Vascular white matter lesions negatively correlate with brain metastases in malignant melanoma - results from a retrospective comparative analysis.

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Highlights

- Vascular white matter lesions (WML) reduce brain metastases (BM) in patients with lung cancer
- If presence of WML negatively affects number of BM in melanoma is unknown

- Degree of WML was higher in BM negative patients with melanoma
- Vascular risk factors were more frequent in BM negative patients
- WML appear to reduce BM in different tumor types.

Abstract

Objectives: Brain metastasis (BM) is a major complication of different cancers. There is increasing evidence for influence of vascular factors on BM in patients with non-small cell lung cancer (NSCLC). It is not known if the same is true for other tumors that might rely on different forms of vasculogenesis. The objective of this retrospective study was to evaluate a possible negative association of vascular white matter lesions and vascular risk factors (vasRF) with brain metastases in patients with melanoma. **Patients and Methods:** 3D-brain magnetic resonance imaging (MRI) of 30 patients with brain metastases (BM) from malignant melanoma and screening MRI of 31 BM negative patients were analysed. Number of metastases was calculated and T2 hyperintensive white matter lesions (WML) were classified according to Fazekas-Score (grade I-III) per patient and compared between BM+ and BM- patients. **Results**: Patients without BM showed more pronounced WML (median = WML 1, mean = 1.3; SD = 1.04,) than patients with BM (median=WML 0, mean = 0.6; SD = 0.8, p=0.017). With respect to vascular risk factors, brain metastases were more likely (p^{x2} = 0.019) in patients without vasRF. **Conclusions:** White matter lesions and possibly vascular risk factors may reduce the risk of brain metastases in different malignant tumors including melanoma. Presence of WML in patients with brain metastases could potentially influence treatment choice regarding local or whole brain treatment after further multicentric prospective validation.

Keywords

Melanoma; Brain metastases; White Matter Hyperintensities; White Matter Lesions; Cerebral Small Vessel Disease; Vascular Risk Factor

Introduction:

Cerebral metastases are severe complications in patients with cancer. They occur in up to 40% of patients with solid tumors [1]. According to diagnosis specific graded prognostic assessment (DS-GPA) number of brain metastases has prognostic impact in several tumors (lung cancer, melanoma, renal cell cancer) [2]. In addition, number of brain metastases is highly relevant for decision between local and whole brain treatment [1,3,4]. Interestingly, factors that determine metastasis number are poorly described. Systemic tumor control and CNS-proneness of tumor cells are major determinants [5,6,7]. However, blood supply is also of relevance in brain metastasis. Most metastases develop in well perfused areas (e.g. the border of white and grey matter) while worse perfused areas (e.g. deep white matter) appear protected from metastases [8]. In addition, there is increasing evidence that microvascular damage in the brain (cerebral microangiopathy) that leads to white matter lesions (WML) in cerebral MRI can reduce number of BM in malignant disease e.g. in non-small cell lung cancer (NSCLC) [9, 10]. In the present retrospective analysis the influence of white mater lesions and vascular risk factors on number of brain metastases was analyzed for patients with diagnosed melanoma.

Material and Methods:

Charts of all patients diagnosed with "malignant melanoma" (MM) that presented at the University Hospital Leipzig from October 2004 – January 2015 were retrospectively filtered. Patients with malignant melanoma were included. One group of patients that developed BM

from melanoma was included as the "case" group at time of diagnosis of BM. A second group of patient was included as "control" group if 1) advanced melanoma with at least AJCC stage III at initial diagnosis was present and 2) if regular 3 monthly cerebral MRI was available with a follow up period of at least 3 years. Of patients of both groups a) complete clinical charts with medical history and age and b) 3 tesla cerebral MRI with 3D T1-weighted sequence after contrast agent injection (slice thickness of 1–1.5 mm) and T2/FLAIR sequence at diagnosis of brain metastasis or as regular screening needed to be available. Presence of vascular risk factors (arterial hypertension (AH), diabetes mellitus (DM), hypercholesterolemia (HC) and smoking were retrospectively compiled on basis of medical files. For diagnosis of AH patients needed to receive anti-hypertensive medication at time of documentation. Patients with DM, hypercholesterolemia and PAOD could be with or without pharmacological treatment. Smokers and Ex-smokers that stopped smoking ≤ 5 years before presentation were defined as smokers.

