Neurological Complications of Immuno - Therapies: Assessment, Evaluation and Treatment Paradigms

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The Warrior…

- **Fate whispers to the warrior – you will not withstand the storm – the warrior whispers back – I am the storm**

Albert Einstein…

- **A person who never made a mistake never tried anything new**

Overview

- **Introduction and Definition**
- **Pathophysiology**
- **Different Syndromes**
- **Treatment Paradigms**

Introduction:

- **Immunotherapy has emerged as a powerful therapeutic approach in many areas of clinical oncology and hematology**
- **The approval of ipilimumab, a monoclonal antibody targeting the immune cell receptor CTLA-4 marked the inception of the era of immune checkpoint inhibitors**
- **Antibodies targeting the PD-1 pathway have expanded the class of clinically approved immune checkpoint inhibitors**
- **Novel antibodies directed against other immune checkpoints are currently in clinical evaluation**
- **Bispecific antibodies, which link T cells directly to tumor cells as well as adoptive T cell transfer**
- **Immune cells engineered to express a chimeric antigen receptor, have been approved in certain indications**

Introduction:

- **Neurological complications associated with the use of these novel immunotherapeutic concepts have been recognized frequently**
- **Immune checkpoint inhibitors may cause various neurological deficits mainly by alterations of the central and peripheral nervous system's integrity**
- **These include radiculopathies, neuropathies, myopathies as well as myasthenic syndromes**
- **Side effects involving the central nervous system are less frequent but may result in severe clinical symptoms and syndromes**

Introduction:

- **The administration of chimeric antigen receptor (CAR) T cell is subject to rigorous patient selection**
- **Their use is frequently associated with neurological complications including encephalopathy and seizures**
- **These require immediate action and appropriate therapeutic measures**
- **Close clinical monitoring for neurological symptoms is key for early recognition of immunotherapy-related side effects**
- **Comprehensive diagnostic work-up and adequate therapeutic measures are essential to avoid further clinical deterioration and residual neurological deficits**

Pathophysiology:

- **Immune checkpoint inhibitors (ICPI) are a group of monoclonal antibodies, which aim at restoring and boosting the anti-tumor activity of cytotoxic T cells**
- **They act by interfering with inhibiting signals, which reduce the activity of T cells**
- **This can be achieved by blocking immune cell receptors expressed on T cells or by binding to the respective ligand, which is present on antigen-presenting or tumor cells**
- **The therapeutic efficacy of this concept has been demonstrated in many clinical trials across various types of cancer**

Pathophysiology:

- **The field is now dominated by drugs targeting the programmed cell death-1 (PD-1) pathway**
- **The first ICPI that obtained clinical approval was ipilimumab**
- **Ipilimumab binds to cytotoxic T-lymphocyte antigen 4 (CTLA-4) and thereby abrogates the inhibiting function of this molecule**
- **Ipilimumab has been approved for the treatment of advanced metastatic melanoma**
- **Most data on its clinical activity but also side effects and toxicity stem from melanoma patients**
- **The administration of drugs targeting either PD-1 or PD-L1 aims at allowing anergic but potentially cancer targeting T cells to execute their function**

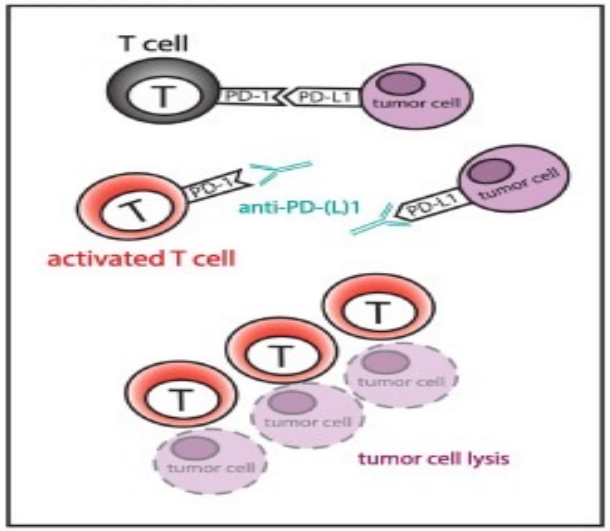
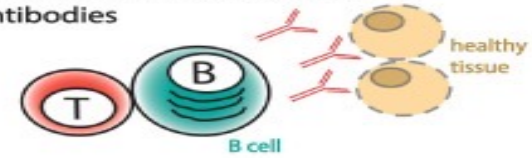
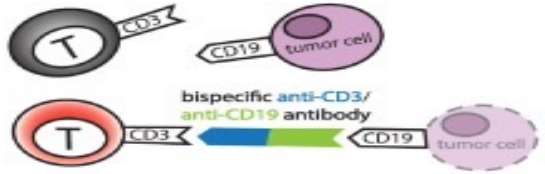
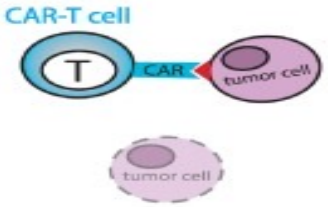
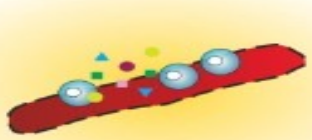
Pathophysiology:

- **Most, if not all, side effects might be due to overshooting T cell activation, the exact underlying pathophysiological mechanisms remain only partially understood**
- **It remains unclear if there are differences in the immune response in different organs in terms of timing, duration and intensity**
- **ICPI-associated side effects, frequently referred to as "immune-related adverse events" (irAE), are considered an inflammatory reaction which is promoted by different factors**
- **These include increasing T cell activity against antigens that are also expressed in healthy tissue This situation, with T cells recognizing antigens jointly expressed on tumor cells but also healthy tissue**

Pathophysiology:

- **Among the organs, which are frequently affected by irAE, are the skin, liver, gastrointestinal tract (mainly colon), different endocrine organs such as the thyroid and pituitary glands, but also lung, kidney, joints and muscles**
- **There is an increasing body of literature suggesting that virtually all organs may be affected by irAE**
- **More frequent irAE's were noticed with the use of CTLA-4-targeting agents compared to drugs, which interfere with the PD-1/PD-L1 axis The toxicity of the anti-CTLA-4 antibody ipilimumab is dose-dependent**
- **Combined approaches, which interfere with both pathways, have been reported to induce irAE more frequently and more severely compared to either treatment alone**

Different Syndromes:

	Mode of action	Pathophysiology of neurological irAE	Clinical manifestation
Immune checkpoint inhibitors		1. Elevated titers of autoreactive antibodies  2. Autoreactive cytotoxic T cells  3. Increased levels of pro-inflammatory cytokines and complement activation  IL-1,-2,-3,-4, -9,-13,-17 IFN-α2, G(M)-CSF, VEGF-A ...	**Peripheral nervous system:** - Polyradiculopathies - Neuropathies - Myasthenic syndromes - Myopathies **Central nervous system:** - Hypophysitis - Aseptical meningitis - Encephalitis (confusion, ataxia, headache, seizures)
Bispecific antibodies		Supraphysiological expression of pro-inflammatory cytokines and their receptors  IL-6, soluble IL-6R, soluble IL-2R, IFN-γ, GM-CSF, ...	**Cytokine release syndrome:** - Systemic symptoms: Fever, tachycardia, hypotension, hypoxia - Encephalopathy (dizziness, confusion, altered consciousness)
CAR-T cells		Blood-brain barrier disruption, extra-vasation of immune cells and cytokines 	**Immune effector cell-associated neuro-toxicity syndrome (ICANS):** - Encephalopathy including delirium and hallucinations - Cerebral edema, ischemia, hemorrhage

