

ORIGINAL ARTICLE

Neuronal autoantibodies associated with cognitive impairment in melanoma patients

F. Bartels^{1,2†}, T. Strönisch^{1,2†}, K. Farmer^{1,2}, K. Rentzsch³, F. Kiecker⁴ & C. Finke^{1,2*}

¹Department of Neurology, Charité—Universitätsmedizin Berlin, Berlin; ²Berlin School of Mind and Brain, Humboldt-Universität zu Berlin, Berlin; ³Institute of Experimental Immunology, Euroimmun AG, Lübeck; ⁴Department of Dermatology, Charité—Universitätsmedizin Berlin, Berlin, Germany

*Correspondence to: Prof. Carsten Finke, Department of Neurology, Charité—Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany. Tel/Fax: +49-30-450-560-216; E-mail: carsten.finke@charite.de

†Both authors contributed equally.

Background: Cancer-related cognitive impairment is an important complication in cancer patients, yet the underlying mechanisms remain unknown. Over the last decade, the field of paraneoplastic neurological syndromes has been dramatically changed by the discovery of new neuronal autoantibodies, some of them associated with cognitive impairment. We aimed to assess the prevalence of neuronal autoantibodies in melanoma patients and their association with neurological and cognitive dysfunction.

Patients and methods: A total of 157 consecutive melanoma patients with a median age of 63 years were recruited at the Department of Dermatology, Charité—Universitätsmedizin Berlin and tested for neuronal autoantibodies. A comprehensive neuropsychological assessment was carried out in a selected subgroup of 84 patients after exclusion of patients with confounding factors for a cognitive dysfunction, including brain metastases, relevant medication, and neurological disorders.

Results: Neuronal autoantibodies were found in 22.3% of melanoma patients. The most frequent antibodies were IgA/IgM anti-NMDAR antibodies. Applying the International Cognition and Cancer Task Force criteria, 36.9% had cognitive impairment, however, with a threefold higher odds in antibody-positive compared with antibody-negative patients (57.1% versus 30.2%, OR = 3.1, 95% CI: 1.1 to 8.6; $P = 0.037$). In patients with anti-NMDAR antibodies, this impairment increased with higher antibody titers ($P = 0.007$). Antibody-positive patients had a significantly impaired overall cognitive performance (z -value: -0.38 ± 0.69 versus 0.00 ± 0.56 ; $P = 0.014$) as well as significant impairments in tests of memory, attention, and executive function. In a multiple linear regression analysis, autoantibodies were an independent risk factor for cognitive impairment ($B = -0.282$; 95% CI: -0.492 to -0.071 ; $P = 0.009$). Autoantibody seropositivity was associated with immune checkpoint inhibitor treatment and a history of autoimmune diseases.

Conclusions: A large number of melanoma patients harbor neuronal autoantibodies that are associated with significant cognitive impairment affecting memory, attention, and executive function. Neuronal autoantibodies might represent a pathophysiological factor and possible biomarker in the development of cancer-related cognitive impairment.

Key words: melanoma, cancer-related cognitive impairment, neuronal autoantibodies, paraneoplastic neurological syndromes, immune checkpoint inhibitor

Introduction

Paraneoplastic neurological syndromes (PNS) are cancer-associated neurological disorders that are caused by autoimmune mechanisms including autoantibodies targeting neuronal epitopes [1]. Although PNS are most frequently associated with lung cancer, they can occur with any type of tumor including melanoma [2]. While there is no systematic study on PNS in melanoma,

there are several reports of melanoma patients with PNS such as cerebellar degeneration [3], limbic encephalitis [4], Guillain-Barre syndrome [5], and chronic inflammatory demyelinating polyneuropathy [6].

PNS can be associated with neuronal autoantibodies targeting intracellular neuronal antigens (AICAbs) or neuronal surface epitopes (NSAbs) [7]. While diseases associated with AICAbs

usually show little to no treatment response, patients with NSAbs respond well to immunotherapy and tumor removal. A rapidly increasing number of new NSAbs has been discovered in the last years [7]. This has led to the identification of several novel neurological disorders such as anti-NMDA receptor (NMDAR) encephalitis, a disease caused by immunoglobulin G (IgG) NMDAR antibodies [8]. In contrast, NMDAR antibodies of immunoglobulin A (IgA) and immunoglobulin M (IgM) isotype were identified in association with cognitive impairment and dementia [9, 10].

In a recent retrospective study of more than 300 patients with different types of cancer including melanoma, we observed a high prevalence of NSAbs that were associated with cognitive impairment [11]. Cancer-related cognitive impairment (CRCI) is an important complication in tumor patients and will likely become more relevant in the future given the growing number of long-term survivors [12], however, the underlying mechanisms of CRCI remain largely unknown. While CRCI has been studied in detail in other types of cancer, previous studies in melanoma have only assessed subjective cognitive function using questionnaires without detailed neuropsychological testing [13, 14].

Here, we aimed to assess the prevalence of neuronal autoantibodies in melanoma patients and their association with neurological and cognitive dysfunction in an exploratory study. We, therefore: (i) tested a large group of melanoma patients for neuronal autoantibodies; (ii) systematically investigated cognitive function using formal neuropsychological assessment in a carefully selected subgroup of eligible patients without confounding factors such as brain metastases, central nervous system-active medications, or relevant neurological or psychiatric disorders; and (iii) compared cognitive function between antibody-positive and antibody-negative patients.

