Data in Brief 53 (2024) 110062

Contents lists available at ScienceDirect

Data in Brief

journal homepage: www.elsevier.com/locate/dib

Data Article

Dataset for: Autoantibody profiles in patients with immune checkpoint inhibitor-induced neurological immune-related adverse events

Leonie Müller-Jensen[a,b], Samuel Knauss[a,b], Lorena Ginesta Roque[a], Christian Schinke[a,b], Smilla K. Maierhof[a,c,d], Frederik Bartels[a,b], Carsten Finke[a,c,e], Kristin Rentzsch[f], Claas Ulrich[g,h], Raphael Mohr[i], Werner Stenzel[j], Matthias Endres[a,c,k,l,m,n,1], Wolfgang Boehmerle[a,c,k,1,*], Petra Huehnchen[a,c,k,1]

[a] *Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Department of Neurology with Experimental Neurology, Charitéplatz 1, 10117 Berlin, Berlin, Germany*
[b] *Berlin Institute of Health at Charité, Universitätsmedizin Berlin, BIH Academy, (Junior) Clinician Scientist Program, Charitéplatz 1, 10117 Berlin, Germany*
[c] *Berlin Institute of Health at Charité – Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany*
[d] *Einstein Center for Neurosciences Berlin (ECN) at Charité – Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany*
[e] *Humboldt-Universität zu Berlin, Berlin School of Mind and Brain, Berlin, Germany*
[f] *Clinical Immunological Laboratory Prof. Dr. med. Winfried Stöcker, Groß Grönau, Germany*
[g] *Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Department of Dermatology, Venerology and Allergology, Charitéplatz 1, 10117 Berlin, Germany*
[h] *Collegium Medicum Berlin GmbH, Luisenstrasse 54/55, 10117 Berlin, Germany*
[i] *Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Department of Hepatology & Gastroenterology, Charité Campus Virchow, Augustenburger Platz 1, 13353 Berlin, Germany*
[j] *Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Department of Neuropathology, Charitéplatz 1, 10117 Berlin, Germany*
[k] *Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, NeuroCure Cluster of Excellence, 10117 Berlin, Berlin, Germany*
[l] *Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt Universität zu Berlin, Center for Stroke Research Berlin, 10117 Berlin, Berlin, Germany*
[m] *German Center for Neurodegenerative Diseases, 10117 Berlin, Berlin, Germany*
[n] *DHZK (German Center for Cardiovascular Research), partner site Berlin, 10117 Berlin, Berlin, Germany*

[*] Corresponding author at: Department of Neurology with Experimental Neurology, Charité Universitätsmedizin Berlin, Charitéplatz 1 | 10117 Berlin, Germany.
E-mail address: Wolfgang.boehmerle@charite.de (W. Boehmerle).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.dib.2024.110062

ARTICLE INFO

Article history:
Received 2 March 2023
Accepted 9 January 2024
Available online 18 January 2024

Dataset link: Dataset for: Autoantibody profiles in patients with immune checkpoint inhibitor-induced neurological immune related adverse events. (Original data)

Keywords:
Immune checkpoint inhibitors
Immune-related adverse events
Neurotoxicity
Autoimmunity
Neuronal autoantibodies
Myositis
Paraneoplastic syndromes

ABSTRACT

The rise of cancer immunotherapy has been a milestone in clinical oncology. Above all, immune checkpoint inhibitor treatment (ICI) with monoclonal antibodies targeting programmed cell death protein 1 (PD-1), programmed cell death-ligand 1 (PD-L1), and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) has improved survival rates for an increasing number of malignancies. However, despite the clinical benefits, ICI-related autoimmunity has become a significant cause of non-relapse-related morbidity and mortality. Neurological immune-related adverse events (irAE-n) are particularly severe toxicities with a high risk for chronic illness, long-term steroid dependency, and early ICI treatment termination. While the clinical characteristics of irAE-n are well described, little is known about underlying immune mechanisms and potential biomarkers. Recently, high frequencies of neuronal autoantibodies in patients with irAE-n have been reported, however, their clinical relevance is unclear.

Here, we present a dataset on neuronal autoantibody profiles in ICI-treated cancer patients with and without irAE-n, which was generated to investigate the potential role of neuronal autoantibodies in ICI-induced autoimmunity. Between September 2017 and January 2022 serum samples of 29 cancer patients with irAE-n post-ICI treatment) and 44 cancer control patients without high-grade immune-related adverse events (irAEs, $n = 44$ pre- and post-ICI treatment) were collected and tested for a large panel of brain-reactive and neuromuscular autoantibodies using indirect immunofluorescence and immunoblot assays. Prevalence of autoantibodies was compared between the groups and correlated with clinical characteristics such as outcome and irAE-n manifestation. These data represent the first systematic comparison of neuronal autoantibody profiles between ICI-treated cancer patients with and without irAE-n, providing valuable information for both researchers and clinicians. In the future, this dataset may be valuable for meta-analyses on the prevalence of neuronal autoantibodies in cancer patients.