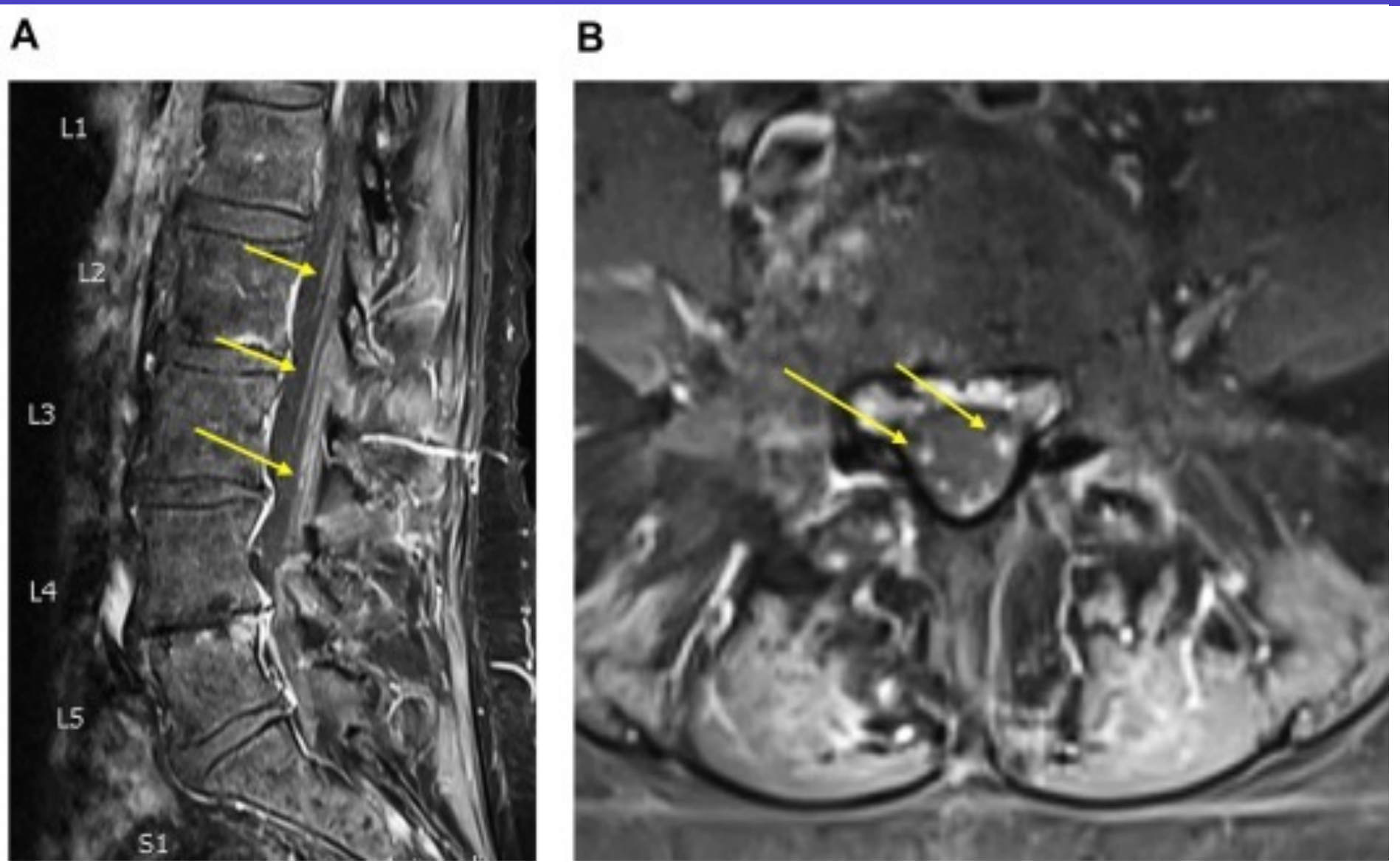
Peripheral Nervous System:

- **Polyradiculopathies and Neuropathies**
- **Clinical Features: Sensory deficits, Motor deficits, Areflexia Facultative involvement of cranial nerves (may be isolated)**
- **Overall Incidence: 1.3%, GBS-like syndrome: 0.1% – 0.2%**
- **Differential Diagnosis: GBS (Postinfectious, Paraneoplastic cases reported, Chronic Inflammatory Demyelinating Polyneuropathy / CIDP, Chemotherapy Associated Neuropathy**

Peripheral Nervous System:

- **Electrophysiological Work-Up**
- **Guillain Barre Syndrome (GBS) – similar / look alike presentation**
- **Laboratory Diagnostics including CSF: "Albumino - Cytological Dissociation" (elevated protein without pleocytosis) may not be present in ICPI-related GBS Type Syndromes**
- **MRI: Contrast - Enhancing Nerve Roots or Peripheral Nerves**
- **Treatment: Steroids, IVIG**

