had a hydrocephalus. Six (15.8%) patients showed a slight and 15 (39.5 %) patients a moderate hydrocephalus, only two patients (5.3 %) had a severe hydrocephalus. Fifteen (39.5%) patients had no hydrocephalus at diagnosis. Tumor signal-intensity in T2WI compared to the supratentorial cortex was predominantly isointense (54.1%) to hypointense (35.1%). Only four tumors (10.8%) were hyperintense in comparison to the signal intensity of the cortex on T2WI. In one child, no standard T2-sequence but a FLAIR-sequence was available for evaluation. Thirty-one (83.8%) tumors showed inhomogeneous signal on T2WI, only 6 of 37 (16.2%) showed homogeneous signal. On T1WI the signal-intensity was hypointense in 27 of 38 (75%). Eight (22.2%) tumors showed an isointense signal and only one tumor (2.8%) showed a completely hyperintense signal. Two patients had

no standard unenhanced T1WI at diagnosis. Signal on T1WI was homogeneous in 41.7 % and inhomogeneous in 58.3%. Thirty-six of 38 (94.7%) WNT-MB showed contrast enhancement in 76 - 100% of the tumor volume, only 1 WNT-MB showed an enhancing volume of 26 - 50% and 1 WNT-MB 0 - 25%. Signs of bleeding in T1WI, T2WI or susceptibility-weighted images were found in 23/38 (60.5%). In 18 of those cases, susceptibility- weighted images as SWI or T2*-sequences had been acquired. Sixteen of 18 (88.9%) susceptibility- weighted images showed iron contents. Five of 18 MB showed iron deposition in more than 50 % of the tumor mass. The extension of perifocal edema ranged from 0 to 2.6 cm (mean 0.66 ± 0.62 cm). Twenty-seven of 38 (71.1%) MBs showed perifocal edema. Tumor volume ranged from 2.68 cm^3 to 68.59 cm^3 (mean 27.79 ± 16.87 cm^3). LCMB are usually significantly smaller than other histological MB-types (mean 15 cm^3) as described previously.[21] Using this value from the literature as cut-off between large and small tumor size 10 of 40 WNT-tumors were very small (range 2.68 - 12.77 cm^3), all of them presented classic histology. The two LC/A MBs had volumes of 29.81 cm^3 and 46.39 cm^3. Leptomeningeal dissemination at diagnosis was assessable in 35 patients and positive in 11.5% (4 of 35). One patient showed cranial dissemination (M2), two had cranial and spinal dissemination (M2+3) and one patient showed isolated spinal dissemination (M3). All four disseminated WNT-MB showed classic histology in the primary tumor.

Table 1: Overview of absolute and relative (%) frequency of MRI features.

		available data	n	%
Sex		38		
	male		14	36.8
	female		24	63.2
Histology		38		
	CMB		36	94.7
	AMB*		1	2.6
	LCMB*		1	2.6
Hydrocephalus		38		
	no		15	39.5
	slight		6	15.8
	moderate		15	39.5
	severe		2	5.3
Enhancement		38		
	no		0	0
	light		4	10.5
	moderate		12	31.6
	strong		22	57.9
Enhancing area		38		
	0 - 25 %		0	0
	26 % - 50 %		1	2.6
	51 % - 75 %		1	2.6
	76 % - 100 %		36	94.7
T2-weighted images		37		
	homogeneus		6	16.2
	inhomogeneus		31	83.8
	hyperintense		4	10.8
	isointense		20	54.1
	hypointense		13	35.1
T1-weighted images		36		
	homogeneus		15	41.7
	inhomogeneus		21	58.3
	hyperintense		1	2.8
	isointense		8	22.2
	hypointense		27	75
Cysts		38		
	no		20	52.6
	as bright as the CSF		3	7.9
	brighter than the CSF		5	13.2
	blood-fluid level		10	26.3