Specifications Table

Subject	Health and medical sciences: Clinical Neurology
Specific subject area	Neuronal autoantibody profiles and clinical data of cancer patients with immune-checkpoint inhibitor treatment and neurological immune-related adverse events
Type of data	Tables
How the data were acquired	Clinical data were collected using patient's electronic medical records. Neuronal autoantibodies were detected using indirect immunofluorescence and immunoblot assays.

(*continued on next page*)

Data format	Raw data, analyzed data
Description of data collection	Between September 2017 and January 2022, we consecutively collected cancer patients that had received immune checkpoint blockade and were diagnosed with a neurological immune-related adverse event (irAE-n). As a control cohort, we prospectively enrolled cancer patients that were scheduled for immune checkpoint inhibitor (ICI) treatment and included those who did not develop any high-grade (Common Terminology Criteria for Adverse Events [CTCAE] grade $\geq$3) irAEs (neither neurological nor non-neurological) within the first three months after ICI treatment initiation. We assessed serum samples from all patients (n = 29 post-ICI treatment samples for irAE-n patients and n = 44 pre- and post-ICI treatment samples, respectively) and screened for a large panel of neuronal autoantibodies, including brain-reactive and neuromuscular autoantibodies. Clinical data (demographics, tumor type, ICI type, type of irAE-n, additional irAE, comorbidities) were retrieved from the patient's chart. Outcome parameters such as unfavorable outcome (defined as CTCAE $\geq$3 at three months after symptom onset) and treatment with corticosteroids at three months after symptom onset (yes / no) were scored retrospectively.
Data source location	Institution: Charité - Universitätsmedizin Berlin City/Town/Region: Berlin Country: Germany
Data accessibility	Repository name: Mendeley Data Data identification number: 10.17632/9b5jhshbgk.4 Direct URL to data: https://data.mendeley.com/datasets/9b5jhshbgk
Related research article	L. Müller-Jensen, S. Knauss, L. Ginesta Roque, et al. Autoantibody profiles in patients with immune checkpoint inhibitor-induced neurological immune related adverse events. *Front Immunol.* 2023;14 doi: 10.3389/fimmu.2023.1108116 [1]

1. Value of the Data

- These data give new insight into the prevalence of neuronal autoantibodies in (ICI-treated) cancer patients and their clinical significance in neurological immune-related adverse events (irAE-n).
- The dataset reveals a strong association between neuromuscular autoantibodies and ICI-induced neuromuscular disease, providing the groundwork for future studies to investigate the predictive value and diagnostic accuracy of autoantibody screening in patients prior to and during ICI treatment.
- This dataset can serve as a reference for future studies on immunotherapy-associated neurotoxicity, but also on the pathological significance of neuronal autoantibodies in general.

2. Objective

Immune checkpoint inhibitors (ICIs) have become standard-of-care in the treatment of more than 20 different cancer types [2]. However, high tumor response rates are often counteracted by autoimmune phenomena, referred to as immune-related adverse events (irAEs). Albeit rare with an incidence of 2–12% [3–5], neurological irAEs (irAE-n) are particularly severe immunotoxicities with potentially fatal outcome [6–10]. Diagnosing and treating irAE-n is challenging, as the underlying immunological mechanisms are poorly understood and biomarkers are missing. Here, we aimed to characterize neuronal autoantibody profiles in patients with irAE-n compared to ICI-treated cancer patients without irAEs to (1) identify autoantibodies that may serve as diagnostic markers for irAE-n and (2) shed light into the immunopathology of ICI-induced neurotoxicity.

In addition to the related research article [1], this data article provides clinical information and autoantibody data - including autoantibody titers - of all cancer patients that participated

in our study, which may be used for meta-analyses on autoantibody prevalence in (ICI-treated) cancer patients.

3. Data Description

All files below are deposited at Mendeley Data.

Neuronal_Autoantibodies_in_irAE-n_raw_data.xlsx provides the raw data from both study cohorts including clinical data, results for brain-reactive autoantibodies, and results for neuromuscular autoantibodies with antibody titers. Analysis of brain-reactive autoantibodies was performed at the Labor Prof. Winfried Stöcker, Germany. Analysis of neuromuscular autoantibodies was conducted by Labor Berlin GmBH, Berlin, Germany. Two authors (LMJ and PH) extracted the clinical data from patient's charts. Missing values are indicated as "NA" (= not available).