Peripheral Nervous System:



Myasthenia Type Syndrome:

- **Clinical Features: Ocular Myasthenia: Bilateral Ptosis, Diplopia**
- **Generalized Myasthenia: Generalized Weakness, Dysphagia, Dyspnea - may be accompanied by Myositis, Myocarditis**
- **Overall Incidence 0.12% – 1.16%**
- **Differential Diagnosis: Myasthenia Gravis / MG**

Myasthenia Type Syndrome:

- **Diagnostic Workup: Acetylcholine Receptor Auto - Antibodies in 60% of patients (more frequent in Myasthenia Gravis patients)**
- **Treatment: Acetylcholine Esterase Inhibitors (such as Pyridostigmine), Steroids (risk of initial clinical deterioration), IVIG, Plasmapheresis / PLEX**

Myopathies:

- **Clinical Features: Muscle pain, Progressive limb weakness (typically proximally accentuated), Necrotizing Autoimmune Myositis, Dermatomyositis and Polymyositis - Cardiac involvement more frequent than in Idiopathic Dermatomyositis/ Polymyositis (up to 30%)**
- **Overall Incidence: 0.58% – 1.67%**
- **Differential Diagnosis: Dermatomyositis, Polymyositis**

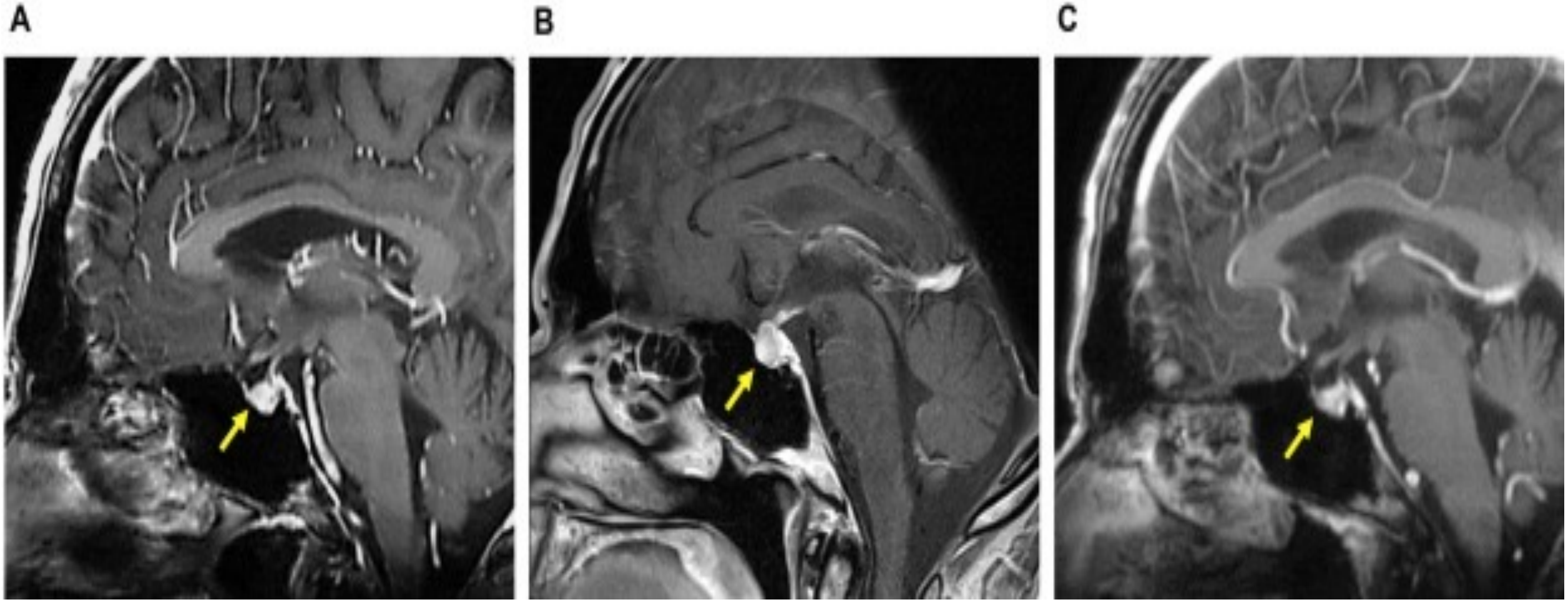
Myopathies:

- **Diagnostic Workup: Increased Serum CK, Muscle biopsy will reveal a Lymphocyte Infiltration**
- **Electromyography / EMG**
- **Cardiological workup if suspected Cardiac involvement**
- **Auto - Antibodies less frequently observed than in Dermatomyositis and Polymyositis**
- **Treatment: Steroids**

CNS / Hypophysitis:

- **Clinical Features: Fatigue, Generalized weakness, Headaches**
- **Overall Incidence: 1.00%**
- **Differential Diagnosis: Metastasis and Pituitary Apoplexy**
- **Diagnostic Workup: Hormonal Diagnostics and Panels**
- **Treatment: Hormonal Replacement Therapy, Neuro – Endocrinological Evaluation**

Hypophysitis:



CNS / Aseptic Meningitis:

- **Clinical Features: Neck stiffness, Headache, Fever, Nausea**
- **Overall Incidence: 0.36%**
- **Differential Diagnosis: Bacterial / Viral Meningitis, Neoplastic Meningitis / Leptomeningeal Disease (LMD)**
- **Diagnostic Workup: CSF Evaluation, Lymphocytosis, absence of Neoplastic cells / Infectious elements**
- **MRI: Meningeal Contrast Enhancement**
- **Treatment: Steroids, IVIG, Plasmapheresis / PLEX**

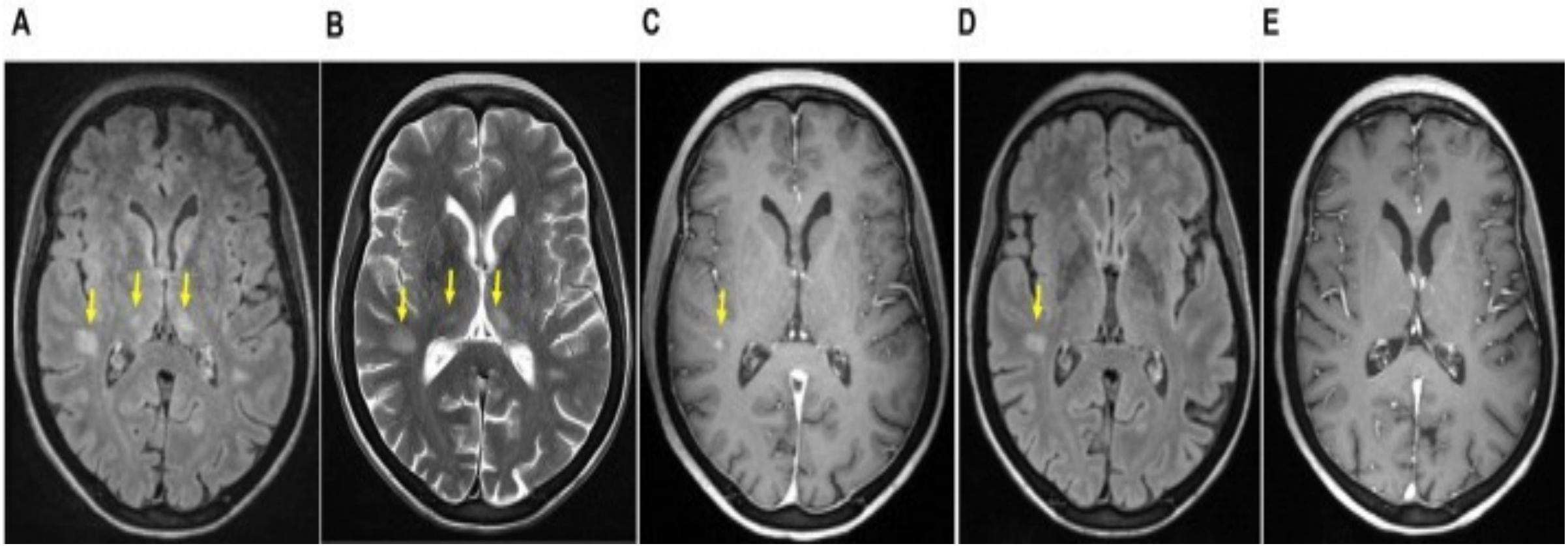
CNS / Encephalitis:

- **Clinical Features: Confusion, Fever, Headache, Seizures**
- **Overall Incidence: 0.84%**
- **Differential Diagnosis: Paraneoplastic Encephalitis, Infectious Encephalitis, Metabolic Encephalopathy**
- **Diagnostic Workup: Elevated IL-6 may be seen, exclusion of a metabolic etiology**
- **Paraneoplastic Autoantibodies: Anti - Ma2, Anti - Hu, Anti - NMDA**

CNS / Encephalitis:

- **Absence of Leptomeningeal Disease (LMD) evidence in CSF or an Infectious Etiology**
- **MRI Findings: T2 / FLAIR Hyperintensities, Contrast - Enhancing esions**
- **Treatment: Steroids, IVIG, Plasmapheresis / PLEX, Rituximab (Anti CD20)**

CNS / Encephalitis:



Cytokine Release Syndrome:

- **Clinical Feature: Encephalopathy, Altered Sensorium, Dizziness, Confusion, Headache, Tremor, Fever, Tachycardia, Tachypnea, Hypotension, Hypoxia**
- **Overall Incidence: Blinatumomab: 11% – 14.2% (≥Grade III: 0.8% – 5%)**
- **Chimeric Antigen Receptor (CAR) T Cell Therapy / CAR-T Cells: 18% – 100% (≥Grade III: 8% – 46%)**

Cytokine Release Syndrome:

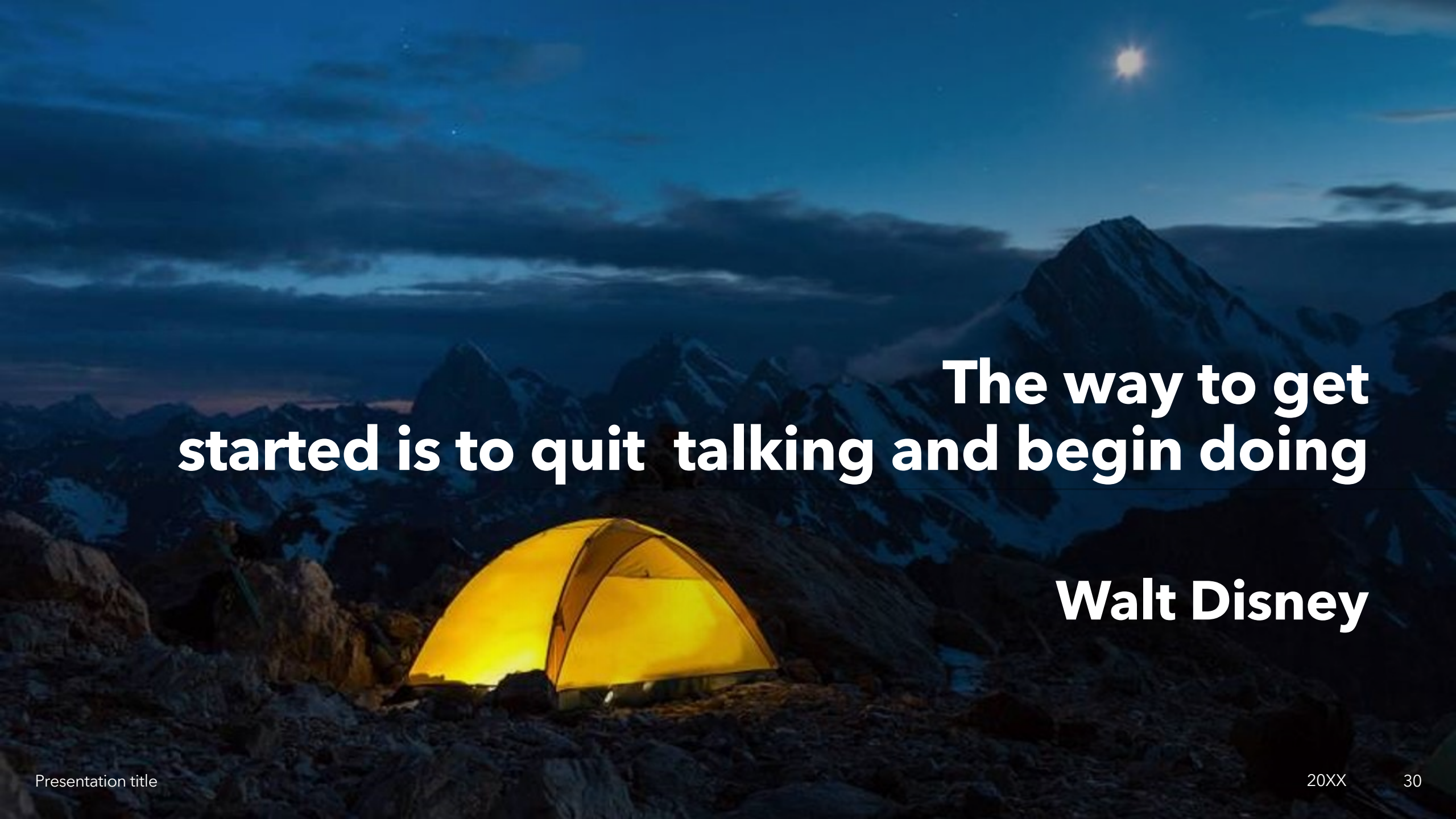
- **Differential Diagnosis: Immune Effector Cell Associated Neurotoxicity Syndrome (ICANS)**
- **Diagnostic Workup: Elevated Serum C-reactive protein, Ferritin, IL-6**
- **Treatment: Steroids**
- **Tocilizumab (Anti - IL-6R)**
- **Siltuximab (Anti - IL6)**