Methods

Patients

A total of 157 consecutive melanoma patients with all tumor stages were recruited at the Department of Dermatology, Charité—Universitätsmedizin Berlin, Germany, between February and September 2015 in an exploratory hypothesis-generating cross-sectional study. Charts of all patients were reviewed. Detailed information about demographic and clinical data is provided in [supplementary Table S1](#) (available at *Annals of Oncology* online). Patients had a median age of 63 years (range 21–91), and 75 patients (47.8%) were female. Twenty-four patients (15.3%) had advanced/metastatic stage melanoma (according to The American Joint Committee on Cancer (AJCC) classification 7th edition). The primary lesion was resected in all patients followed by histopathological diagnosis. All patients gave written informed consent for research and publication. The study was approved by the ethics committee of the Charité—Universitätsmedizin Berlin, Germany.

To analyze an association of neuronal antibodies with neurological and cognitive dysfunction, detailed neuropsychological assessment was carried out in 84 patients after exclusion of patients with possible confounding factors for a cognitive dysfunction using the following a priori defined exclusion criteria: brain metastases, history of or current neurological or psychiatric diseases, central nervous system-active medications, cranial irradiation, patients not fluent in German, and depressive symptoms [Beck Depressions-Inventar - Fast Screen (BDI-FS) score ≥ 4]. Importantly, the tested subgroup eligible for neuropsychological testing did not differ from non-tested patients with respect to age, sex,

autoantibody frequency, treatments, or medical history ([supplementary Table S2](#), available at *Annals of Oncology* online, Table 1). As expected, there was a difference regarding tumor stage with fewer stage IV patients in the tested subgroup, mainly due to the a priori exclusion of patients with brain metastases.

Neuronal antibody detection

Serum samples were analyzed for autoantibodies targeting neuronal antigens by indirect immunofluorescence using well-established commercial cell-based assays (Institute of Experimental Immunology, Euroimmun AG, Lübeck, Germany) (see supplementary 'Methods' section, available at *Annals of Oncology* online).

Neuropsychological and neurological assessment

The cognitive test battery covered the domains of working memory, verbal and visuospatial long-term memory, attention, executive functions, language, and intelligence level (see supplementary 'Methods' section, available at *Annals of Oncology* online). Analysis of neuropsychological tests followed the recommended criteria established by the International Cancer and Cognition Task Force (ICCTF) [15].

Further details on applied methods are provided in the [supplementary material](#) (available at *Annals of Oncology* online).

Results

Neuronal autoantibodies were detected in 35 of 157 (22.3%) melanoma patients (Table 1). Most antibodies were NSAbs, mainly targeting the NMDAR and were of IgM/IgA isotype. Other, less frequently detected NSAbs were all of IgG isotype and included antibodies against NMDAR (IgG), MOG, pre-GLRA1b, and IgLON5. AICAbs included GAD65, Homer3, Recoverin, ARHGAP26, Amphiphysin, Hu, and ITPR1.

Applying the ICCTF criteria, 36.9% (31/84) of all tested melanoma patients had cognitive impairment, however, with a three-fold higher odds in patients with neuronal autoantibodies compared with antibody-negative patients [57.1% (12/21) versus 30.2% (19/63), odds ratio (OR) = 3.1, 95% CI: 1.1 to 8.6; $P = 0.037$; Figure 1A, [supplementary Figure S1A](#), available at *Annals of Oncology* online). Antibody-positive patients also had a significantly higher number of deficits in neuropsychological tests compared with antibody-negative patients (2.2 versus 1.4 deficits, $t = -2.0$, $P = 0.045$; Figure 1B, [supplementary Figure S1B](#), available at *Annals of Oncology* online). Importantly, years of education and intelligence level were similar between groups ([supplementary Table S3](#), available at *Annals of Oncology* online).

NMDAR antibodies of IgA/IgM isotype were the most frequently detected antibodies in our study and have been previously identified in association with cognitive impairment and dementia [9, 10]. In order to more clearly identify the association of these antibodies with the observed cognitive deficits in melanoma patients, we carried out a subgroup analysis of patients with IgA/IgM NMDAR antibodies that showed a titer-dependent increase in the number of patients with cognitive impairment: while in patients with low titers (1 : 10), the percentage of patients with cognitive impairment was comparable to that of patients without antibodies [28.6% (2/7) and 30.2% (19/63)], the prevalence of cognitive impairment increased to 66.7% (4/6) (titer 1 : 32) and 100% (2/2) (titer 1 : 100) in patients with higher titers

