Immuntherapien und Neurologie

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GESUNDHEIT NORD
KLINIKVERBUND BREMEN

Erklärung zu Interessenkonflikten

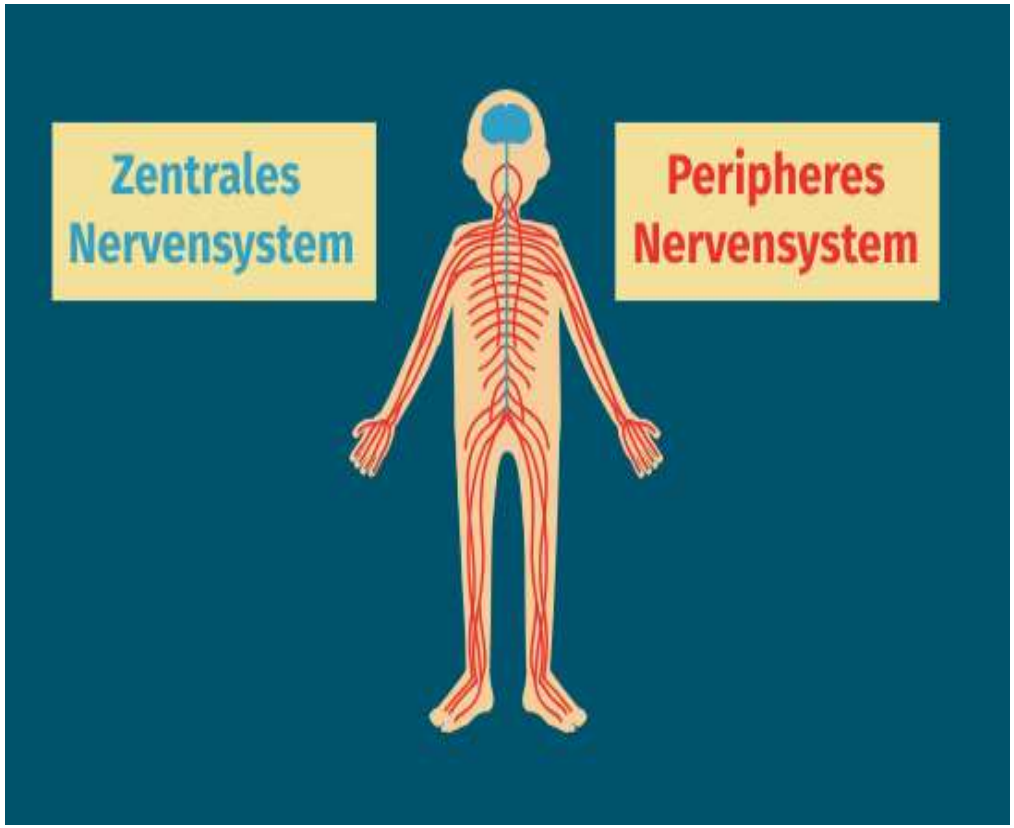
GESUNDHEIT NORD
KLINIKVERBUND BREMEN

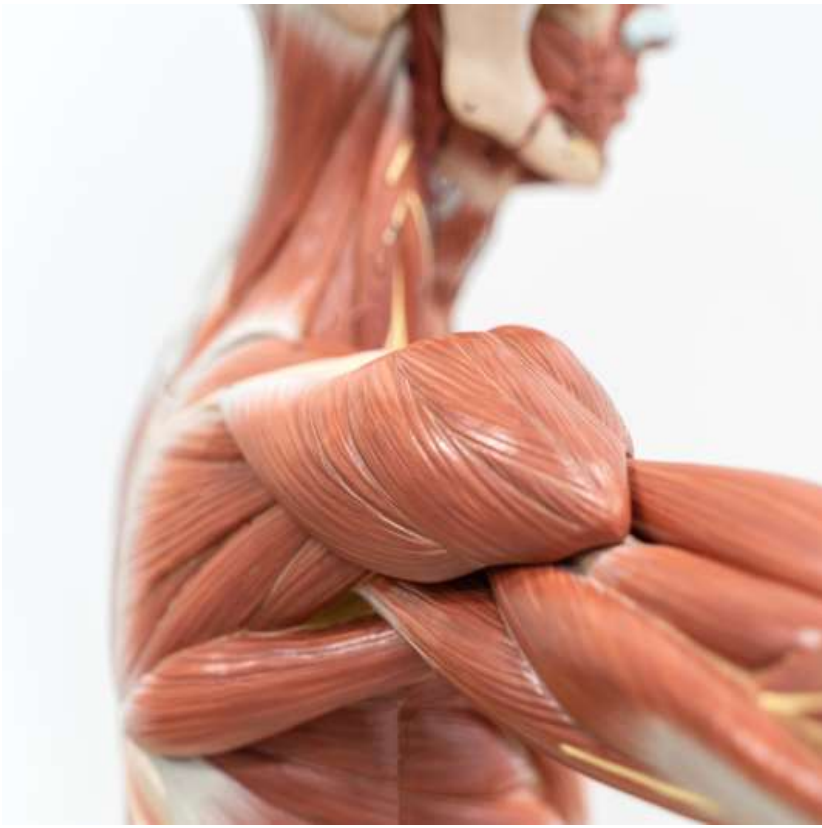
Honorar für Vorträge und Reiseunterstützung	Genzyme, Shire, Bristol-Myers Squibb, Boehringer-Ingelheim Pharma, Sanofi Aventis, Eisai, Novartis, Bayer Vital, Merz Pharma, Actelion, Lundbeck, Amicus, Merck-Serono, Lilly, Berlin-Chemie, Roche, Chiesie, NovoNordisk
Beraterhonorare	Genzyme, Shire, Bristol-Myers Squibb, AstraZeneca, Actelion, Amicus, Novartis, Teva, Roche, Lilly
Forschungsförderung	Amicus, Genzyme, Shire, Actelion, Novartis, Roche, Biogen

Neurologie

GESUNDHEIT NORD
KLINIKVERBUND BREMEN

Was machen Neurologen?





Neurologische Manifestationen der onkologischen Immuntherapie

GESUNDHEIT NORD
KLINIKVERBUND BREMEN

VIEWS & REVIEWS

Neurologic Adverse Events of Immune Checkpoint Inhibitors

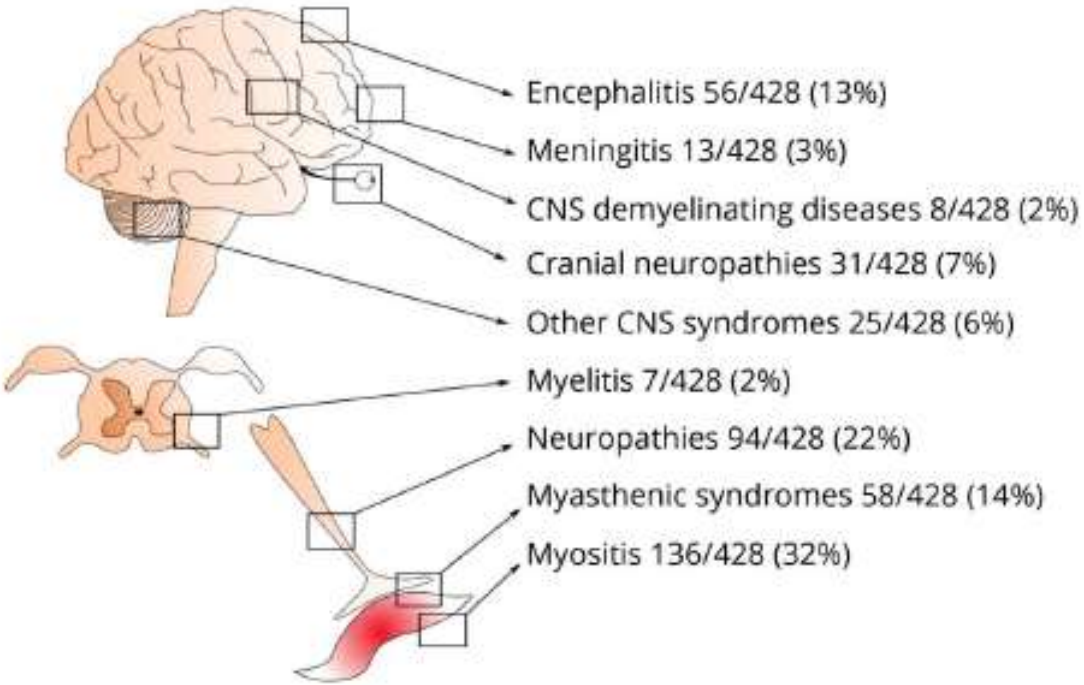
A Systematic Review

Alessandro Marini, MD,* Andrea Bernardini, MD,* Gian Luigi Gigli, MD, Mariarosaria Valente, MD, Sergio Muñiz-Castrillo, MD, Jérôme Honnorat, MD, PhD, and Alberto Vogrig, MD