Neuronal_Autoantibodies_in_irAE-n_Supplemental_Table_1.xls shows the p-values that were calculated by comparing clinical characteristics (e.g., age, sex, neoplasm, ICI type) between autoantibody-positive and autoantibody-negative patients with irAE-n.

4. Experimental Design, Materials, and Methods

4.1. Patients

Between September 2017 and January 2022 we enrolled all consecutive patients that met the following inclusion criteria: (1) Age $>$ 18 years, (2) previous ICI treatment and (2) diagnosis of irAE-n according to the consensus criteria of "probable" or "definite" irAE-n published by Guidon et al. [11]. We included one additional patient with preexisting myasthenia gravis whodeveloped a myasthenic crisis after ICI treatment. One other patient was double-blinded for ICI treatment versus placebo but was included as he presented multiple irAEs, so placebo treatment was implausible. Diagnosis of irAE-n was confirmed by three investigators (*LMJ, SK, PH*).

As a control cohort, we collected ICI-, cancer, age- and sex-matched cancer patients that (1) were $>$ 18 years old, (2) were scheduled for ICI treatment and did not receive previous ICI treatment within the last six months, (3) did not develop any irAE-n or high-grade (Common Terminology Criteria for Adverse Events [CTCAE] grade $\geq$3) irAEs within the first three months of ICI treatment.

4.2. Clinical data and outcome

Using the patients' charts and routine care data, we assessed the following data from all patients: Demographics (age, sex), neoplasm, ICI type, ICI duration (cycle), type and treatment of irAE-n, other irAEs, rechallenge of ICI, presence of brain metastases, neurological comorbidities, worst CTCAE grade of irAE-n (1–5), and medication with corticosteroids at three months after onset. Outcome parameters such as CTCAE grade of irAE-n at three months after onset and unfavorable outcome (defined as CTCAE grade $\geq$ 3 after three months) were scored retrospectively.

4.3. Neuronal autoantibody testing

Blood serum samples of irAE-n patients were assessed during the acute disease stage. For nine patients with irAE-n cerebrospinal fluid (CSF) samples were available that were collected during the routine diagnostic workup. In the control cohort, blood serum samples were assessed prior to ICI treatment and six weeks (equal to two ICI cycles) after ICI treatment onset. To increase sensitivity, we included low-titer and borderline positive results. Specifications of all tested autoantibodies are described in our reference article [1].

4.3.1. Brain-reactive autoantibodies

Brain-reactive autoantibodies were tested in all patients using cell-based and tissue-based assays (EUROIMMUN Medizinische Labordiagnostika AG, Germany). Tissue-based assays were performed using immunohistochemistry of frozen monkey or rat brain tissue and cell-based assays were done using antigen-expressing HEK293-cells as described previously [12]. In addition, immunoblot assays (EUROLINE) were conducted to confirm the results from indirect immunohistochemistry. If an autoantibody was detected using immunohistochemistry but immunoblot and cell-based assays were negative, the respective autoantibody was considered an autoantibody with unknown antigen reactivity.

The following brain-reactive autoantibodies were tested: anti-α-amino-3–hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR1/2), anti-amphiphysin, anti-aquaporin 4 (AQP4), anti-RhoGTPase-activating protein 26 (ARHGAP26), anti-ATP1A3, anti-carbonic anhydrase related proteins VIII (CARP VIII), anti-contactin-associated protein-like 2 (CASPR2), anti-collapsin response-mediator protein 5 (CV2/CRMP5), anti-dipeptidyl-peptidase-like protein 6 (DPPX), anti-Flotillin1/2, anti-gamma-aminobutyric-acid A receptor ($GABA_AR$), anti-gamma-aminobutyric-acid B receptor ($GABA_BR$), anti-glutamic acid decarboxylase 65 (GAD65), anti-glial fibrillary acidic protein (GFAP), anti-glutamate receptor delta 2 (GluD2), anti-glycine receptor (GlyR), anti-Homer protein homolog 3 (Homer-3), anti-Hu (Anna-1), anti-immunoglobulin LON5 (IgLON5), anti-inositol 1,4,5-trisphosphate receptor 1 (ITPR-1), anti-leucine-rich glioma-inactivated 1 (LGI1), anti-Ma2, anti-metabotropic glutamate receptor 1 (mGluR1), anti-metabotropic glutamate receptor 5 (mGluR5), anti-myelin oligodendrocyte glycoprotein (MOG), anti-myelin, anti-neuroendothelium, anti-neurexin, anti-neurochondrin, anti-N-methyl-D-aspartate receptor IgG (NMDA IgG), anti-N-methyl-D-aspartate receptor IgA/IgM (NMDA IgA/IgM), anti-recoverin, anti-Ri (Anna-2), anti-septin complex, anti-Tr (DNER), anti-Yo (PCA-1), and anti-zinc finger 4. (Zic4).