Table 1. Neuronal autoantibodies

	All melanoma patients (n = 157)		Subgroup of patients with cognitive tests (n = 84)	
	No. ^a	Percent ^a	No. ^a	Percent ^a
Antibody-positive	35	22.3	21	25.0
One antibody only	27	17.2	16	19.0
Combination of two antibodies ^b	7	4.5	4	4.8
Combination of three antibodies ^c	1	0.6	1	1.2
Surface antigens	28	17.8	18	21.4
NMDAR	25	15.9	16	19.0
NMDAR IgM ^{b,c}	18	11.5	12	14.3
NMDAR IgA ^{b,c}	8	5.1	5	6.0
NMDAR IgG	2	1.3	1	1.2
MOG ^b	2	1.3	2	2.4
pre-GLRA1b ^c	2	1.3	2	2.4
IgLON5	1	0.6	0	0.0
Synaptic intracellular antigens	5	3.2	2	2.4
GAD65 ^b	2	1.3	2	2.4
Homer3 ^b	2	1.3	0	0.0
Amphiphysin ^b	1	0.6	0	0.0
Intracellular non-synaptic antigens	6	3.8	3	3.6
Recoverin	2	1.3	0	0.0
ARHGAP26 ^b	2	1.3	2	2.4
Hu	1	0.6	1	1.2
ITPR1	1	0.6	0	0.0

IgA, immunoglobulin A; IgM, immunoglobulin M; NMDAR, anti-NMDA receptor.

^aNumbers do not add up to 100% due to antibody combinations.

^bCombinations of two antibodies include NMDAR IgM + IgA (n = 2), NMDAR IgM + GAD65, NMDAR IgM + Homer3, NMDAR IgA + MOG, NMDAR IgA + Amphiphysin, GAD65 + ARHGAP26; NMDAR IgM + IgA (n = 1), NMDAR IgM + GAD65, NMDAR IgA + MOG, GAD65 + ARHGAP26.

^cCombination of three antibodies includes NMDAR IgM + IgA + pre-GLRA1b.

(titers $\leq 1:10$ versus $\geq 1:32$; $P = 0.007$) (Figure 1C, [supplementary Figure S1C](#), available at *Annals of Oncology* online).

Next, we analyzed performance of patients in different cognitive domains. Patients with neuronal autoantibodies showed significantly impaired visuospatial memory, working memory, and attention when compared with antibody-negative patients. The subgroup of patients with IgA/IgM NMDAR antibodies showed additional impairment in tests for executive function (Figure 2A–E, [supplementary Figure S2A–E](#) and [Table S3](#), available at *Annals of Oncology* online).

Z-transformation of cognitive test raw scores allowed for a comparison of patients' performance across cognitive tests and domains, and for the calculation of a composite cognitive score. Figure 3 illustrates that antibody-positive patients performed worse than antibody-negative patients in 20 out of 22 cognitive tests, indicating a robust and global impairment of cognitive function (Figure 3A and B, [supplementary Figure S3A](#) and B, available at *Annals of Oncology* online). Significant group differences were again observed in tests for visuospatial memory, short-term memory, and attention, with additional impairment in executive functions in the subgroup of patients with IgA/IgM NMDAR antibodies. Importantly, both the patients with neuronal autoantibodies as well as the subgroup of patients with IgA/IgM NMDAR antibodies had significantly lower composite cognitive

scores in comparison to antibody-negative patients (z-scores -0.38 ± 0.69 versus 0.00 ± 0.56 ; $d = 0.68$, $P = 0.014$ and -0.40 ± 0.71 versus 0.00 ± 0.56 ; $t = 2.3$, $d = 0.71$, $P = 0.023$).

Quality of life regarding physical health was significantly reduced in patients with IgA/IgM NMDAR antibodies compared with antibody-negative patients ([supplementary Table S3](#) and [Figure S4](#), available at *Annals of Oncology* online). There was no difference regarding mental health-related quality of life, fatigue, or prevalence of depressive symptoms between antibody-positive and antibody-negative patients.

Factors other than neuronal autoantibodies associated with cognitive impairment in melanoma patients included age (patients with versus no cognitive impairment; mean age \pm SD: 64.3 ± 15.5 versus 56.3 ± 14.9 ; $P = 0.022$), prior history of a neurological disease (OR = 5.8, 95% CI: 1.4 to 23.9; $P = 0.016$), arterial hypertension (OR = 3.1, 95% CI: 1.2 to 7.7; $P = 0.02$), and an elevated serum S100 level [relative risk (RR) 2.9; $P = 0.018$]. In a multiple linear regression model including these four factors as well as autoantibody seropositivity as predictors for cognitive performance, autoantibodies were an independent risk factor for cognitive impairment (regression coefficient $B = -0.282$; 95% CI: -0.492 to -0.071 ; $P = 0.009$; model $R^2 = 0.574$; [supplementary Table S4](#), available at *Annals of Oncology* online). Tumor stage or therapeutic interventions