Neurology® 2021;96:754-766. doi:10.1212/WNL.0000000000011795

AMERICAN ACADEMY OF NEUROLOGY®

A. Type and frequency of n-irAEs



Neurologische Manifestationen der onkologischen Immuntherapie

GESUNDHEIT NORD
KLINIKVERBUND BREMEN

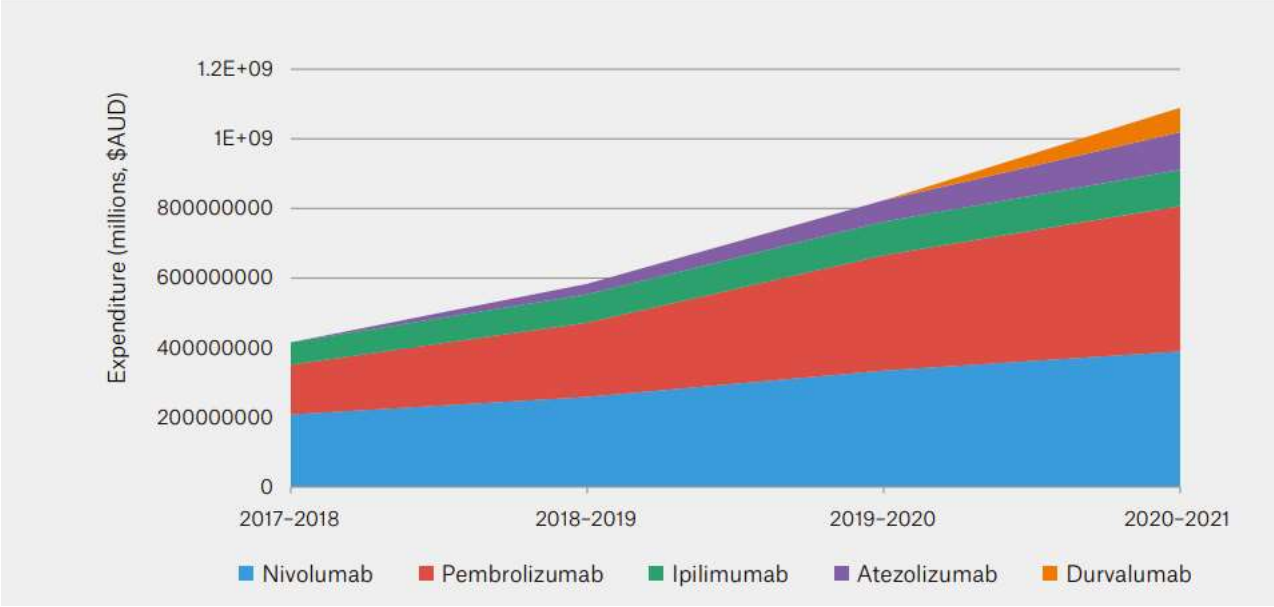
molecules

MDPI

Review

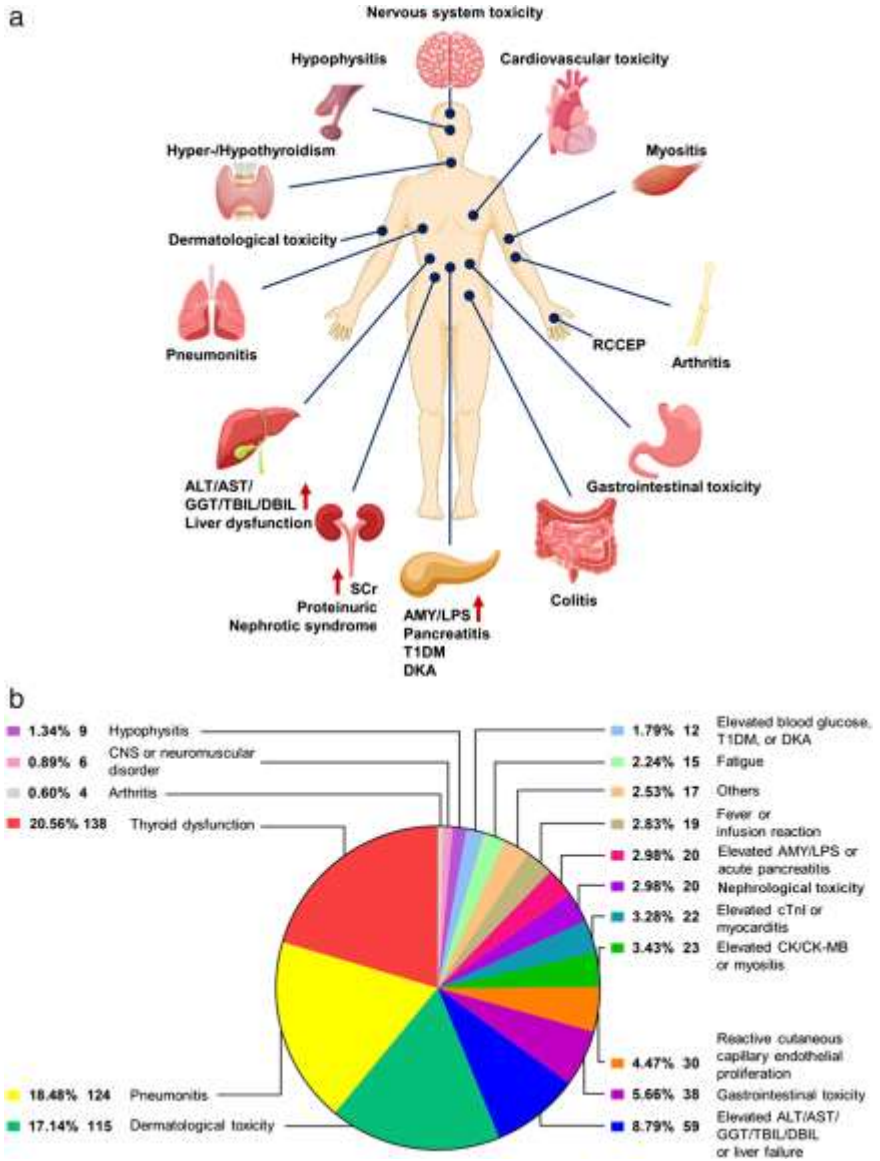
Emerging Management Approach for the Adverse Events of Immunotherapy of Cancer

Md. Mominur Rahman [1], Tapan Behl [2,*], Md. Rezaul Islam [1], Md. Noor Alam [1], Md. Mohaimenul Islam [1], Ali Albarrati [3], Mohammed Albratty [4], Abdulkarim M. Meraya [5] and Simona Gabriela Bungau [6,7,*]



Neurologische Manifestationen der onkologischen Immuntherapie

GESUNDHEIT NORD
KLINIKVERBUND BREMEN



Mogado et al., Vaccines 2022

Relevanz der neurologischen Manifestationen?

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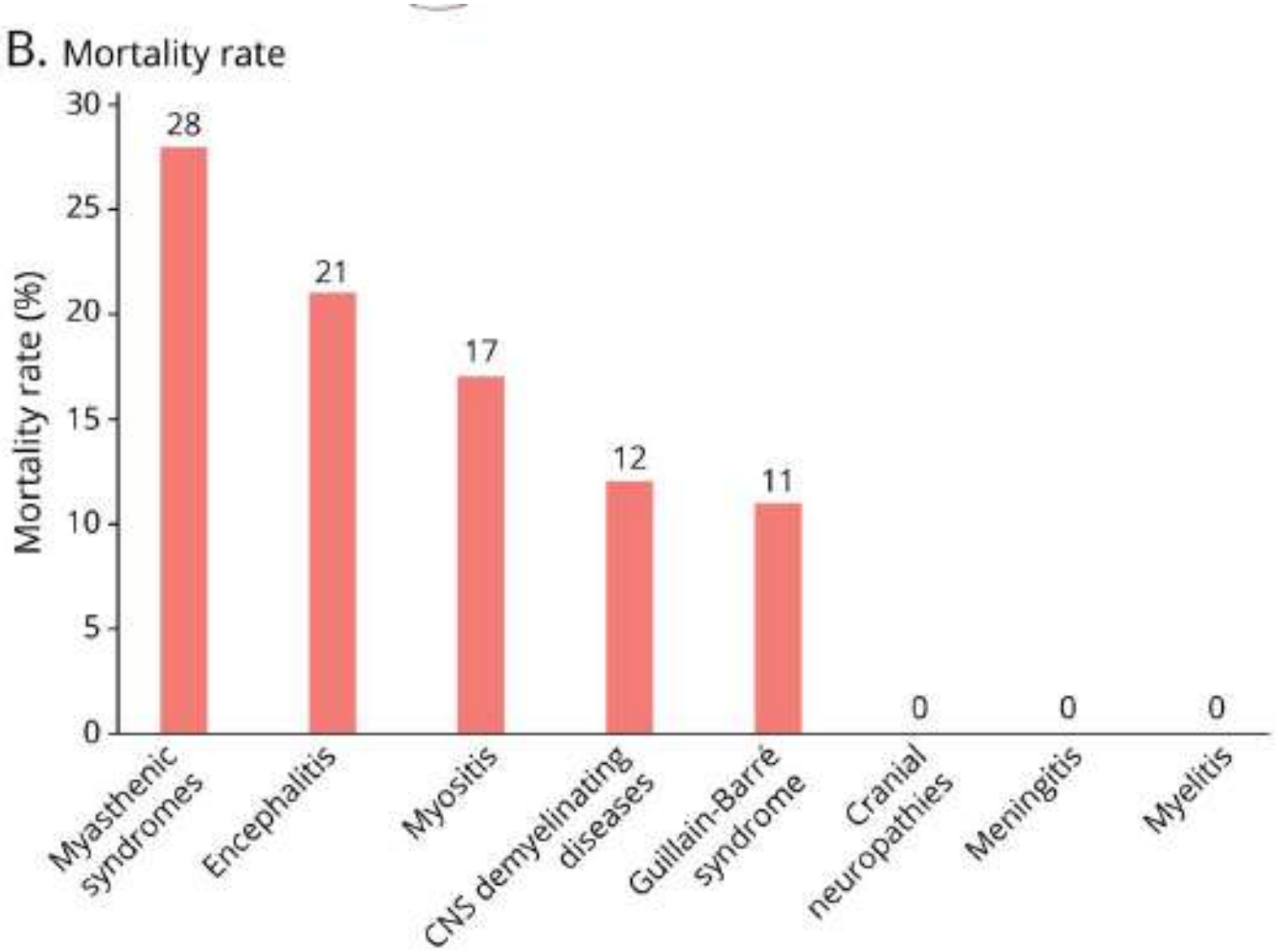
KLINIKVERBUND BREMEN



Marini et al. Neurology2022

Relevanz der neurologischen Manifestationen?

GESUNDHEIT NORD
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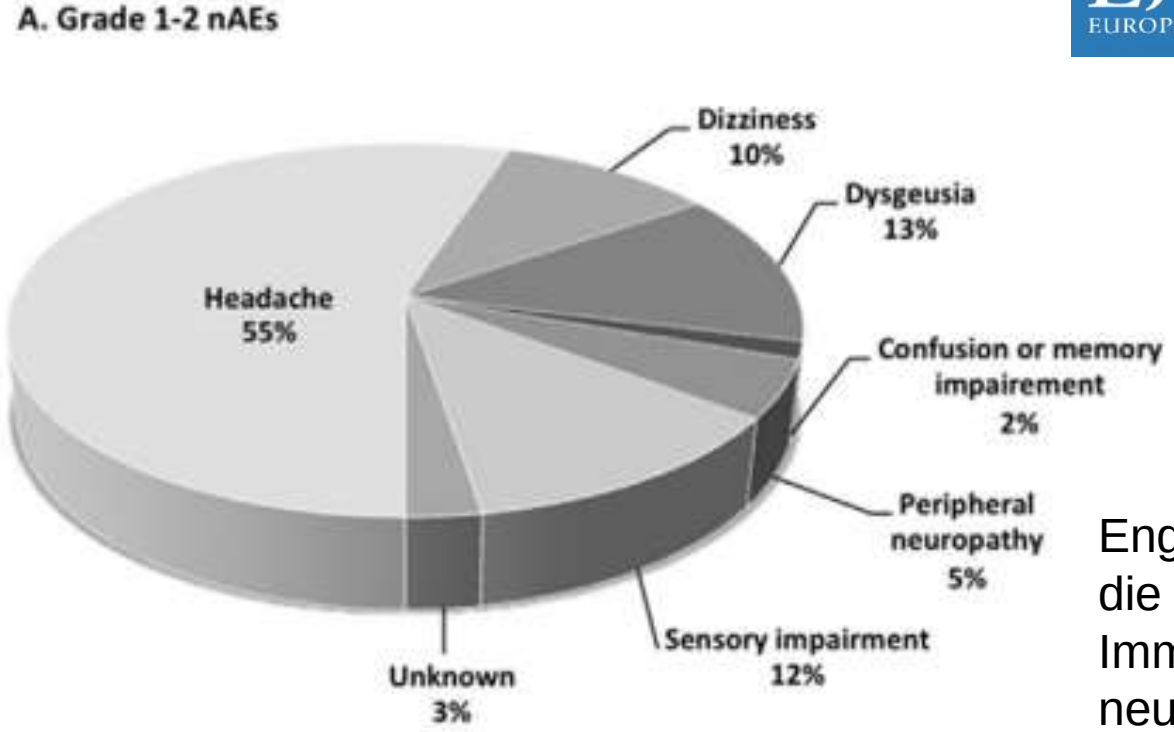
Neurological adverse events associated with immune checkpoint inhibitors: Review of the literature

S. Cuzzubbo • F. Javeri • M. Tissier • ... C. Belin • R. Ursu • A.F. Carpentier • Show all authors

EJC
EUROPEAN JOURNAL OF CANCER



Engmaschiges Monitoring für die Früherkennung von Immuntherapie-assoziierten, neurologischen Komplikationen ist essentiell!