Eight of nine CSF samples were analyzed for anti-amphiphysin, anti-AQP4, anti-CASPR2, anti-DPPX, anti-GAD65, anti-$GABA_BR$, anti-AMPAR1/2, anti-NMDAR, anti-mGluR5, anti-GlyR, anti-LGI1, anti-myelin, anti-CV2/CRMP5, anti-Hu (Anna-1), anti-Ma2, anti-Ri (Anna-2), anti-Tr (DNER), and anti-Yo (PCA-1) autoantibodies. One CSF sample was only tested for anti-amphiphysin, anti-CV2/CRMP5, anti-GAD65, anti-Hu (Anna-1), anti-Ma2, anti-Ri (Anna-2), anti-Tr (DNER), and anti-Yo (PCA-1) autoantibodies. If not declared otherwise, the IgG isoform was tested.

4.3.2. Neuromuscular autoantibodies

Neuromuscular autoantibodies were tested in 24 of 29 patients with irAE-n and 41 of 44 controls. To that end, the following commercially available assays (Labor Berlin GmbH, Germany) were used: Anti-titin and anti-SRY-related HMG-box 1 (SOX1) autoantibodies using line assays; anti-lipoprotein receptor-related protein 4 (LPR4), anti-skeletal muscle and anti-heart muscle autoantibodies using indirect immunofluorescence; anti-myelin-associated glycoprotein (MAG), anti-muscle-specific tyrosine kinase (MuSK), and anti-acetylcholine receptor (AchR) autoantibodies using enzyme linked immunosorbent assays; anti-ryanodine receptor (RyR) autoantibodies using western blot and anti-P/Q-type voltage-gated calcium channel (P/Q VGCC) autoantibodies using a radioimmunoassay. Due to limited specimen size serum of three control patients could not be tested for anti-LRP4, anti-RyR and anti-P/Q-type VGCC autoantibodies.

5. Statistical Analysis

Statistical analyses were performed using RStudio (version 2022.02.3 + 492 "Prairie Trillium"). Graphs and figures were illustrated using Graphpad Prism (version 7). Group differences of categorical and continuous variables were calculated using the Fisher's exact or the Chi-squared test and the *t*-test (in case of normal distribution) or Wilcoxon rank test (in case of no normal distribution), respectively. To assess the diagnostic accuracy for selected autoantibodies, we calculated sensitivity, specificity, positive predictive value, and negative predictive value including 95% confidence intervals using the "EpiR" package in R. A p-value ≤ 0.05 was considered statistically significant.

Ethics Statements

The institutional review board of Charité Universitätsmedizin Berlin (EA1/099/17 and EA4/219/21) approved this prospective registered observational study (DRKS00012668). Written informed consent was obtained from all participants. The research described here was carried out in accordance with the Declaration of Helsinki.

Data Availability

Dataset for: Autoantibody profiles in patients with immune checkpoint inhibitor-induced neurological immune related adverse events. (Original data) (Mendeley Data)

CRediT Author Statement

Leonie Müller-Jensen: Conceptualization, Methodology, Investigation, Formal analysis, Funding acquisition, Writing – original draft, Visualization; **Samuel Knauss:** Conceptualization, Funding acquisition, Writing – review & editing; **Lorena Ginesta Roque:** Methodology, Investigation; **Christian Schinke:** Methodology, Writing – review & editing; **Smilla K. Maierhof:** Methodology, Writing – review & editing; **Frederik Bartels:** Resources, Writing – review & editing; **Carsten Finke:** Resources, Writing – review & editing; **Kristin Rentzsch:** Investigation, Methodology, Writing – review & editing; **Claas Ulrich:** Resources, Writing – review & editing; **Raphael Mohr:** Resources, Writing – review & editing; **Werner Stenzel:** Investigation, Writing – review & editing; **Matthias Endres:** Funding acquisition, Supervision, Resources, Writing – review & editing; **Wolfgang Boehmerle:** Conceptualization, Funding acquisition, Methodology, Supervision, Writing – review & editing; **Petra Huehnchen:** Conceptualization, Funding acquisition, Methodology, Supervision, Writing – review & editing.