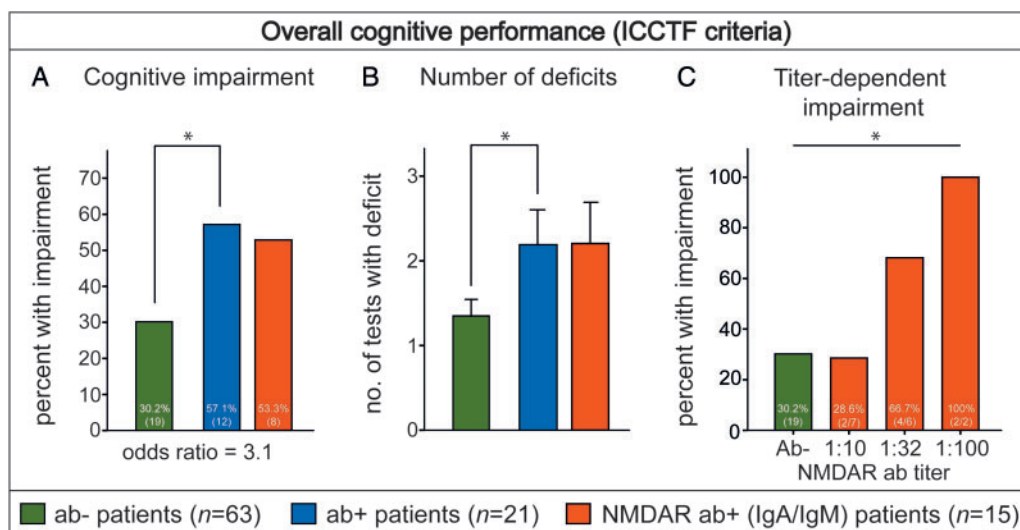


Figure 1. (A) Ab+ patients showed significantly more often a cognitive impairment compared with ab– patients [57.1% (ab+) versus 30.2% (ab–), OR = 3.1 (95% CI: 1.1 to 8.6), Fisher's exact test: $P=0.037$]. Cognitive impairment was considered when a patient had ≥ 2 deficits whereas a deficit was a cognitive performance 1.5 SDs below that of the normative controls of the respective test systems. (B) Ab+ patients had significantly more deficits in cognitive subtests than ab– patients (2.2 versus 1.4 deficits, t -test = -2.04 , $P=0.045$). (C) In patients with low titers (1:10), the percentage of patients with cognitive impairment was comparable to that of patients without antibodies (28.6% and 30.2%), whereas the prevalence of cognitive impairment increased to 66.7% (titer 1:32) and 100% (titer 1:100) in patients with higher titers (titers $\leq 1:10$ versus $\geq 1:32$; $P=0.007$) suggesting a NMDAR ab titer-dependent decline in cognitive function. Error bars: +1 SEM, $*P < 0.05$; ab, antibody; NMDAR, anti-NMDA receptor.

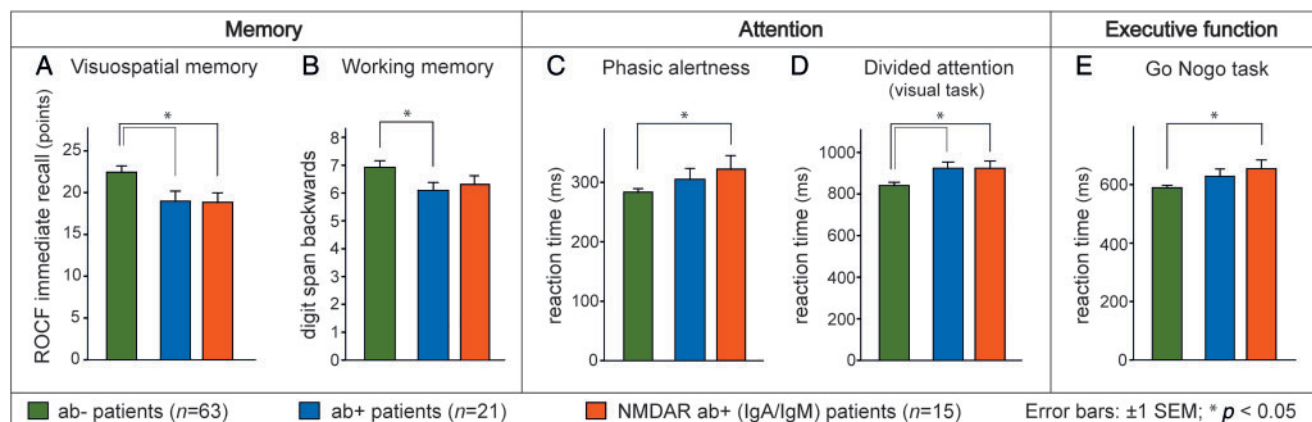


Figure 2. (A) Compared with ab– patients, ab+ patients achieved significantly less points in the immediate recall of the ROCF (19.0 ± 5.5 versus 22.4 ± 6.1 , $d=0.56$, $t=2.3$; $P=0.024$) which indicates reduced visuospatial memory. The same applies for the subgroup of the NMDAR ab+ patients (19.0 ± 4.9 versus 22.4 ± 6.1 , $t=2.1$, $d=0.56$, $P=0.044$). (B) Decrease in working memory of ab+ patients is depicted as reduced points in the task to reversely recall digit spans compared with ab– patients (6.1 ± 1.3 versus 6.9 ± 1.9 , $d=0.42$, $t=2.23$; $P=0.031$). (C) In the phasic alertness trial, NMDAR ab+ patient's reaction time was significantly prolonged compared with ab– patients ($320.3 \text{ ms} \pm 93.5$ versus $283.4 \text{ ms} \pm 47.5$, $d=0.78$, $t=2.2$; $P=0.032$). (D) Both the ab+ group and the NMDAR ab+ subgroup showed a prolonged reaction time in the visual task of the divided attention task (ab+ versus ab–: $921.5 \text{ ms} \pm 137.9$ versus $840.6 \text{ ms} \pm 125.0$, $t=-2.5$, $d=0.65$; $P=0.014$); for NMDAR ab+ versus ab–: $926.9 \text{ ms} \pm 145.1$ versus $840.6 \text{ ms} \pm 125.0$, $d=0.69$, $t=-2.3$; $P=0.022$). (E) In comparison to ab– patients NMDAR ab+ patient's reaction time for an adequate response in the Go Nogo task was significantly prolonged which demonstrates impaired executive function ($654.5 \text{ ms} \pm 100.3$ versus $589.3 \text{ ms} \pm 67.1$, $d=0.97$, $t=-2.7$; $P=0.008$). Error bars: +1 SEM, $*P < 0.05$; ab, antibody; NMDAR, anti-NMDA receptor; ROCF, Rey Osterrieth Complex Figure.