Relevanz der neurologischen Manifestationen?

GESUNDHEIT NORD
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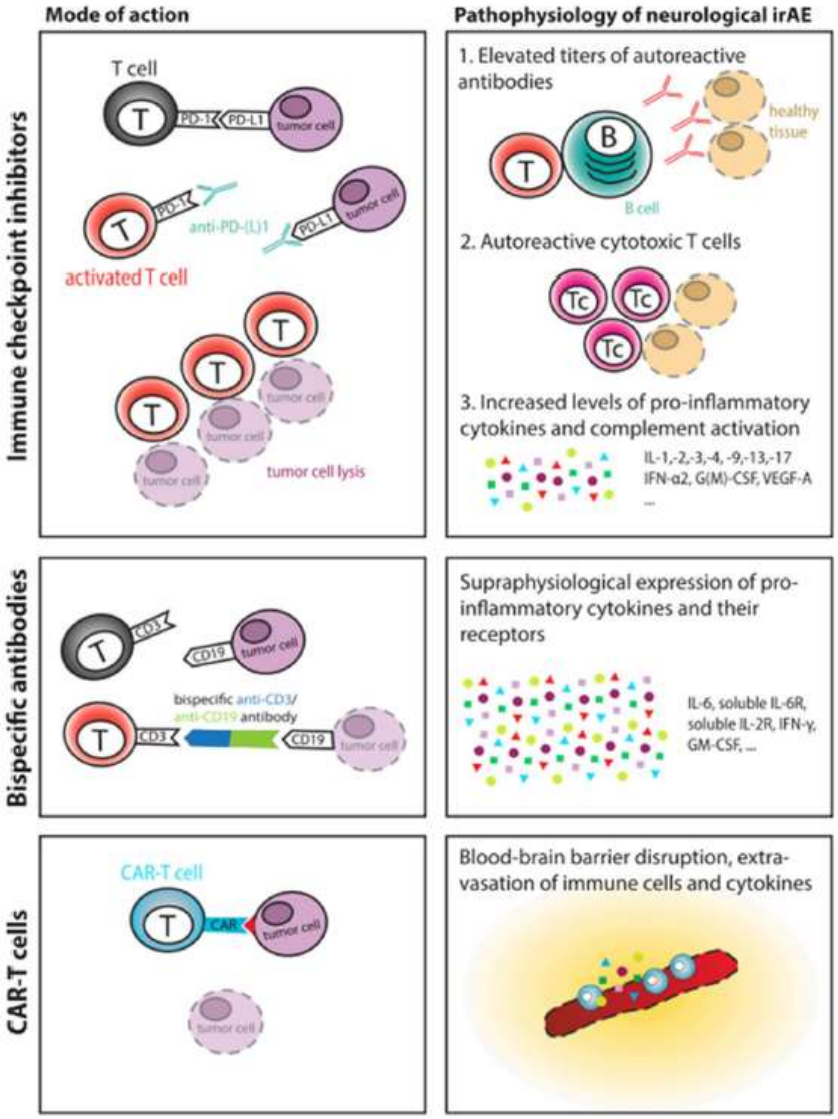
Immunmodulatorische Therapie	Neurologische NW
Immuncheckpoint-Inhibitoren (ICIs)	Peripheres Nervensystem: Myasthenie, Myositis, GBS/Neuropathien/Radikulitiden, Hirnnervenausfälle Zentrales Nervensystem: Enzephalitis, Meningitis, Myelitis
CAR-T-Zellen	Parästhesien, Extremitätenparesen, Sprachstörungen, Enzephalopathie, Delirium, kognitive Störungen, epileptische Anfälle, zerebrales Ödem
BiTE-Antikörper	Schwindel, Tremor, Vigilanzveränderungen, Delir, epileptische Anfälle, Enzephalopathie, zerebrales Ödem

Silvaieh et al. Spectrum Immunonkologie 2023

Strategien zur Detektion neurologischer Manifestationen

GESUNDHEIT NORD
KLINIKVERBUND BREMEN



Neurology of cancer immunotherapy

Amedeo De Grado[1] · Federica Cencini[1] · Alberto Priori[1]

Received: 23 April 2022 / Accepted: 22 July 2022 / Published online: 16 September 2022

- **CAR-T-Zellen und BiTE-Antikörper führen ausschließlich zu NW des zentralen Nervensystems**
- **Checkpoint-Inhibitoren: ZNS und peripheres Nervensystem sowie Muskel**

ZNS-Beteiligungen

GESUNDHEIT NORD
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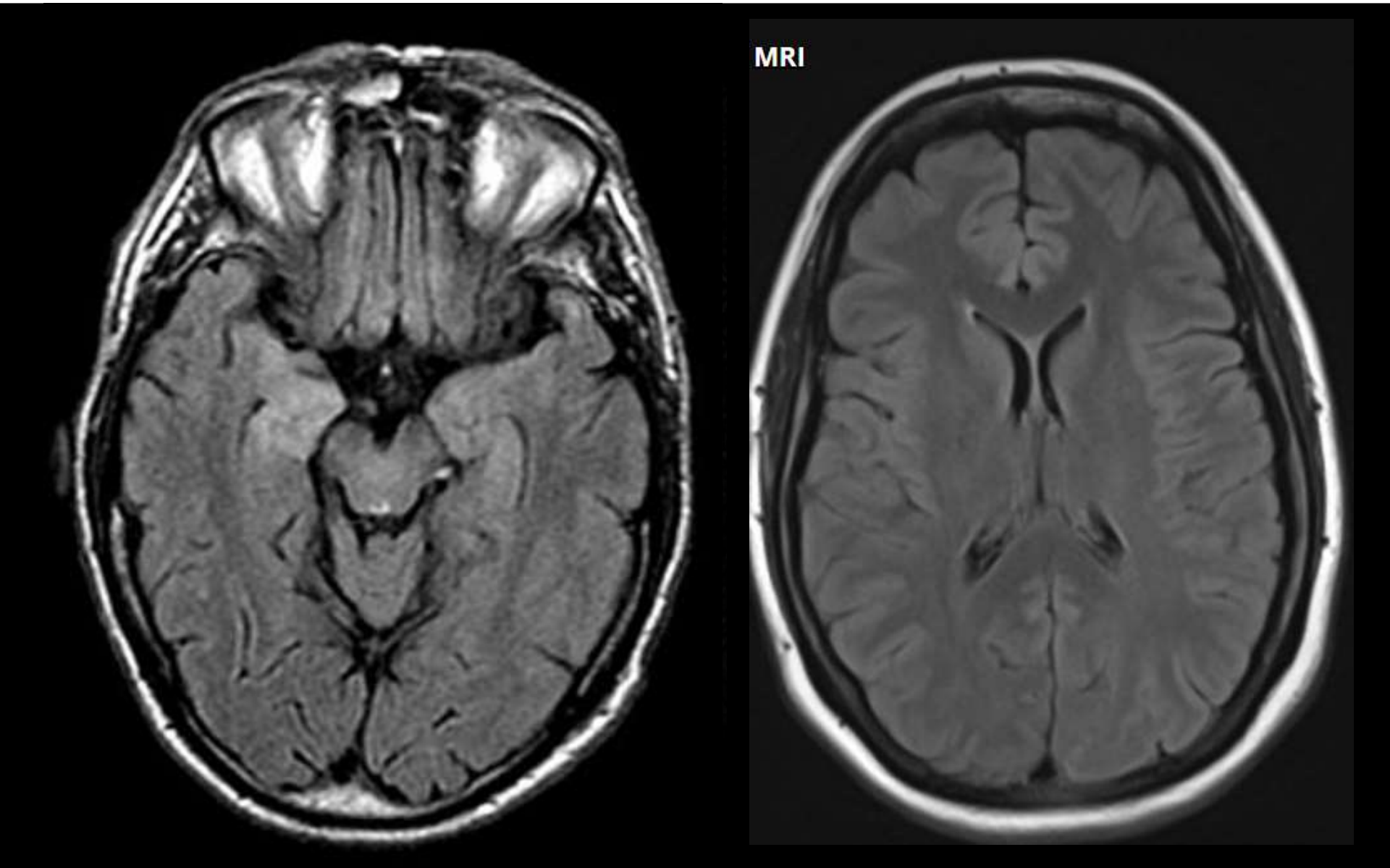

ZNS-Beteiligungen

GESUNDHEIT NORD
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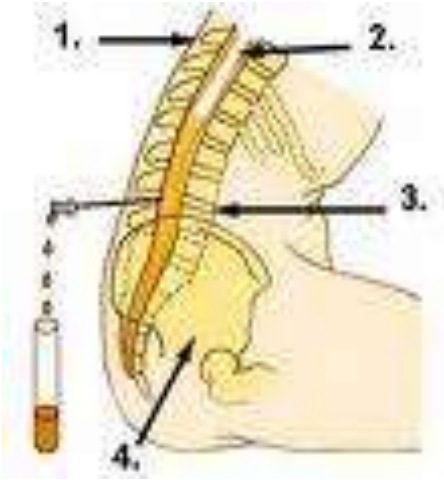
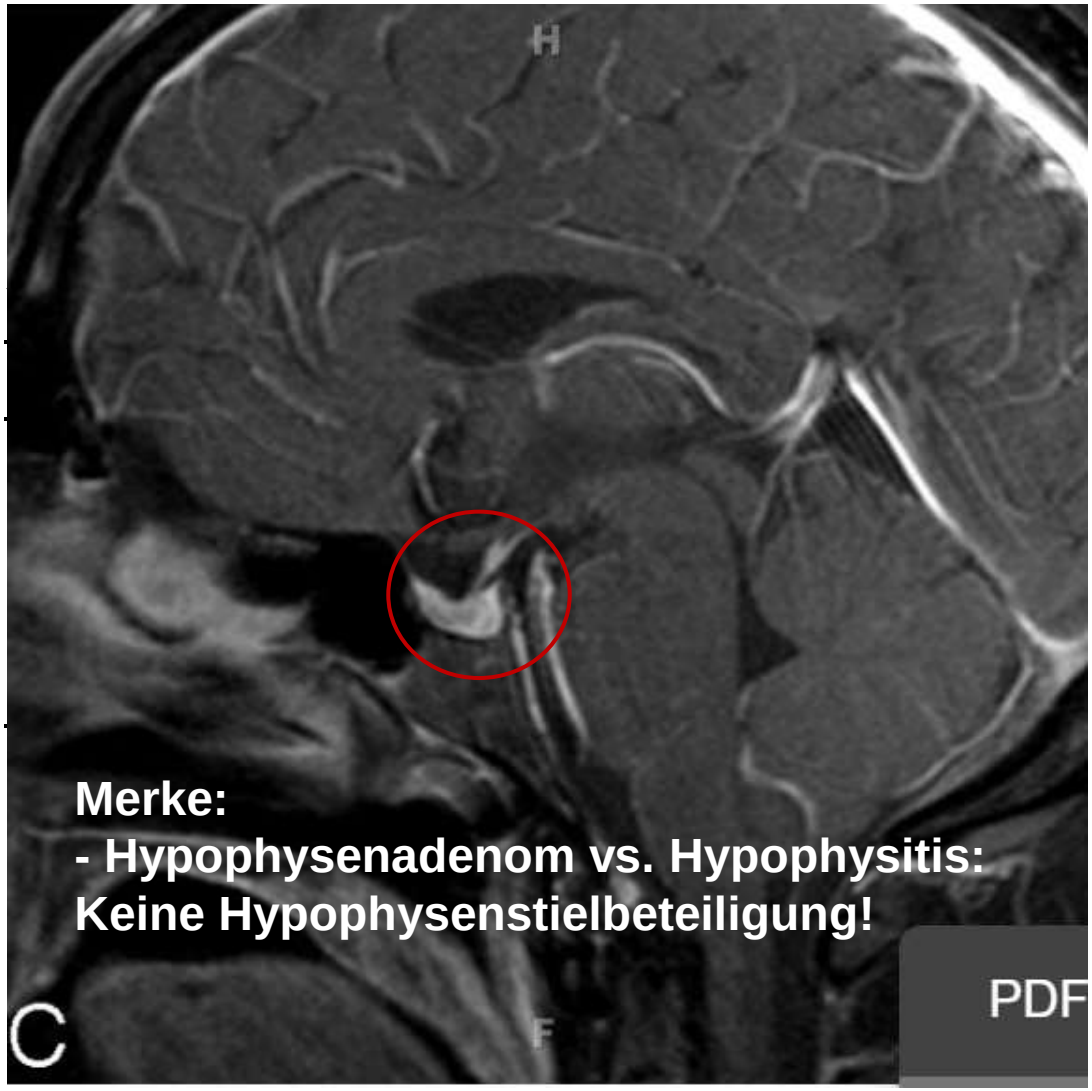
Enzephalitis
Meningitis