Blood degradation products on T1w, T2w or T2*/SWI		38		
	yes		23	60.5
	no		15	39.5
Mass of iron contents on T2*/SWI		18		
	no		2	11.1
	< 50 %		11	61.1
	> 50 %		5	27.8
Dissemination		35		
	no		31	88.6
	M2		1	2.9
	M3		1	2.9
	M2+3		2	5.7

* according to the WHO classification of 2007

Table 2: Overview of the tumor proposed epicenter and direction of extension.

primary location	number of WNT-MB (n)	extension		further extension		LS
fourth ventricle	n = 25 (66 %)	unilateral recess	n = 7	plus uni CPA	n = 1	2
				no	n = 6	1
		bilateral recesses	n = 16	plus uni CPA	n = 4	1
				plus bi CPA	n = 0	0
				no	n = 12	0
		no extension	n = 2			0
cerebellar vermis	n = 3 (8 %)	unilateral recess	n = 1			1
		bilateral recesses	n = 1			0
		fourth ventricle only	n = 1			0
		no extension	n = 0			0
CPA	n = 5 (13 %)	unilateral recess	n = 4	plus fourth ventricle	n = 4	2
		bilateral recesses	n = 0			2
		no extension	n = 1			2
deep white matter	n = 3 (8 %)	unilateral recess	n = 1	plus uni CPA	n = 1	2
		bilateral recesses	n = 0			2
		fourth ventricle only	n = 1			2
		no extension	n = 1			
cerebellar hemisphere	n = 2 (5 %)	unilateral recess	n = 2	plus uni CPA	n = 1	2
		bilateral recesses	n = 0			2
		fourth ventricle only	n = 0			2
		no extension	n = 0			2

Discussion

To our knowledge, this series represents the largest cohort of WNT-MBs analyzed for characteristic MRI features thus far. Our results show that the preferred primary position of our WNT-MBs is the midline fourth ventricle or vermis 28 of 38 (74%). Perreault et al.[12] were the first to report that WNT-MB are characterized by an off-midline position in 75% (3 of 4 were located in the CPA or cerebellar peduncle) leading to a positive predictive value of 100% for this tumor site. In our cohort only 5 of 38 (13%) WNT-MB had their epicenter in the CPA, altogether only 26% were primarily located in an off-midline position. This is much lower compared to earlier study results.[12,13,14] Gibson et al.[22] indicated that WNT-MB arise in the lower rhombic limb from progenitor cells of nuclei in the dorsal brainstem. However, all six WNT-MB in this publication were reported as midline tumors and were opposed to the SHH-activated MBs. Similarly, Łastowska et al.[23] found 5/6 and Teo et al.[24] described five WNT-MB in midline position. Based on Gibson`s hypothesis on the individual tumor origin the pathways of extension were evaluated in more detail. With a self-defined score, Patay et al.[14] emphasized the lateralized position of WNT-MB (50% off-midline position). We support Patay's conclusion that WNT-MB are paramedian midline tumors describing a lateralized position in 22/38 tumors in our cohort. However, a purely CPA localization (5 of 38) seems to be much rarer than previously noted.[12] The primary midline position is in line with the hypothesis that WNT-MB arise from the dorsal brainstem and grow within the CSF spaces. Notably the fourth ventricle may be the preferred pathway of tumor growth, as it offers the least resistance. With only three tumors having their epicenter in the deep white matter surrounding the fourth ventricle in our study, this localization was significantly less frequent compared to previous studies (8% versus 20%).[13] While Perreault et al.[12] and Mata-Mbemba et al.[13] assigned a cerebellar

hemispheric origin as highly predictive of SHH-activated MB, we found 2 WNT-tumors located in the cerebellar hemisphere. However, both tumors were large, rendering the definition of their origin in differentiation between hemisphere and paraventricular white matter to be challenging. These different tumor locations in our cohort and partially divergent results compared to the previous studies questions whether off-midline or midline position is of any useful diagnostic predictive value. The four genetic subgroup model was refined by Taylor et al.[25] in 2012 and has been updated recently.[26,27,28] Further refined definitions of substructures within the four WHO entities of MB may be expected. The existence of such substructures might be a possible cause for the heterogeneity of the tumor's epicenter in our study and the divergent reports of the typical location of WNT-MB in previous studies.