(immunotherapy OR = 1.8; $P=0.459$) were not associated with cognitive impairment. There was also no indication for chemotherapy to be a confounding factor: the rate of patients treated with chemotherapy was generally low [antibody-positive, 8.6% (3/35); antibody-negative, 6.6% (8/122; $P=0.71$); and patients

with chemotherapy did not have a higher risk for cognitive impairment (chemotherapy versus chemotherapy-naïve: 33.3% (1/3) versus 37.0% (30/81), OR 0.9, $P=1.0$]. Neither tumor stage nor chemotherapy were significant predictors in or improved the multiple regression model for cognitive performance.

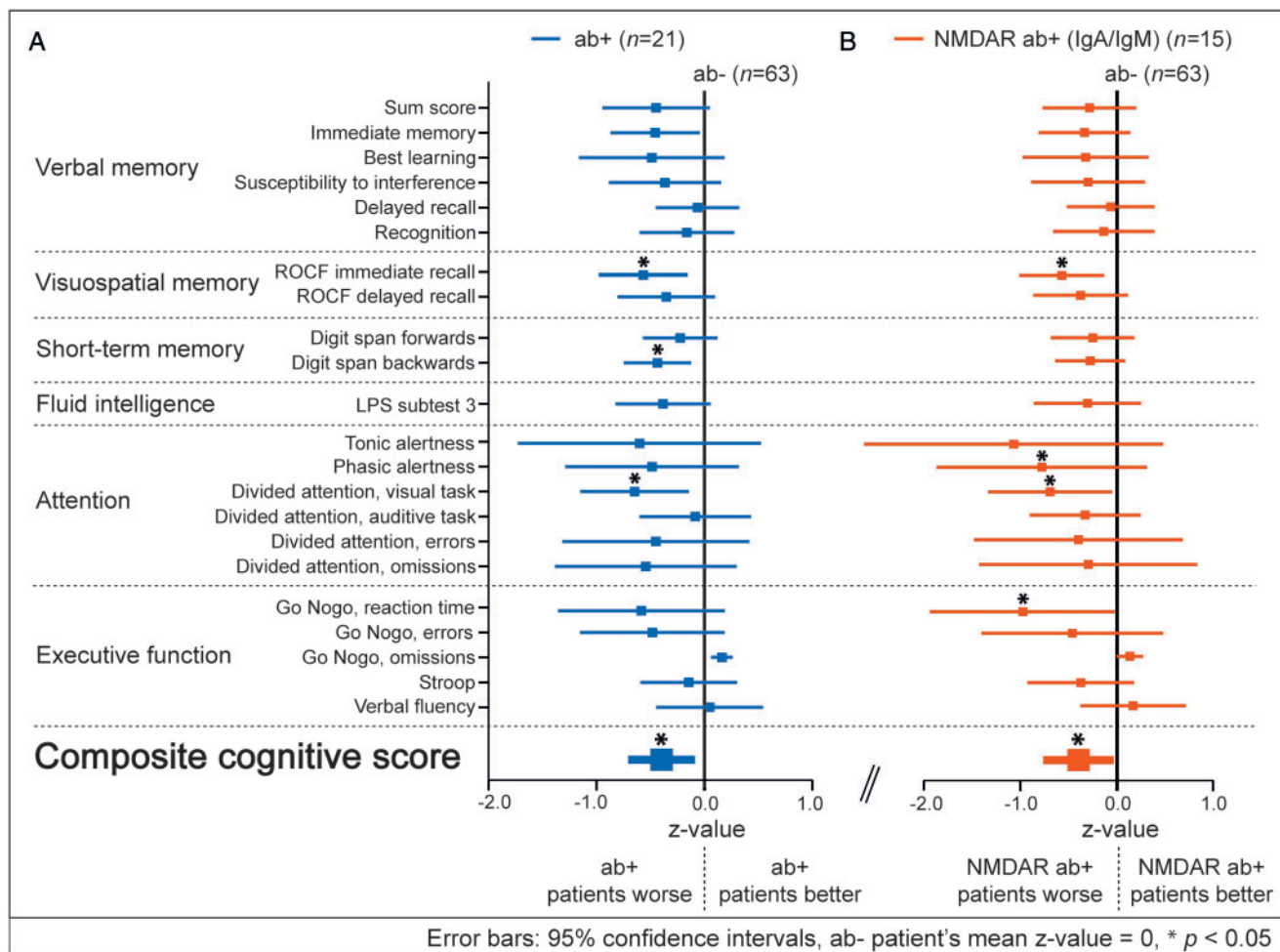


Figure 3. (A and B) Group comparison between ab- and ab+ patient's neuropsychological results and between the NMDAR ab+ subgroup and the ab- patients. Z-transformation of neuropsychological raw data with ab- patients as reference group: from all test results we subtracted ab- patient's group mean and divided by ab- patient's SD to set ab- patient's mean test results to 0 and their SD to 1. Test scales with lower values representing a better performance were multiplied by -1 so that lower values always stand for lower performance. The composite cognitive score was calculated by averaging the obtained z-values from the 22 substests for every patient. Significant group differences between cognitive substests are marked with an asterisk (* $P < 0.05$). Ab+ patients systematically scored worse in almost all substests and also significantly in the composite cognitive score (z-values: -0.38 ± 0.69 versus 0.00 ± 0.56 ; $t = 2.5$, $d = 0.68$; $P = 0.014$) (A). In the NMDAR ab+ subgroup, patients also received a significantly lower composite cognitive score than ab- patients (z-values: -0.40 ± 0.71 versus 0.00 ± 0.56 ; $t = 2.3$, $d = 0.71$; $P = 0.023$) (B). Error bars: 95% confidence intervals; ab, antibody; LPS, Leistungsprüfungssystem; NMDAR, anti-NMDA receptor; ROCF, Rey Osterrieth Complex Figure.

Importantly, there were no differences in age, sex, tumor stage, treatments, or ECOG performance status comparing tested antibody-positive to antibody-negative patients (supplementary Table S5, available at *Annals of Oncology* online).

On neurological examination, patients with AICAbs had a significantly higher frequency of polyneuropathy, gait ataxia, and abnormal oculomotor function compared with antibody-negative patients (supplementary Table S6, available at *Annals of Oncology* online).

Next, we investigated clinical factors associated with seroprevalence of autoantibodies. Patients with anti-NMDAR antibodies had a significantly higher prevalence of prior autoimmune diseases compared with antibody-negative patients [16.0% (4/25) versus 3.3% (4/122); $P = 0.029$, supplementary Figure S5A, available at *Annals of Oncology* online]. Patients treated with the

immune checkpoint inhibitor (ICI) ipilimumab exhibited a significantly higher prevalence of neuronal autoantibodies compared with patients without ICI treatment [75.0% (3/4) versus 21.1% (32/152), $P = 0.035$, supplementary Figure S5B, available at *Annals of Oncology* online]. Other demographic or clinical characteristics, including age, sex, tumor stage, prior medical history, or tumor therapy were not significantly different between antibody-positive and antibody-negative patients (supplementary Table S1 and Figure S6, available at *Annals of Oncology* online).