MRI analysis

Pre-treatment MR axial 3D T1-weighted images of the brain of the included patients were retrospectively analyzed by SN and BAB under the supervision of CS (with more than 7 years experience in clinical neuroradiology). Number and diameter of all metastases were determined blinded for presence of vascular risk factors. In addition, presence and degree of cerebral small vessel disease (also called white matter lesions (WML) was determined with the Fazekas score [11]. In Fig. 1 examples of grades of WML according to Fazekas Score are displayed

Written informed consent regarding scientific use of anonymized medical data was received from all patients at initial presentation in our department.

Statistical analysis

Type and number of vascular risk factors and stage of white matter lesions (WML 0-III) were compared between patients with and without BM. IBM SPSS V23.0 was applied for statistical analysis. Normal distribution of continuous variable was tested using the Kolmogorov–Smirnov test [12]. As data was not normally distributed ($p = 0.001$) statistical evaluation was performed with Mann-Whitney-U-Test ($N_{group} = 2$) or multiple Independent-Samples Kruskal-Wallis-Test ($N_{group} > 2$) [12]. Statistical significance was accepted at $p < 0.05$. Univariate (UVA) and multivariate data analyses (MVA) [14] were used. Evaluation or interaction of more than one vascular risk factor was possible in multivariate analyses. One MVA was conducted by recoding the categorical subtypes (S, AH, DM, HC) based on clinical history into positive or negative status (0, 1) and another by amount of vascular risk factors per investigation period (0, > 1 to 4). By using Pearson's Chi square test of Independence (p $\chi 2$), comparisons between different categorical variables were made and associations identified. Interactions of categorical variables were further explored by using logistic regression under description of odds ratio and estimation via the maximum-likelihood method. Figures were assembled with IBM SPSS V23.0 and Microsoft Office 365, Version 2017.

Results:

Patient characteristics (Table 1)

Overall, 61 patients fulfilled the inclusion criteria for this analysis, 30 patients with BM and 31 patients without BM. Median initial AJCC tumor stage was not different (stage 3) between both groups (p=0.339). At time of analysis, about 50% of all patients were pre-treated with immune - and/or chemotherapy, without significant differences between the two groups (p=0.332). Follow up time from initial diagnosis appeared somewhat higher (mean: 70.9 months vs. 58.6 months, median: 36.5 months vs. 32.5 months) in patients with BM but was

not significantly different (p=0.686). Median patient age was significantly higher in patients with BM (72 years vs. 62 years, p = 0.029). BM positive patients were more frequently male (70% vs. 58%, p=0.373) without reaching significance.

Vascular risk factors (Table 1)

Within both patient cohorts 42 patients (68.9 %) had a clinical history of vascular risk factors (smoking (n = 9; 14.8 %), diabetes mellitus (n = 9; 14.8 %), hypercholesterolemia (n = 10; 16.4 %), systemic hypertension (n = 35; 57.4 %). Between BM+ and BM- group the frequency of AH (50% vs. 64%, p=0.252) and smoking (13% vs. 16%, p=0.758) was not significantly different. There was a trend for more patients with DM (23% vs. 7%, p=0.080) and significant more patients with HC (29% vs. 3%, p=0.007) in BM- patients.

In total, 80% of patients without BM had at least one vascular risk factor while only 56% of patients with BM had at least one vascular risk factor in their medical charts (p=0.019). The number of vascular risk factor was significantly higher in patients without (mean N = 1.3; p=0.019) than with BM (mean N = 0.7), Fig. 2.

Monovariate logistic regression modelling of each vascular risk factor with the BM status confirmed no significant interaction as above (AH: b= -0.598, Exp (B) = 0.550 : 1, df = 1, p= 0.254; S: b= -0.223, Exp (B) = 0.8 : 1, df = 1, p= 0.759; DM: b= -1,407, Exp (B) = 0.245 : 1, df = 1, p= 0.097), except of hypercholesterolemia (b= -2473, Exp (B) = 0.084 : 1, df = 1, p= 0.023).

In multivariate analysis, across BM+ and BM- group, vascular risk factor status appeared being associated with BM status ($\chi 2(1) = 4.087$, px2 = 0.043, r = -0.259). In logistic regression, BM status was explored on interaction with vascular risk factor status. The chance for patient with brain metastasis being positive for vascular risk factors was significantly

reduced (b= -1,159, Exp (B) = 0.314 : 1, df = 1, p= 0.048). Similar, the amount of vascular risk factors was found being negatively related to brain metastasis ($\chi 2(4) = 6.098$, p x2 = 0.019, r = -0.308). In further logistic regression modelling, the unspecified amount of vascular risk factors (1-4) supported the suspected negative interaction with the brain metastasis status (b= -0.721, Exp (B) = 0.486 : 1, df = 1, p= 0.022).