- Inzidenz: Um 1% der Patienten
- Symptome:
  - Unspezifische kognitive Defizite (100%)
  - Epileptische Anfälle (30%)
  - Vigilanzstörung
- Diagnostik:
  - Bildgebung: MRT
- Liquordiagnostik:
  - Sterile lymphozytäre Pleozytose (90%)
  - Antineuronale/Onkoneuronale Antikörper (50%)



ZNS-Beteiligungen

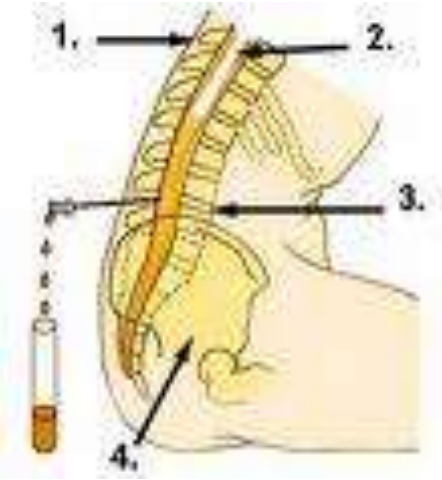
GESUNDHEIT NORD
KLINIKVERBUND BREMEN



Merke:
- Hypophysenadenom vs. Hypophysitis:
Keine Hypophysenstielbeteiligung!

300)

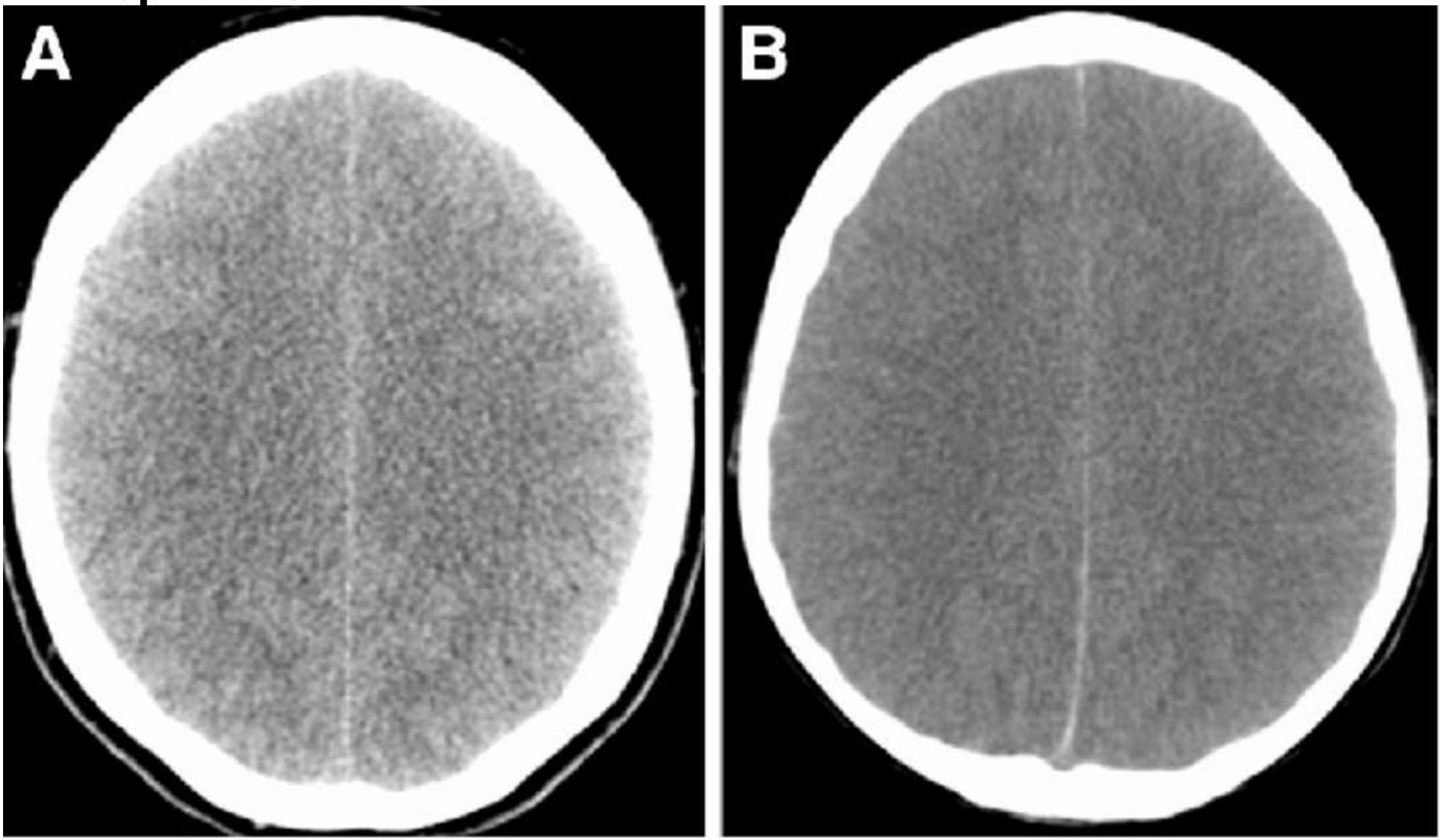
(30%)



ZNS-Beteiligungen

GESUNDHEIT NORD
KLINIKVERBUND BREMEN

Enzephalitis

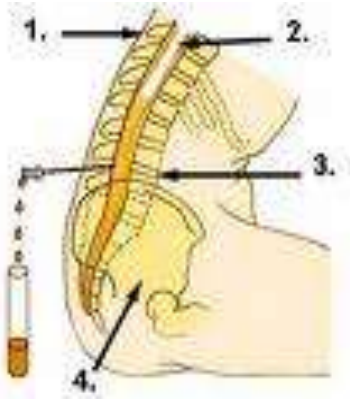


ZNS-Beteiligungen

GESUNDHEIT NORD
KLINIKVERBUND BREMEN

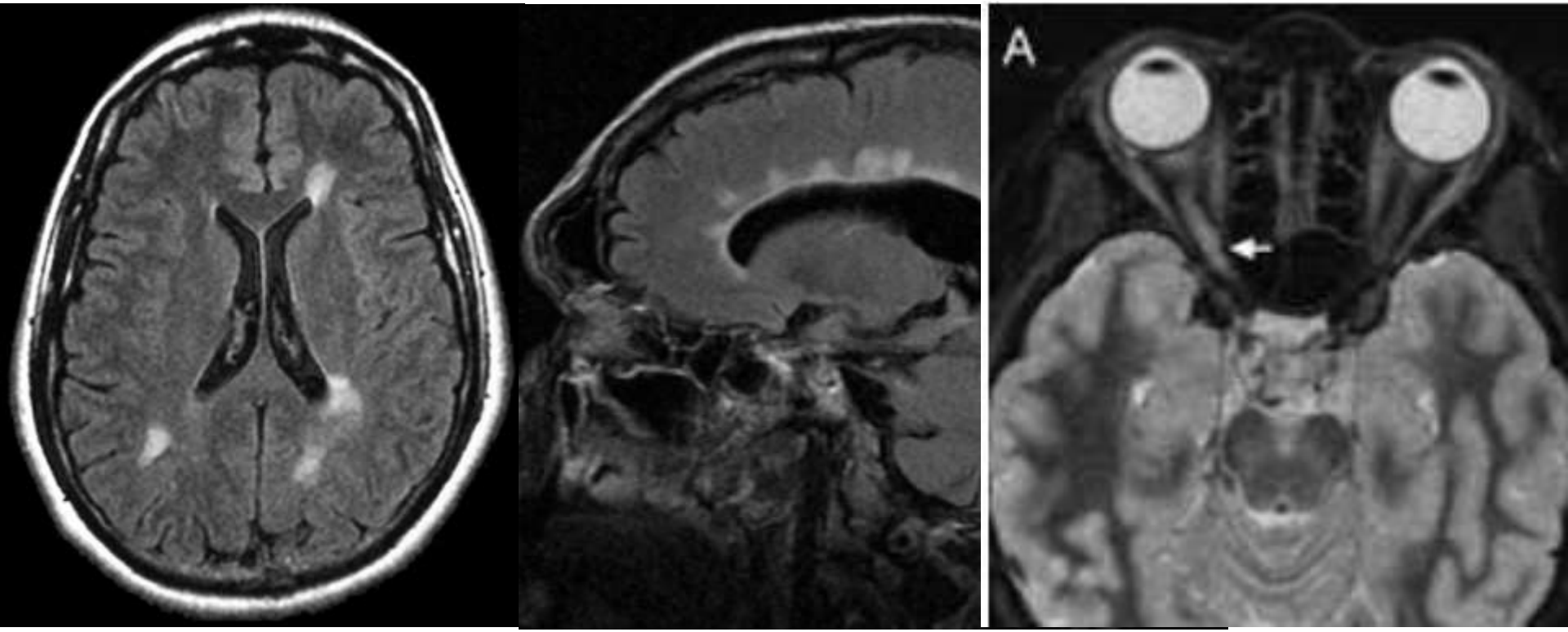
Demyelinisierende Erkrankungen

- Inzidenz: < 1% der Patienten
- Symptome:
  - Fokal-neurologische Ausfälle
  - Optikusneuritits
  - Myelitissymptome
- Diagnostik:
  - Bildgebung: MRT
- Liquordiagnostik:
  - Lymphozytäre Pleozytose (70%)
  - OKB / Autochtone Immunglobolinsynthese (95%)