Acknowledgments and funding

The authors thank Petra Loge for excellent technical assistance processing the blood samples. The project was funded by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) under Germanyś Excellence Strategy (EXC-2049 – 390688087 to ME) as well as the Berlin Institute of Health SPARK program (to WB). PH receives funding from the Else-Kröner-Fresenius-Stiftung (2020_EKEA.80). LMJ, CS, SK and PH are members of the BIH Clinician Scientist program. PH is the recipient of a Rahel-Hirsch stipend by Charité Universitätsmmedizin Berlin.

Declaration of competing interest

LMJ, SK, LGR, CS, SM, FB, KR, RM, CU, WS and *PH* declare no conflicts of interest. *CF* receives research support from EUROIMMUN AG. *WB* has received lecture fees from Bristol-Meyers-Squibb and NOGGO eV. *ME* reports grants from Bayer and fees paid to the Charité from Abbot, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, BMS, Daiichi Sankyo, Sanofi, Novartis, Pfizer, all outside the submitted work.

Supplementary Materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dib.2024.110062.

References

[1] L. Müller-Jensen, S. Knauss, L. Ginesta Roque, et al., Autoantibody profiles in patients with immune checkpoint inhibitor-induced neurological immune related adverse events, Front. Immunol. 14 (2023), doi:10.3389/fimmu.2023.1108116.

[2] J.D. Twomey, B. Zhang, Cancer immunotherapy update: FDA-approved checkpoint inhibitors and companion diagnostics, AAPS J. 23 (2) (2021) 39, doi:10.1208/s12248-021-00574-0.

[3] D. Dubey, W.S. David, K.L. Reynolds, et al., Severe neurological toxicity of immune checkpoint inhibitors: growing spectrum, Ann. Neurol. 87 (5) (2020) 659–669, doi:10.1002/ana.25708.

[4] T. Mikami, B. Liaw, M. Asada, et al., Neuroimmunological adverse events associated with immune checkpoint inhibitor: a retrospective, pharmacovigilance study using FAERS database, J. Neurooncol. 152 (1) (2021) 135–144, doi:10.1007/s11060-020-03687-2.

[5] S. Cuzzubbo, F. Javeri, M. Tissier, et al., Neurological adverse events associated with immune checkpoint inhibitors: review of the literature, Eur. J. Cancer 73 (2017) 1–8, doi:10.1016/j.ejca.2016.12.001.

[6] J.B.E. Janssen, T.Y.S. Leow, K.H. Herbschleb, et al., Immune checkpoint inhibitor-related Guillain-Barré syndrome: a case series and review of the literature, J. Immunother. 44 (7) (2021) 276–282, doi:10.1097/CJI.0000000000000364.

[7] D.B. Johnson, C.A. Nebhan, J.J. Moslehi, J.M. Balko, Immune-checkpoint inhibitors: long-term implications of toxicity, Nat. Rev. Clin. Oncol. 19 (4) (2022) 254–267, doi:10.1038/s41571-022-00600-w.

[8] L. Zimmer, S.M. Goldinger, L. Hofmann, et al., Neurological, respiratory, musculoskeletal, cardiac and ocular side-effects of anti-PD-1 therapy, Eur. J. Cancer 60 (2016) 210–225, doi:10.1016/j.ejca.2016.02.024.

[9] J.C. Kao, B. Liao, S.N. Markovic, et al., Neurological complications associated with anti-programmed death 1 (PD-1) antibodies, JAMA Neurol. 74 (10) (2017) 1216–1222.

[10] L. Müller-Jensen, S. Zierold, J. Versluis, et al., Characteristics of immune checkpoint inhibitor-induced encephalitis and comparison with HSV-1 and anti-LGI1 encephalitis: a retrospective multicentre cohort study, Eur. J. Cancer 175 (2022) 224–235, doi:10.1016/j.ejca.2022.08.009.

[11] A.C. Guidon, L.B. Burton, B.K. Chwalisz, et al., Consensus disease definitions for neurologic immune-related adverse events of immune checkpoint inhibitors, J. Immunother. Cancer 9 (7) (2021) 1–18, doi:10.1136/jitc-2021-002890.

[12] F. Bartels, M.M. Wandrey, A. Aigner, et al., Association between neuronal autoantibodies and cognitive impairment in patients with lung cancer, JAMA Oncol. 7 (9) (2021) 1302–1310, doi:10.1001/jamaoncol.2021.2049.