Discussion

In this cross-sectional exploratory study on cognitive function in melanoma patients, we found that more than one-third of

melanoma patients suffer from relevant cognitive impairment. More than 22% of melanoma patients harbor neuronal autoantibodies that were associated with a significantly increased risk for cognitive impairment affecting memory, attention, and executive function as well as reduced physical health. In patients with IgA/IgM anti-NMDAR antibodies, cognitive impairment increased with higher antibody titers. Autoantibody seroprevalence was associated with a history of autoimmune diseases and prior treatment with an ICI.

CRCI is increasingly recognized as an important complication in cancer patients and will become even more relevant given the growing number of long-term survivors [12]. Although mainly investigated in breast cancer, CRCI has also been studied in other cancer types, including colorectal cancer, prostate cancer, and leukemia [12, 16–19]. While there have been studies in melanoma patients evaluating health-related quality of life measures including self-reported cognitive function, these studies used questionnaires without formal cognitive testing [13, 14]. One early study evaluated neuropsychological effects of interferon- α treatment, but only reported differences between the treated and untreated group without informing on cognitive dysfunction compared with a normative control group [20]. Using detailed cognitive testing and applying the ICCTF criteria, we here show that more than one-third of melanoma patients exhibit cognitive impairment.

The underlying mechanisms of CRCI remain largely unknown. Most studies on CRCI have focused on systemic cancer treatment, e.g. chemotherapy, but accumulating evidence shows that cognitive impairment can already occur before and independently of cancer treatment [17, 21]. Previous studies have therefore suggested that additional factors, e.g. elevated levels of pro-inflammatory cytokines, are involved in the pathogenesis of CRCI [22]. Here, we identified neuronal autoantibodies as a potential mechanism underlying CRCI based on a significantly increased risk for cognitive impairment in antibody-positive compared with antibody-negative patients, a higher number of pathological cognitive test results, and a reduced overall cognitive performance. This confirms findings of our prior retrospective study that found a similarly high prevalence of neuronal antibodies in association with cognitive dysfunction in more than 300 patients with different types of cancer [11]. The detailed neuropsychological assessment carried out in our current study now allowed disentangling the affected cognitive domains that included memory, attention, and executive function. Importantly, all patients with possible confounding factors for a cognitive dysfunction (e.g. cerebral metastases, brain irradiation, and depression) were excluded from our analyses. In addition, the very low rate of patients with chemotherapy was similar between antibody-positive and antibody-negative patients and we observed no correlation between chemotherapy and cognitive impairment.