Frequency of white matter lesions

Overall, 25 (41 %) patients had no white matter lesions (WML0), while 16 (26.2 %) showed punctate foci (WML1), 16 patients (26.2 %) had confluent foci (WML2) and 4 cases (6.6%) large confluent areas were noted (WML3); (Fig. 3A).WML were significantly more frequent and severe in patients without BM (median WML 1, mean = 1.3; SD = 1.04,) compared to patients with BM (median WML0, mean = 0.6; SD = 0.8, p = 0.017); (Fig. 3B).

Correlation of brain metastasis and white matter lesions

Significant inverse correlation between brain metastasis and WML was identified by Pearson's Chi square test of Independence ($\chi 2(3) = 6.945$; p $\chi 2 = 0.03$; r =-0.337). The higher the WML grade, the significant less brain metastases (p = 0.017), (Fig. 4). The overall suspected negative correlation was support in multinomial logistic regression modelling (b= -0.721, Exp (B) = 0.486 : 1, df = 1, p= 0.015).

Discussion:

There is increasing evidence that cerebral small vessel disease (represented by WML) can reduce number of brain metastases. However, most of this evidence is derived from patients with NSCLC (9, 10). It is not known, if this mechanism is also important in other tumor types. Potentially, different types of tumor can use distinct pathways of vasculogenesis

(15,16). Hence the relevance of "host" vessels might be different in other tumors e.g. in malignant melanoma.

In the present retrospective analysis patients with advanced stage melanoma that did not develop brain metastases in course of their disease had significantly more signs of cerebral microangiopathy on cerebral MRI. In addition there appeared an inverse correlation of degree of WML and brain metastases. These findings are coherent with the results from NSCLC and indicate that cerebral small vessel disease can reduce incidence of brain metastasis or prolong time to onset in different tumor types.

Small vessel disease of the brain is characterized by histopathological changes, such as loss of structure in arteriolar walls, narrowing of the vessels lumen and thickening of the vessels walls [17-20]. WML are common in patients with vascular risk factors like arterial hypertension [21] and are associated with strokes, dementia and intracerebral bleeding (ICB) [22-24]. For the process of brain metastasis embolization of cancer cells to cerebral vessels is essential. It occurs early in the multi-step process of cerebral metastasation [25]. Subsequently, endothelial factors contribute to successful seeding of tumor cells to and growth in the brain [26]. Carbonell et al. [6] described a β1-integrin mediated active interaction of the basement membrane of cerebral blood vessels with circulating tumor cells as a requirement for tumor cell adhesion and development of brain metastasis. In addition, deficiencies of endothelial proteins can reduce metastatic ability of adjacent tumor cells [27]. From this it can be hypothesized that levels of functional proteins like that of integrins are decreased in small vessel disease of the brain and ability for metastasis formation in the brain is reduced. However, there is only indirect experimental evidence for this e.g. from a rare inherited vasculopathy (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, CADASIL), in which levels of integrins (incl. β1-subtypes) are generally decreased [28]. Propably, cancers with proneness to CNS (NSCLC, SCLC, melanoma) that rely on co-option of physiological pre-existing vessels [29] are more

influenced by small vessel disease/WML than tumors that predominantly perform neo-angiogenesis (e.g. renal cell carcinoma [29].

If vascular risk factors can also affect brain metastasis is less clear from the literature. One clinical study demonstrated that an alteration of vascular architecture occurring in long-standing diabetes mellitus patients could be a protective factor against metastases from lung cancer [30]. However, in a recent retrospective first screening approach a general protective effect of vascular risk factors against BM across several tumor types was not detectable [31]. In the present analysis restricted to melanoma vascular risk factors were somewhat more frequent in patients without BM. This could point to a possible influence but is a very weak indication and needs to be validated in a larger cohort of patients with objectively measured vascular risk factors and reported co-medication.