ZNS-Beteiligungen

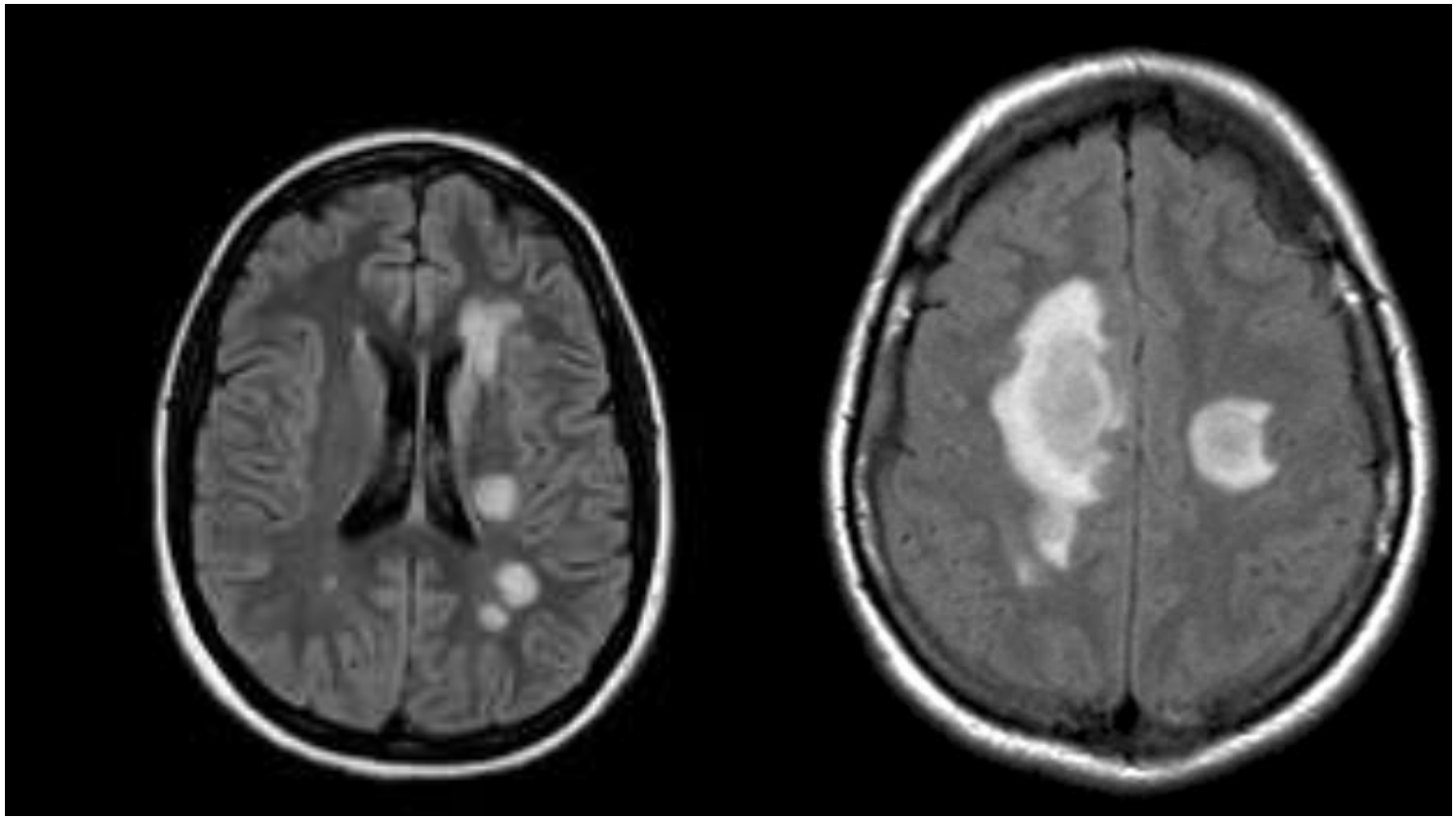
GESUNDHEIT NORD
KLINIKVERBUND BREMEN



„Klassische“ Multiple Sklerose

ZNS-Beteiligungen

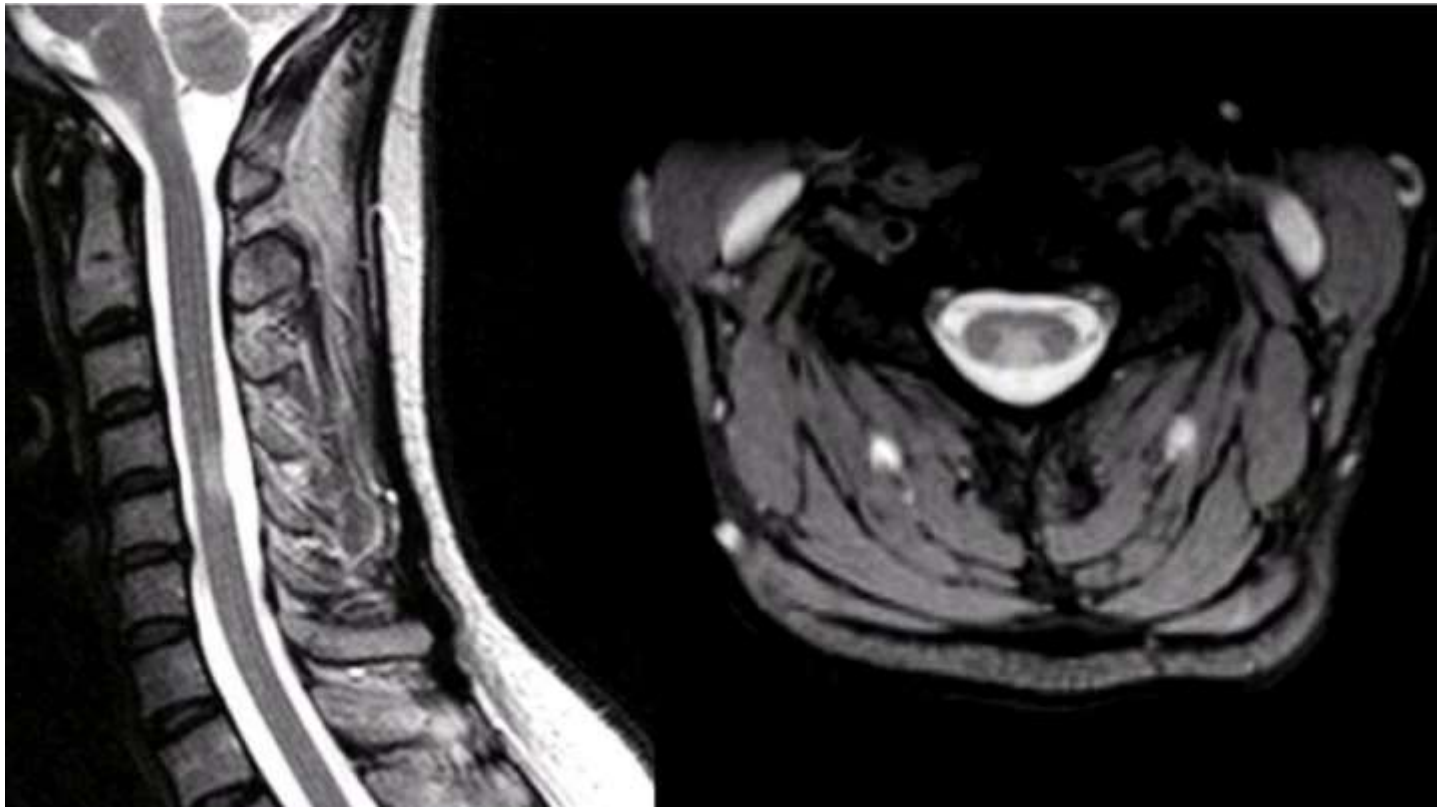
GESUNDHEIT NORD
KLINIKVERBUND BREMEN



ADEM
Akute demyelinisierende Enzephalomyelitis

ZNS-Beteiligungen

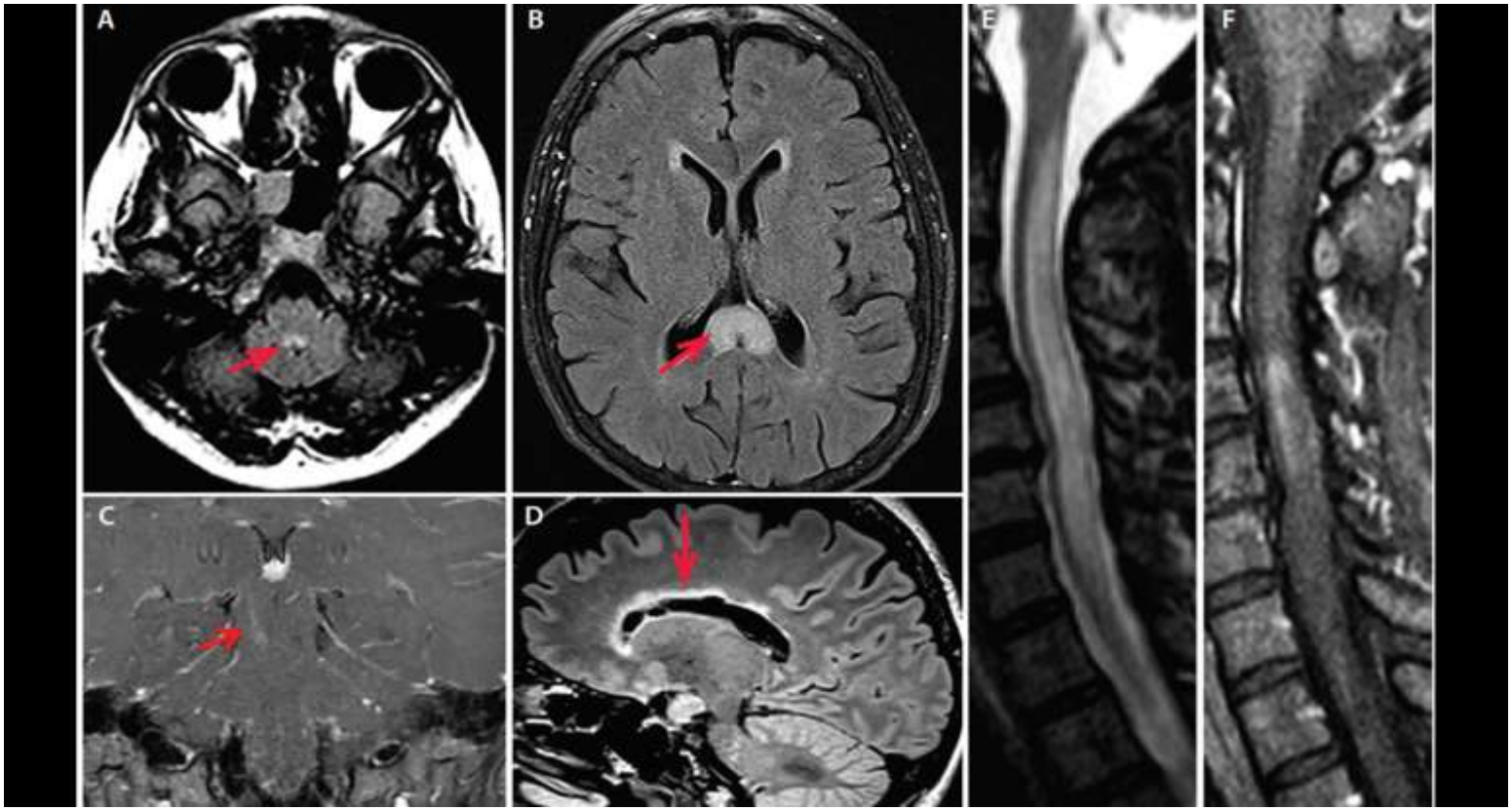
GESUNDHEIT NORD
KLINIKVERBUND BREMEN



Transverse Myelitis

ZNS-Beteiligungen

GESUNDHEIT NORD
KLINIKVERBUND BREMEN

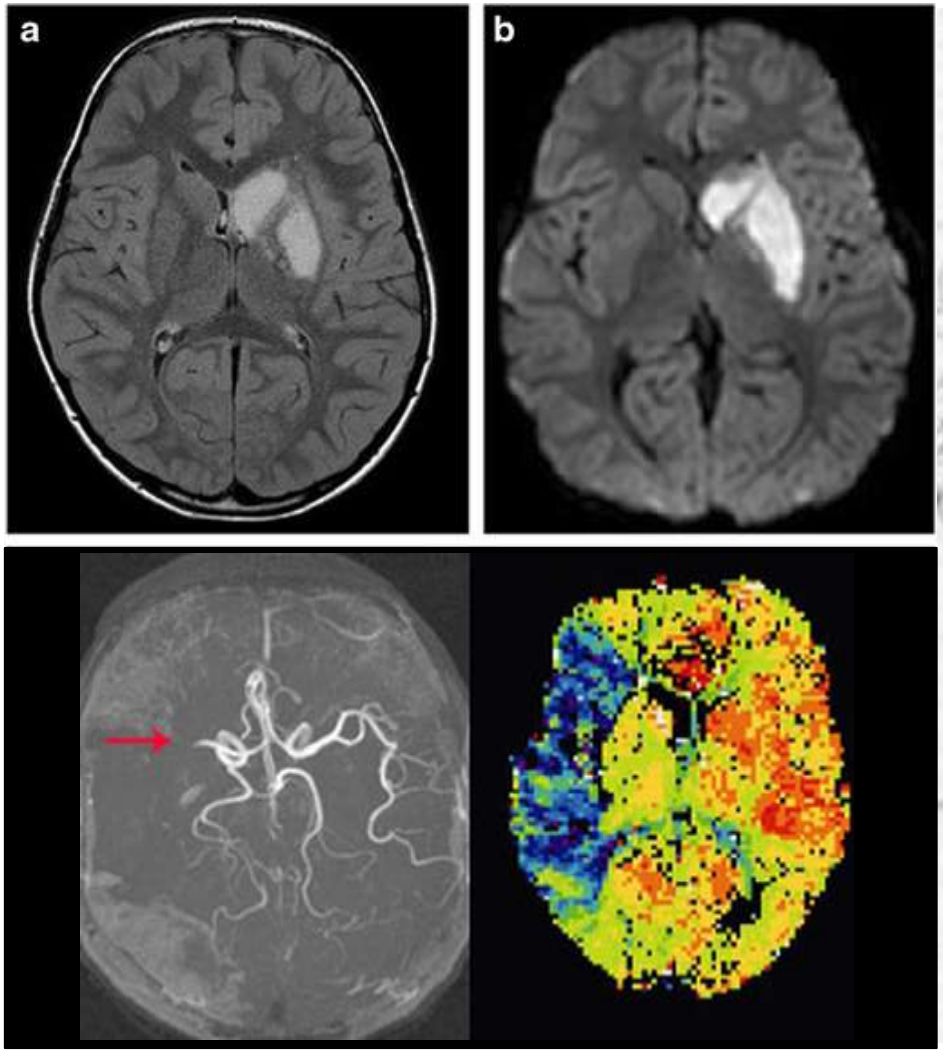


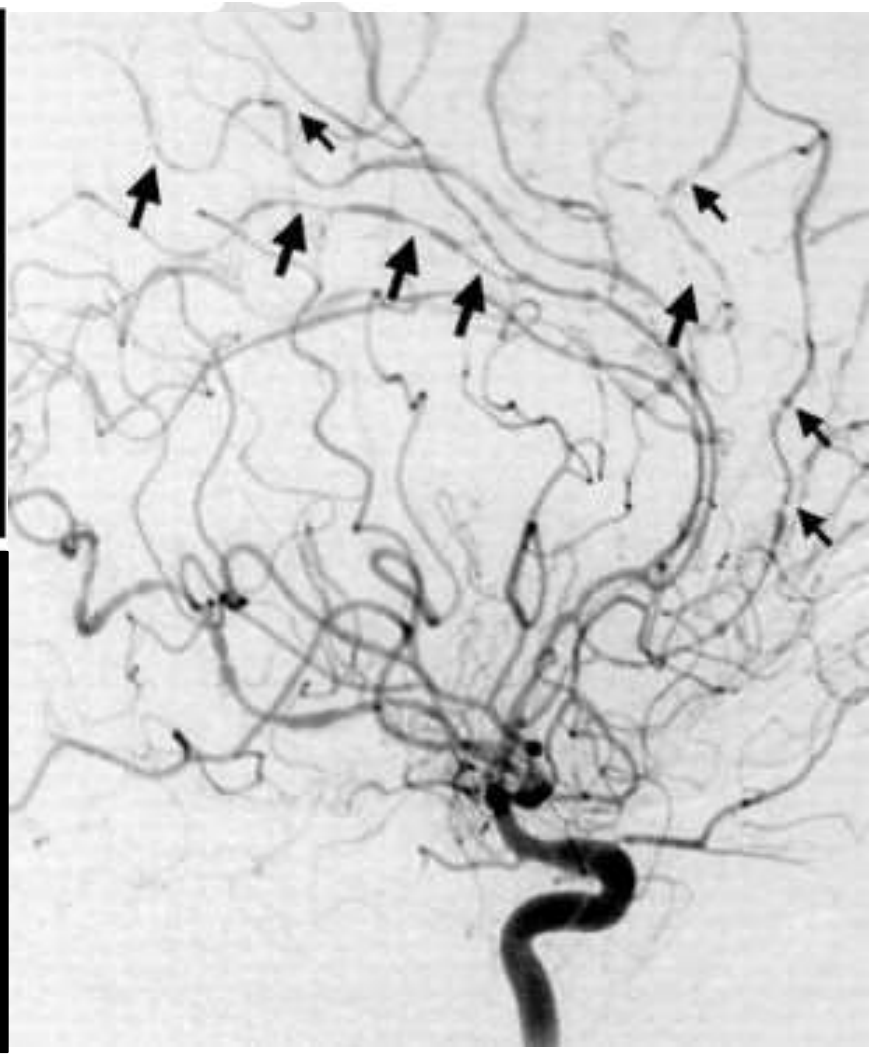
Neuromyelitis optica spectrum disease (NMOSD)

Aquaporin 4- AK

ZNS-Beteiligungen

GESUNDHEIT NORD
KLINIKVERBUND BREMEN

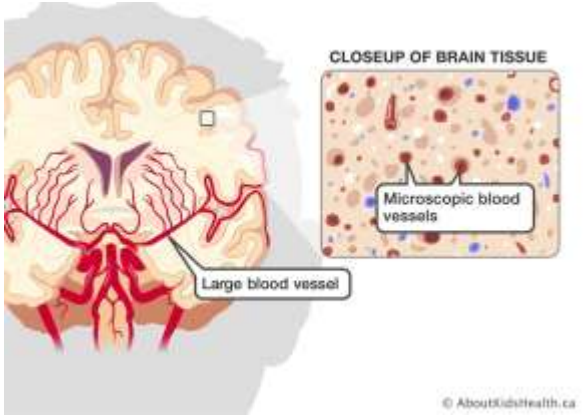




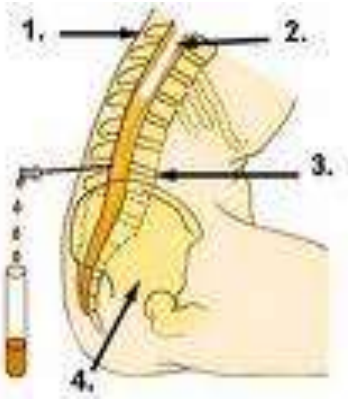
ZNS-Beteiligungen