IgA/IgM NMDAR antibodies accounted for more than two-thirds of all detected antibodies. The subgroup of patients with these autoantibodies showed a titer-dependent increase in cognitive impairment. It is important to note that NMDAR encephalitis is associated with IgG antibodies as opposed to the IgA/IgM isotype [8]. IgA/IgM NMDAR antibodies have previously been described in patients with slow cognitive impairment and a subset of dementia patients [9, 10] and were also shown to reduce NMDAR protein

levels in neurons and induce changes in NMDAR-mediated currents [9, 23]. Furthermore, IgA/IgM NMDAR antibodies were the most frequently detected antibodies and were associated with cognitive deficits in our retrospective study of cancer patients [11]. There is an ongoing debate regarding the direct pathogenic effects of IgA/IgM NMDAR [10, 24]. Nevertheless, we here provide strong evidence for the clinical association between IgA/IgM NMDAR antibodies and cognitive impairment, although the exact nature of this association requires further study. Interestingly, these antibodies have also been found in up to 8.5% in a large group of blood donors [25], however, using the same antibody detection kit, IgA/IgM NMDAR antibodies were almost twice as frequent in our study of melanoma patients and more than six times as frequent as in our previously described group of healthy controls (2.5%) [11]. In contrast to previous studies, we observed no increase of antibody prevalence with age, further speaking to the specificity of the here observed effects [25].

AICAbs were associated with neuropathy and cerebellar syndromes, i.e. common PNS associated with classic onconeural antibodies (i.e. AICAbs). Our study thus emphasizes the importance to consider PNS, although rare, as a potential differential diagnosis in melanoma patients presenting with neurological symptoms.

Possible trigger factors for autoantibody production in melanoma patients include endogenous and exogenous factors. We identified a history of autoimmune diseases as potential endogenous factor in patients with IgA/IgM NMDAR antibodies, suggesting a combination of autoimmune predisposition and tumor tissue as potential additive risk factors. One common hypothesis of antibody formation in PNS is an immune reaction against shared antigens that are expressed by tumor tissue and the nervous system [26]. Indeed, the gene coding for the NMDAR subunit GluN2A has been found to be frequently mutated in melanoma samples, suggesting a potential tumor-directed immune surveillance response against the NMDAR [27]. In addition, we identified treatment with the ICI ipilimumab as a possible external trigger factor, although only in a small sample size. ICIs fundamentally changed treatment strategies in melanoma patients and also show promising results in other cancer types [28]; however, there is increasing evidence that ICIs cause severe autoimmune neurological side effects, including NMDAR encephalitis [29, 30]. With rising numbers of cancer patients treated with ICIs, their association with neuronal autoantibodies and possible neurological and cognitive side effects should be further investigated. Importantly, antibody prevalence was not associated with tumor stage and independent of brain metastases or prior neurological diseases.

Limitations of the current study include the lack of longitudinal data on autoantibody seroprevalence and patients' clinical outcome and survival. Follow-up studies of antibody-positive patients are thus needed to provide a more detailed insight on long-term clinical effects. Another limitation is the small sample size, especially in the subgroup analyses. Future studies are needed to confirm the observed correlations between autoantibodies and cognitive impairment in larger sample sizes. These studies should also include more detailed assessment of subjective cognitive functioning. Furthermore, a detailed analysis of the effects of neuronal autoantibodies other than the NMDAR antibodies was not possible due to their low frequency.

Conclusions

We found that a high proportion of melanoma patients harbor autoantibodies against neuronal antigens and that these patients were significantly more likely to have cognitive impairment compared with patients without antibodies. Based on the promising outcomes after immunosuppressive therapy of other neurologic syndromes associated with NSAbs, these results suggest a potentially treatable mechanism of immune-mediated cognitive impairment in melanoma patients and possibly also in other cancer patients with CRCI.

Funding

This research was supported by the Berlin School of Mind and Brain, Humboldt-Universität zu Berlin (no grant number applicable).

Disclosure

The authors have declared no conflicts of interest.