Our analysis is restricted by its small size and monocentric, retrospective nature not fully excluding sampling bias. There was significant imbalance of patient age between the two groups with younger patients in the group without brain metastases. This could be relevant as patient age itself is a vascular risk factor and could influence results. However, in a larger earlier analysis of 200 patients, patient age was not associated with number of brain metastases [32]. In addition, a higher patient age in the group of patients without BM would be expected if age was relevant as a vascular risk factor and as an important confounder. The opposite was the case in the present study, which might strengthen the results. Regarding possible selection bias, median follow up time from diagnosis appeared 4 months (approximately 10%) longer in BM+ patients. This could reflect increasing BM risk with increasing duration of disease. However, with a p-value of 0.686 in comparison between the two groups a significant effect of this difference on present results appears not likely.

In conclusion, our analysis indicates a protective effect of small vessel disease in the brain against BM in melanoma. Presence of WML in patients with brain metastases could

potentially influence treatment choice regarding local or whole brain treatment after further multicentric prospective validation.

Funding :

This work did not receive any funding

Conflict of Interest:

The authors declare that there is no conflict of interest

Ethical approval:

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards

Informed consent:

Written informed consent regarding scientific use of anonymized medical data was received from all patients at initial presentation in our department.

Acknowledgements:

B.A.B was recipient of a merit-based doctoral scholarship from the Hans-Böckler Foundation funded by the Federal Ministry of Education and Research – Germany (BMBF).

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FIGURE CAPTIONS

Figure 1 – WML Staging according to Fazekas Score

A = Stage I: individual hyperintensities in white matter and periventricular regions

B = Stage II: beginning confluent hyperintensities in white matter and periventricular regions

C = Stage III: heavy confluent hyperintensities in white matter and periventricular regions

Figure 1

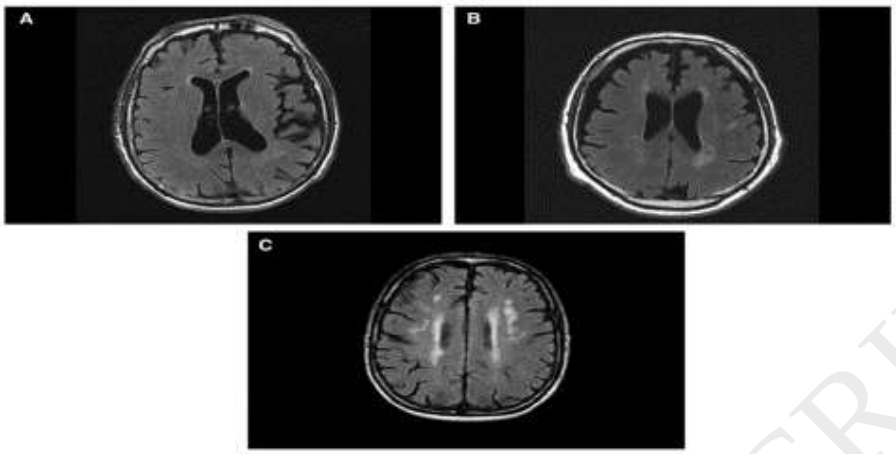

Figure 2 – WML Grade distribution on axial T2/FLAIR MRI based on brain metastasis

A) Bar chart on the absolute amount of patients with different WML grades grouped by BM occurrence

B) Boxplot of WML Fazekas Scoring by Brain Metastasis (Box = interquartile range (IQR), horizontal line = median, whiskers = max 1.5xIQR, N=number of patients)

Figure 2

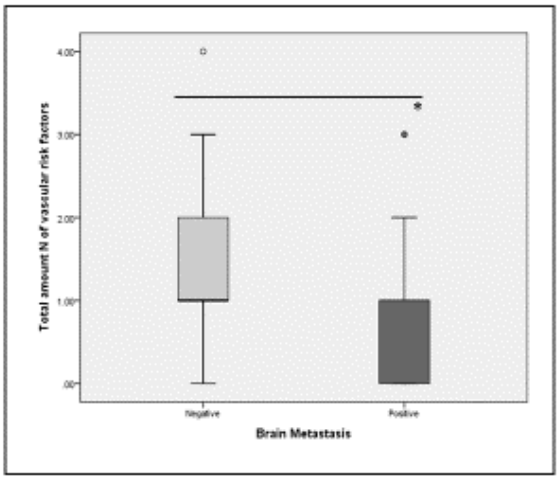

Figure 3 – Influence of WML on brain metastasis: Absolute number of patients with different WML grades illustrated as bars chart by brain metastases.