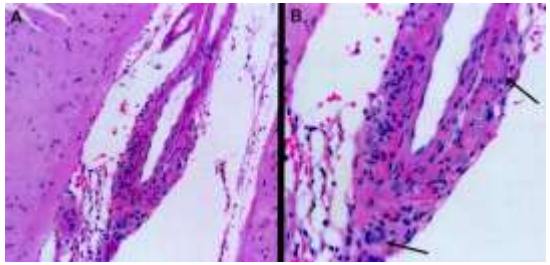
GESUNDHEIT NORD
KLINIKVERBUND BREMEN

Zerebrale Vaskulitiden



- Inzidenz: < 1% der Patienten
- Symptome:
  - Fokal-neurologische Ausfälle
  - Strokes oder ICB
- Diagnostik:
  - Bildgebung: CCT-CTA, Angiographie
- Liquordiagnostik:
  - Lymphozytäre Pleozytose (10%)
- Leptomenigeale Biopsie



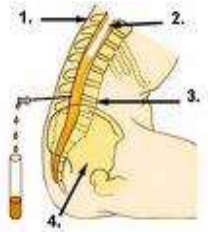


Beteiligungen des peripheren Nervensystems

GESUNDHEIT NORD
KLINIKVERBUND BREMEN

Immunvermittelte Neuroradikulopathien

- Inzidenz: 22% der Patienten
- Symptome:
  - Distal-symmetrische sensible und motorische Defizite
  - Rasch (GBS) oder langsam (CIDP) progredient
  - Beteiligung von Atemmuskulatur und autonomen Nerven
- Diagnostik:
  - Neurographie: Demyelinisierend