ICANS:

- **Immune Effector Cell Associated Neurotoxicity Syndrome (ICANS)**
- **Clinical Features: Encephalopathy, Delirium, Hallucinations, Seizures, Cerebral Edema, Ischemia, Hemorrhage**
- **Overall Incidence: CAR-T cells: 21% – 64% (≥Grade III: 12% – 31%)**
- **Differential Diagnosis: Cytokine Release Syndrome (CRS)**
- **Diagnostic Workup: EEG: Encephalopathic Pattern, MRI: Non - Specific T2 / FLAIR Hyperintensities**
- **Treatment: Steroids, Anti – Seizure Drugs**

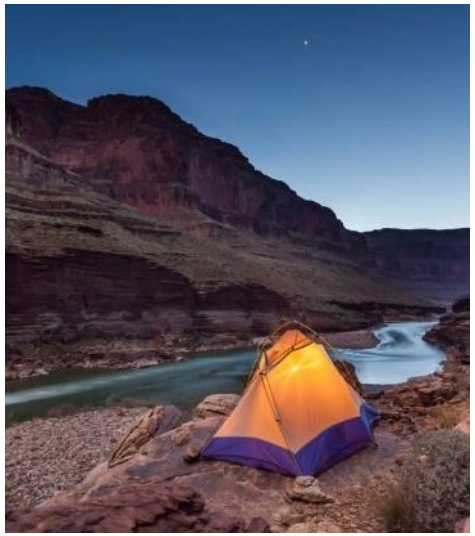
There is nothing impossible to they who will try –

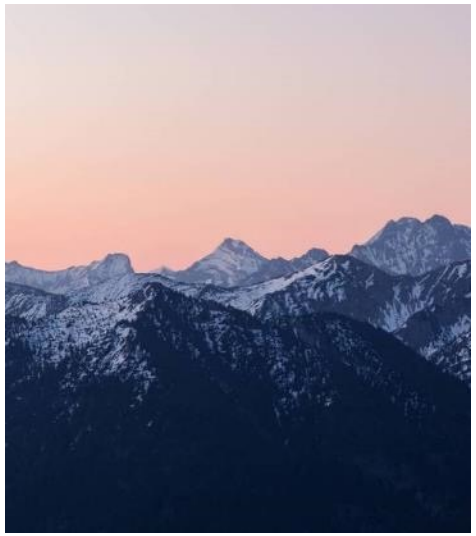
Alexander The Great


The way to get started is to quit talking and begin doing
Walt Disney

The people who are crazy enough to think they can change the world are the ones who do –

Steve Jobs





Thank you