Figure 3

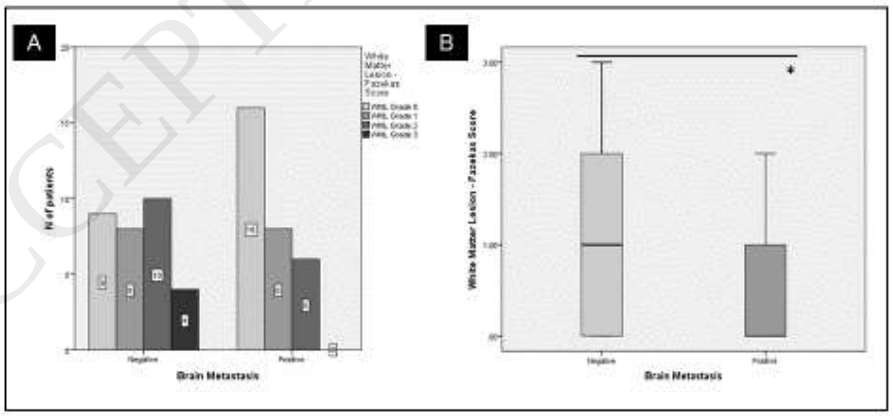

Figure 4 – Vascular risk factors and brain metastasis: Mean number of vascular risk factor according to brain metastasis. Data are displayed as boxplots (Box = interquartile range (IQR), horizontal line = median, whiskers = max 1.5xIQR, N=number of vascular risk factors).

Figure 4

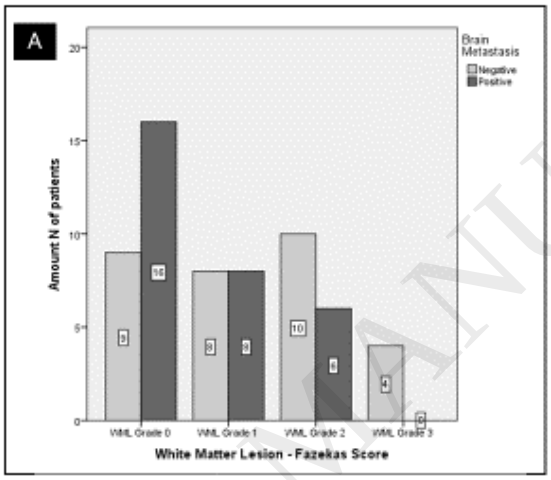

Table 1 – Patients Characteristics:

At time of analysis, about 50% of all patients were pre-treated with immune - and/or chemotherapy, without significant differences between the two groups (p=0.332).

Between BM+ and BM- group the frequency of AH (50% vs. 64%, p=0.252) and smoking (13% vs. 16%, p=0.758) was not significantly different. There was a tendency for more patients with DM (23% vs. 7%, p=0.080) and with HC (29% vs. 3%, p=0.007) in BM-

patients. In total, 80% of BM- patients had at least one vascular risk factor while only 56% of patients with BM had a vascular risk factor in their medical charts. The number of vascular risk factor was significantly higher in patients without (mean N = 1.3; p=0.019) than with BM (mean N = 0.7).

Table 1

PATIENT CHARACTERISTICS		BM + (N=30)		BM- (N=31)		p-Value
		MEAN ± SD	MEDIAN	MEAN ± SD	MEDIAN	BM+ vs. BM-
Patient age		71.8 ± 12.5	75	60.63 ±13.4	62	0.029*
Time from primary tumor diagnosis in months		70.89 ± 100.4	36.45	58.6 ±57.8	32.5	0.686
Median initial AJCC-Tumor stage		3		3		0.339
Prior medical therapy	No therapy	14/30 (46%)		18/31 (58%)		0.373
	Immuno- and /or Chemotherapy	16/30 (53%)		13/31 (42%)		
Gender (m =male, f =female)		m: 70%, f: 30%		m: 58%, f: 42%		0.332
Patients with AH (%)		15/30 (50%)		20/31 (64%)		0.252
Patients Smoking (%)		4/30 (13%)		5/31(16%)		0.758
Patients with DM (%)		2/30 (7%)		7/31 (23%)		0.080
Patients with Hypercholesterolemia (%)		1/30 (3%)		9/31 (29%)		0.007
Cumulated Patients with vascular risk factors (%)		56%		80%		0.019*