The children in our cohort were older than four years, this matches previous observations that WNT-MB do not typically occur in early childhood.[9] Most WNT-MB in our cohort were histologically CMB, but there were single other histological types (LC/A-MB, n = 2) as well. The fact that WNT-MBs are not exclusively CMB has been reported previously.[9,10,13] Our cohort contained one tumor corresponding to LCMB (according to the WHO classification of 2007). This is in accordance with Ellison et al.[9] and Kool et al.[10] reporting 2% LCMB among their group of WNT-MB.[9,10] With a mean tumor volume of 15 cm^3 LCMBs have been described as significantly smaller than other histological types of MB.[21] Interestingly, 10 CMBs in our cohort had a tumor size of less than 15 cm^3 and the only LCMB showed double that size. Leptomeningeal dissemination of WNT-MBs had not yet been reported in other neuroradiological studies.[13,29] In our cohort 11.5% patients showed a macroscopic leptomeningeal dissemination at diagnosis. This percentage is similar to the numbers reported in studies on neuropathology.[9] We found a female predominance which is contrary to the

cohort of Patay et al.[14]. The female predominance in our cohort should be considered with caution due to the small cohort size in comparison to publications that have recorded the demographic data of significantly more WNT-MB and found no predominance for male or female.[9,10,25] MB are tumors of high cellularity for which a lower signal on T2WI can be expected. In our cohort, WNT-MBs were primarily iso- to hypointense in T2WI. The comparatively low T2-signal is useful to differentiate MBs from pilocytic astrocytomas and, to a lesser extent, also from ependymomas. Inhomogeneous signal on T2WI and the moderate to strong contrast enhancement do not seem to be specific criteria to separate WNT-MBs from other highly cellular tumors e.g. atypical teratoid rhabdoid tumors. Blood residues are not common in MBs. Patay et al.[14] reported blood degradation products in 31.25% of assessed tumors, while Perreault et al.[12] did not find subgroup specific features on iron sensitive images. However, the high number of tumors showing large areas of met-hemoglobin or hemosiderin and cysts containing blood degradation products with blood-fluid levels was remarkable in our evaluation.

Conclusion

WNT-MB are found predominately in the fourth ventricle. However, a certain laterality can be noted by their hypothetical point of origin and possible growth characteristics. However, hemispherically positioned WNT-MB and leptomeningeal dissemination can occur and may not be used as a criterion to exclude WNT-MB. Dense intratumoral blood degradation products and cysts with blood contents are frequently found and might help to differentiate WNT-MB from other MB-subtypes.

Acknowledgements

We thank Dr. D. Engel for her support in manuscript correction. This study was supported by grants of the German Children Cancer Foundation (DKKS).

Figure legends

Figure 1: Examples for primary tumor position in WNT-MB: A) midline fourth ventricle, B) cerebellopontine angle, C) cerebellar hemisphere, D) midline cerebellar vermis, E) periventricular deep white matter.

Figure 2: A) Deoxygenated blood in T2*-WI. B) Intratumoral cyst with a blood-fluid level (→). C) Inhomogeneous signal in T2-WI. D) Hypointense signal in T1-WI and small areas of methemoglobin (e.g. →). D) 100% contrast enhancement. E) Leptomeningeal dissemination, M2 on the floor of the third ventricle (→).

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Abbreviations

AMB	anaplastic medulloblastoma (according to the WHO classification of 2007)
CMB	classic medulloblastoma
CPA	cerebellopontine angle
DNMB	desmoplastic / nodular medulloblastoma
IHC	immunohistochemistry
LCMB	large cell medulloblastoma (according to the WHO classification of 2007)
LC/A-MB	large cell / anaplastic medulloblastoma
LS	laterality score
MB	medulloblastoma
MBEN	medulloblastoma with extensive nodularity
MS-MIMIC	mass spectrometry-minimal methylation classifier
SHH-MB	sonic hedgehog activated medulloblastoma
WNT-MB	WNT activated medulloblastoma