References

- Dalmau J, Rosenfeld MR. Paraneoplastic syndromes of the CNS. *Lancet Neurol* 2008; 7(4): 327–340.
- Giometto B, Grisold W, Vitaliani R et al. Paraneoplastic neurologic syndrome in the PNS Euronetwork database: a European study from 20 centers. *Arch Neurol* 2010; 67(3): 330–335.
- Jarius S, Steinmeyer F, Knobel A et al. GABAB receptor antibodies in paraneoplastic cerebellar ataxia. *J Neuroimmunol* 2013; 256(1–2): 94–96.
- Becquart C, Ryckewaert G, Desmedt E et al. Limbic encephalitis: a new paraneoplastic auto-immune manifestation associated with metastatic melanoma? *Ann Dermatol Venereol* 2013; 140(4): 278–281.
- Kraft RR, Pires de Souza ME, Fernanda Hilgert S et al. Melanoma metastasis to the gastric mucosa preceded by Guillain-Barré as a paraneoplastic syndrome. *Gastrointest Cancer Res* 2013; 6(5–6): 150–151.
- Bird SJ, Brown MJ, Shy ME, Scherer SS. Chronic inflammatory demyelinating polyneuropathy associated with malignant melanoma. *Neurology* 1996; 46(3): 822–824.
- Lancaster E, Dalmau J. Neuronal autoantigens—pathogenesis, associated disorders and antibody testing. *Nat Rev Neurol* 2012; 8(7): 380–390.
- Dalmau J, Gleichman AJ, Hughes EG et al. Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. *Lancet Neurol* 2008; 7(12): 1091–1098.
- Prüss H, Hölte M, Maier N et al. IgA NMDA receptor antibodies are markers of synaptic immunity in slow cognitive impairment. *Neurology* 2012; 78(22): 1743–1753.
- Doss S, Wandinger K-P, Hyman BT et al. High prevalence of NMDA receptor IgA/IgM antibodies in different dementia types. *Ann Clin Transl Neurol* 2014; 1(10): 822–832.
- Finke C, Bartels F, Lütt A et al. High prevalence of neuronal surface autoantibodies associated with cognitive deficits in cancer patients. *J Neurol* 2017; 264(9): 1–10.
- Wefel JS, Kesler SR, Noll KR, Schagen SB. Clinical characteristics, pathophysiology, and management of noncentral nervous system cancer-related cognitive impairment in adults. *CA Cancer J Clin* 2015; 65(2): 123–138.
- Coens C, Suciú S, Chiarion-Sileni V et al. Health-related quality of life with adjuvant ipilimumab versus placebo after complete resection of high-risk stage III melanoma (EORTC 18071): secondary outcomes of a multinational, randomised, double-blind, phase 3 trial. *Lancet Oncol* 2017; 18(3): 393–403.
- Long GV, Atkinson V, Ascierto PA et al. Effect of nivolumab on health-related quality of life in patients with treatment-naïve advanced melanoma: results from the phase III CheckMate 066 study. *Ann Oncol* 2016; 27(10): 1940–1946.
- Wefel JS, Vardy J, Ahles T, Schagen SB. International cognition and cancer task force recommendations to harmonise studies of cognitive function in patients with cancer. *Lancet Oncol* 2011; 12(7): 703–708.
- Ahles TA, Saykin AJ, Furstenberg CT et al. Neuropsychologic impact of standard-dose systemic chemotherapy in long-term survivors of breast cancer and lymphoma. *J Clin Oncol* 2002; 20(2): 485–493.
- Vardy JL, Dhillon HM, Pond GR et al. Cognitive function in patients with colorectal cancer who do and do not receive chemotherapy: a prospective, longitudinal, controlled study. *J Clin Oncol* 2015; 33(34): 4085–4092.
- Chao HH, Uchio E, Zhang S et al. Effects of androgen deprivation on brain function in prostate cancer patients—a prospective observational cohort analysis. *BMC Cancer* 2012; 12(1): 371.
- Hshieh TT, Jung WF, Grande LJ et al. Prevalence of cognitive impairment and association with survival among older patients with hematologic cancers. *JAMA Oncol* 2018; 4(5): 686–693.
- Caraceni A, Gangeri L, Martini C et al. Neurotoxicity of interferon-alpha in melanoma therapy: results from a randomized controlled trial. *Cancer* 1998; 83(3): 482–489.
- Ono M, Ogilvie JM, Wilson JS et al. A meta-analysis of cognitive impairment and decline associated with adjuvant chemotherapy in women with breast cancer. *Front Oncol* 2015; 5: 59.
- Ahles TA, Saykin AJ. Candidate mechanisms for chemotherapy-induced cognitive changes. *Nat Rev Cancer* 2007; 7(3): 192–201.
- Castillo-Gómez E, Oliveira B, Tapken D et al. All naturally occurring autoantibodies against the NMDA receptor subunit NR1 have pathogenic potential irrespective of epitope and immunoglobulin class. *Mol Psychiatry* 2017; 22(12): 1776–1784.
- Hara M, Martinez-Hernandez E, Ariño H et al. Clinical and pathogenic significance of IgG, IgA, and IgM antibodies against the NMDA receptor. *Neurology* 2018; 90(16): e1386–e1394.
- Dahm L, Ott C, Steiner J et al. Seroprevalence of autoantibodies against brain antigens in health and disease. *Ann Neurol* 2014; 76(1): 82–94.
- Dalmau J, Gultekin HS, Posner JB. Paraneoplastic neurologic syndromes: pathogenesis and pathophysiology. *Brain Pathol* 2006; 9(2): 275–284.
- Wei X, Walia V, Lin JC et al. Exome sequencing identifies GRIN2A as frequently mutated in melanoma. *Nat Genet* 2011; 43(5): 442–446.
- Ribas A, Wolchok JD. Cancer immunotherapy using checkpoint blockade. *Science* 2018; 359(6382): 1350–1355.
- Yshii LM, Hohlfeld R, Liblau RS. Inflammatory CNS disease caused by immune checkpoint inhibitors: status and perspectives. *Nat Rev Neurol* 2017; 13(12): 755–763.
- Salam S, Lavin T, Turan A. Limbic encephalitis following immunotherapy against metastatic malignant melanoma. *BMJ Case Rep* 2016; 2016: bcr2016215012.