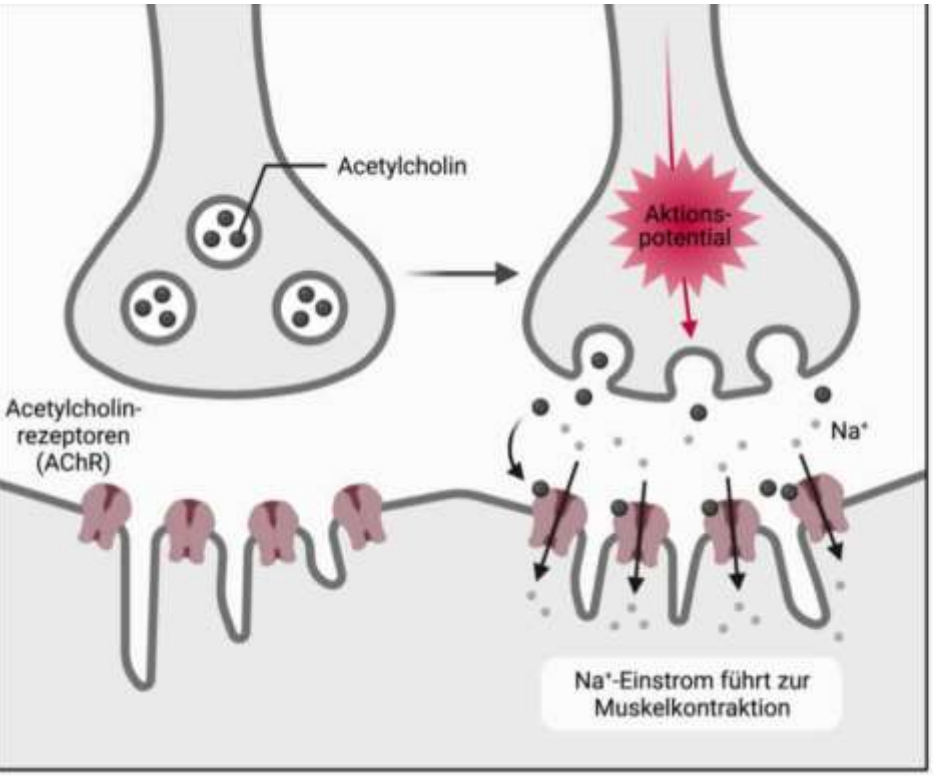


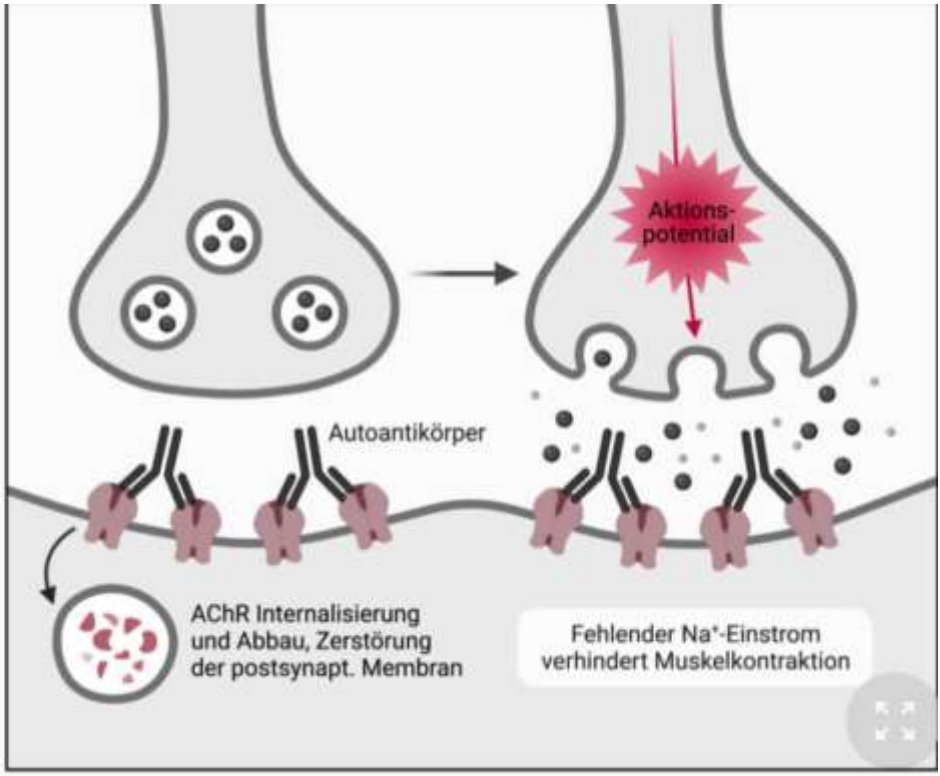
- Liquordiagnostik:
  - Zytalbuminäre Dissoziation (Keine Pleozytose, viel Eiweiß
- Therapie: Keine Wirksamkeit von Steroiden!

Beteiligungen des peripheren Nervensystems

GESUNDHEIT NORD
KLINIKVERBUND BREMEN

Myasthenia gravis



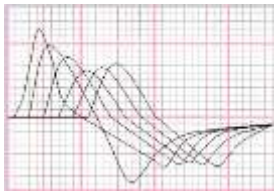


Beteiligungen des peripheren Nervensystems

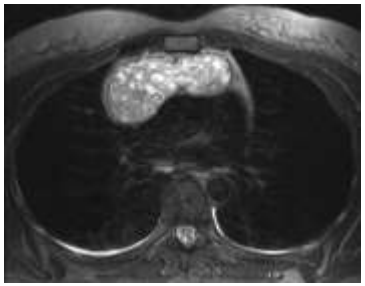
GESUNDHEIT NORD
KLINIKVERBUND BREMEN

Myasthenia gravis

- Inzidenz: 18% der Patienten
- Symptome:
  - *Belastungsabhängige* Paresen
  - Doppelbilder/Ptosis
  - Beteiligung der Atemmuskulatur



- Diagnostik:
  - Neurographie: Repetitive Stimulation (Decrement)
- Laborchemie:
  - Antikörpernachwies (AcholR-AK; MuSK-AK, Titin-AK)
- MRT Thorax: Thymom?



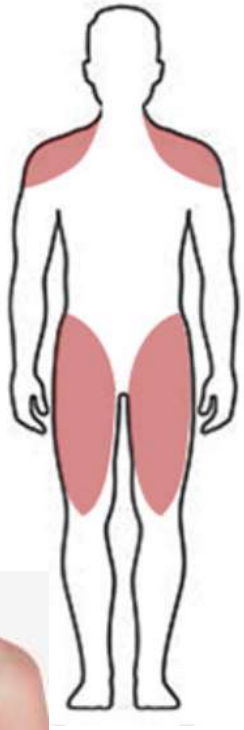
Cave: Unter Steroiden oft Initialverschlechterung!

https://youtu.be/F9Oqdh8Cbl0?si=5o5zpidGPIHFi0wR&t=33

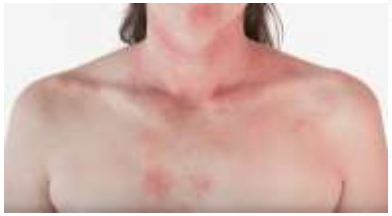
Beteiligungen der Muskulatur

GESUNDHEIT NORD
KLINIKVERBUND BREMEN

Myositiden



- Inzidenz: 32% der Patienten
- Symptome:
  - Proximale Paresen
  - Myalgien
  - Oft assoziiert mit dermatolog. Symptomen (18%)



- Diagnostik:
  - Elektromyographie
  - Laborchemie: CK ↑ + Myositis-AK (50%)

- Echokardiographie:
  - 7% zeigen Myokarditiden

Übersicht: Neurologische AE bei onkolokischen Immuntherapien

GESUNDHEIT NORD
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Zentrales Nervensystem:

- Enzephalitis
  - Hypophysitis
- Demyelinisierende ZNS-Erkrankungen
  - MS und Unterformen, NMOSD, Myelitis, Optikusneuritis
- Zerebrale Vaskulitis
  - Schlaganfälle, zerebrale Blutungen

Peripheres Nervensystem:

- Immunvermittelte Neuropathien (GBS/CIDP)

Muskel / Neuromuskuläre Übertragung:

- (Dermato) Myositis
- Myasthenia gravis

Therapieoptionen

GESUNDHEIT NORD
KLINIKVERBUND BREMEN

Akuttherapie immunvermittelter neurologischer Manifestationen

Hochdosierte Steroidtherapie
IVIG
Plasmapherese

- **Enzephalitis**
  Kraniotomie
  Intrakanielle Druckmessung
  Symptomat. Therapie neuropsychiatrischer Symptome
- **Hypophysitis**
  Hormonsubstitution
- **Demyelinisierende ZNS-Erkrankungen**
  Spezifische Immuntherapien
- **Immunvermittelte Neuropathien**
  Keine Wirksamkeit von Steroiden!
  IVIG, Plasmapherese
- **Myasthenie**
  Pyridostigmin

Prognose

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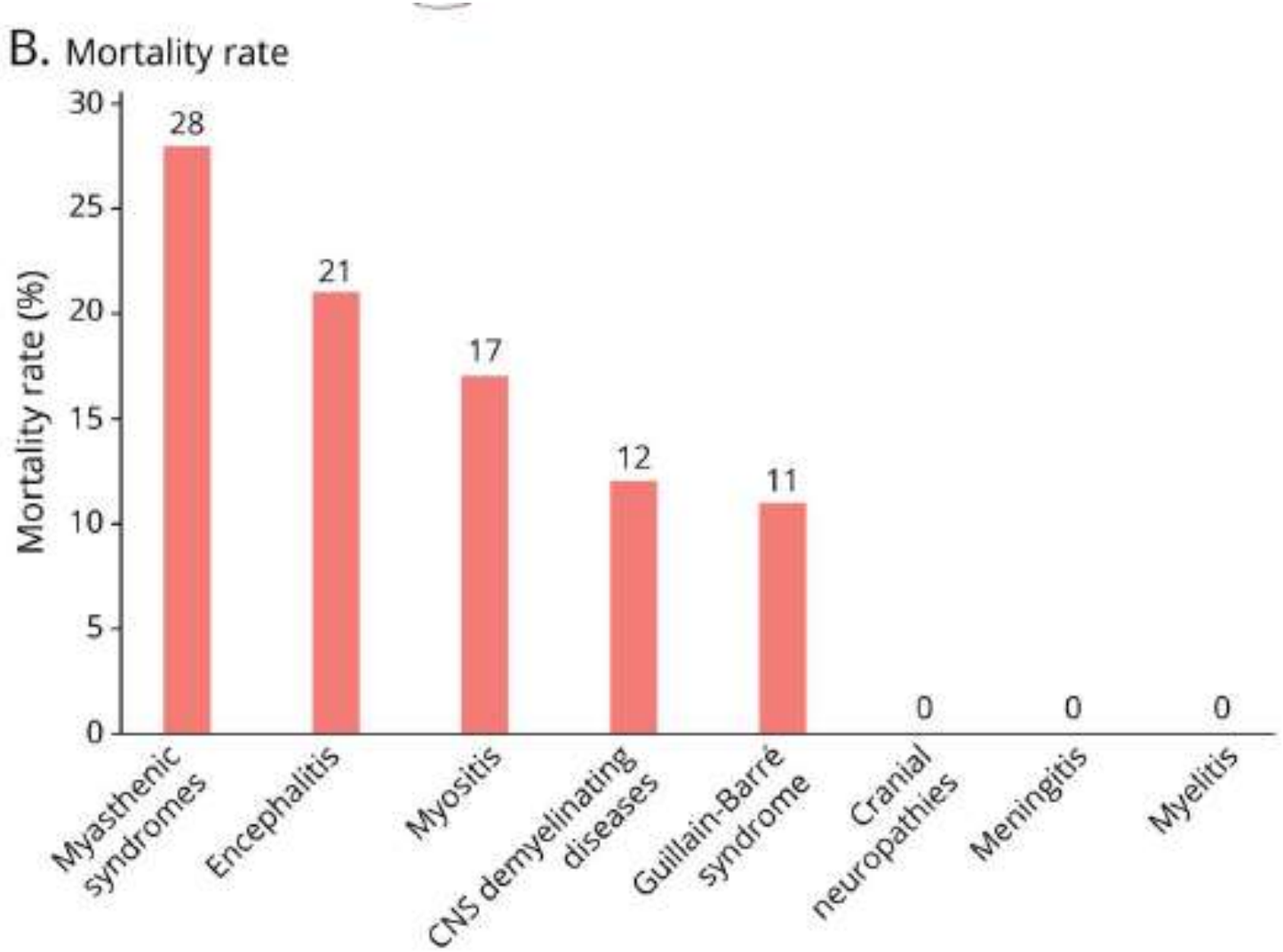

Marini et al. Neurology2022

Fazit für den klinischen Alltag

GESUNDHEIT NORD
KLINIKVERBUND BREMEN

Neurologische Nebenwirkungen bei Immunonkologischen Therapien…

- sind häufig
  (MG, Myositis, Neuropathien)
- haben eine schlechte Prognose
  späte Detektion, aufwendige Diagnostik, Pausieren der onkolog. Therapie
- Benötigen z.T. eine spezifische Therapie
  MS-Formen, NMOSD

Individuelle Risikoabschätzung vor Immuntherapie?

Detaillierte Anamnese auf immunvermittelte neurologische Erkrankungen

AK-Screening oder MRT derzeit nicht empfohlen

Fazit für den klinischen Alltag

GESUNDHEIT NORD
KLINIKVERBUND BREMEN

Table 1. Immune Effector Cell-Associated Encephalopathy (ICE) Score [103].

Domain	Allocated Points
Orientation to year, month, city, hospital	4
Naming of three objects	3
Following a command	1
Writing a standard sentence	1
Attention (counting backwards from 100 by 10)	1
Total number of points	10

Alsalem et al.; Curent Oncology 2023

GESUNDHEIT NORD
KLINIKVERBUND BREMEN

Central nervous system

Meningitis/Encephalitis:

Other considerations: Infectious, neoplastic, chemical meningitis (e.g. intrathecal chemoRx), hypophysitis, PRES, metabolic encephalopathy
Investigations: Serum metabolic panel, ANA and ANCA screen, MRI +/- gadolinium, lumbar puncture with microbiology screen, autoimmune and paraneoplastic antibodies in serum and CSF, anti-GQ1b (if suspected brainstem encephalitis)
Treatment:
- Neurology consultation
- Hold ICI
- Empiric antimicrobials pending investigation results.
- Milder cases of isolated meningitis (grade 1-2) can be monitored clinically or with an oral steroid taper
- 1000 mg IV methylprednisolone for 3-5 days for all cases of encephalitis
- IVIG (2g/kg), plasmapharesis, or rituximab (375 mg/m2) if inadequate response to steroids. Tacrolimus can be considered if no clinical or CSF parameter improvement after 5-7 days of treatment.

Hypophysitis

Other considerations: meningitis, pituitary apoplexy, venous sinus thrombosis
Investigations: MRI brain and sella +/- gadolinium, serum electrolytes, TSH, ACTH, AM cortisol, lumbar puncture
Treatment:
- Endocrinology, neuro-ophthalmology consultation
- Hold ICI
- Grade 1: stress dose corticosteroids, hormonal replacement as needed
- Grade 2-4 (or any sign of optic chiasm compression): 1000 mg IV methylprednisolone for 3-5 days followed by an oral taper to thr lowest possible physiologic maintenance dose, hormonal replacement as needed
- IVIG (2g/kg), plasmapharesis, or rituximab (375 mg/m2) if inadequate response to steroids

CNS demyelination

Other considerations: Infectious (syphilis, ,Lyme, PML), autoimmune (MS, NMO, MOG), toxic-metabolic (B12 or copper deficiency), neoplastic (leptomeningeal disease, metastasis)
Investigations: MRI brain, orbits, or spine +/- gadolinium (depending on clinical presentation), B12, HIV, syphilis, Lyme, ANA screen, lumbar puncture (routine studies, oligoclonal banding, JC virus), aquaporin-4 and MOG antibodies, paraneoplastic antibodies (particularly CRMP-5, Hu).
Treatment:
- Neurology +/- neuro-ophthalmology consultation
- Grade 1: Close observation can be considered if asymptomatic. Hold ICI if clinically symptomatic.
- Grade 2: Hold ICI, exclude alternative etiologies, oral prednisone (1 mg/kg) taper over 1 month.
- Grade 3-4: Permanent discontinuation of ICI. 1000 mg IV methylprednisolone for 5 days. Plasmapharesis if no improvement following 3 days of steroids. IVIG (2g/kg) or rituximab (375 mg/m2) may be considered persistent severe symptoms.

Acute Inflammatory Demyelinating Polyradiculopathy (AIDP)

Other considerations: Infectious polyradiculopathy, neoplastic (esp. leptomeningeal disease),
Investigations: Electrodiagnostics (NCS/EMG), MRI spine +/- contrast, lumbar puncture (routine studies, IgG index, infectious workup, cytology, flow cytometry), syphilis, Lyme, pulmonary function testing (ICU consultation for higher level airway support once vital capacity <20 ml/kg or mean inspiratory pressure <30 cmH2O)
Treatment:
- Neurology consultation
- Hold ICI for all grades given risk of rapid deterioration and respiratory decline
- Admit to hospital for frequent neurologic and respiratory monitoring. Close monitoring for autonomic dysfunction.
- IVIG (2 g/kg) or plasmapheresis.
- IV methylprednisolone (1000 mg daily for 5 days) followed by an oral steroid taper for grades 3-4. This is a distinction in treatment approach compared to idiopathic AIDP where steroids are not recommended.

Peripheral neuropathy

Other considerations: chemotherapy induced neuropathy, infectious, metabolic, nutritional, infiltrative (e.g. amyloidosis, neurolymphomatosis), paraneoplastic (i.e. anti-MAG, anti-Hu).
Cranial neuropathies (leptomeningeal disease, chemotherapy induced).
Investigations: Electrodiagnostics (NCS/EMG),serum HbA1c, vitamin B12, folate, TSH, serum protein electrophoresis, syphilis, Lyme, HIV, hepatitis B/C, ANA and ANCA, cryoglobulins. Anti-Hu or anti-Mag if clinical presentation or electrodiagnostic studies are suggestive of these syndromes.
Treatment:
- Neurology consultation
- Grade 1: Hold ICI and monitor clinically if ongoing progression after 1 week
- Grade 2: Hold ICI +/- oral prednisone taper (0.5-1 mg/kg) if ongoing symptom progression beyond 1 week. Re-challenge after symptom resolution could be considered.
- Grade 3-4: Permanent discontinuation of ICI. 1000 mg IV methylprednisolone daily for 5 days followed by an oral steroid taper. IVIG or plasmapheresis should be considered if no improvement with steroids occurs.

Peripheral nervous system

Myasthenia Gravis

Other considerations: Lambert Eaton myasthenic syndrome, myositis (commonly concurrent), AIDP variant (e.g. Miller-Fisher syndrome if ophthalmoparesis is the prominent feature)
Investigations: Electrodiagnostics (NCS/EMG), AChR +/- MuSK or LRP antibodies, CK and aldolase (for concurrent myositis), troponin, ECG, +/- echocardiogram (for concurrent myocarditis). Consider MRI brain or orbits to exclude leptomeningeal or infiltrative orbital disease causing multiple cranial nerve dysfunction. Pulmonary function testing (ICU consultation for higher level airway support once vital capacity <20 ml/kg or mean inspiratory pressure <30 cmH2O).
Treatment:
- Neurology consultation
- Medication review; discontinue any medication that could worsen MG if safe to do so.
- All grades: Hold ICI given risk of respiratory decline. Inpatient treatment and frequent respiratory monitoring is recommended.
- Grade 2: Hold ICI. Pyridostigmine (start 30 mg PO TID, titrate to symptom relief, max 120 mg QID; use is limited in those with excessive secretions). Oral prednisone (0.5 mg/kg daily), tapering after 3-4 weeks. If no improvement after 3-4 weeks, increase prednisone by 5 mg every 3 days to 1 mg/kg daily for 4-8 weeks before starting taper. May consider ICI re-challenge in Grade 2 if asymptomatic and steroid taper is complete.
- Grade 3-4: Permanent discontinuation of ICI. Methylprednisolone 1000 mg daily for 5 days followed by oral prednisone 1 mg/kg for 4-8 weeks before starting slow taper PLUS IVIG (2g/kg) or plasmapheresis (at least 5 sessions; initiated urgently in severe or rapidly decompensating patients). Rituximab (375 mg/m2) should be considered if no improvement. Tacrolimus or infliximab may also be considered.

Myositis

Other considerations: Myasthenia gravis (frequently concurrent), dermatomyositis, hypothyroid myopathy, drug-induced myopathy (e.g. statin, MEK inhibitors causing head drop), polymyalgia rheumatica (pain>weakness).
Investigations: Electrodiagnostics (NCS/EMG), ESR/CRP, renal/liver function, LDH, urinalysis, CK and aldolase, troponin, ECG, +/- echocardiogram (for concurrent myocarditis), AChR +/- MuSK or LRP antibodies (for concurrent myasthenia gravis), myositis antibodies if suspecting underlying dermatomyositis or anti-synthetase syndrome (further workup to be tailored according to clinical presentation, e.g. CT chest or skin biopsy). Consider muscle MRI +/- biopsy if diagnosis is unclear. Pulmonary function testing if concurrent myasthenia gravis.
Treatment:
- Neurology or rheumatology consultation
- Pain management: Pain typically improves with prednisone. Otherwise, gabapentin or pregabalin can be considered.
- Grade 1: May continue ICI. Monitor CK. Can consider oral steroids (0.5 mg/kg daily).
- Grade 2: Hold ICI. Oral steroids (0.5-1 mg/kg daily) if CK >3x ULN. May consider ICI re-challenge if strength and CK normalizes and on <10 mg/day of prednisone. Permanent discontinuation if severe muscle weakness or persistently abnormal paraclinical tests (CK, MRI, EMG, or histology).
- Grade 3-4: Permanent discontinuation of ICI. Inpatient management recommended. Oral prednisone (1 mg/kg daily) or IV methylprednisolone (1000 mg daily for 3-5 days) followed by oral prednisone 1 mg/kg daily. Plasmapheresis can be considered for refractory cases. Rituximab (375 mg/m2) or other immunosuppressive agents can be considered for maintenance therapy if no improvement occurs within 4 weeks.

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Fazit für den klinischen Alltag

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Table 1. Immune Effector Cell-Associated Encephalopathy (ICE) Score [103].

Domain	Allocated Points
Orientation to year, month, city, hospital	4
Naming of three objects	3
Following a command	1
Writing a standard sentence	1
Attention (counting backwards from 100 by 10)	1
Total number of points	10

The clinical presentation is heterogenous, but there are several distinct clinical patterns of neurologic irAEs that are becoming more evident with time. However, evaluation by a neurologist is recommended in order to characterize the syndrome and exclude other potential etiologies.

Onkologische Zentren benötigen eine neurologische Anbindung!

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Vielen Dank für Ihre Aufmerksamkeit!

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1904	2000	905	19000
foundation year	staff	beds	patients per year

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