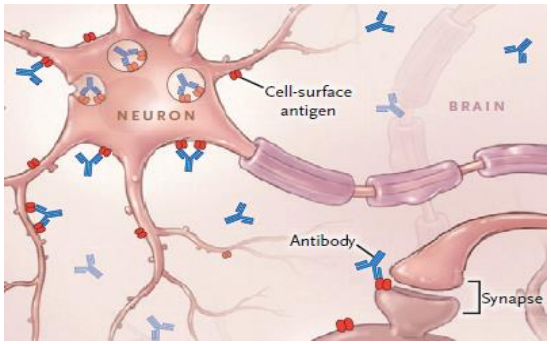
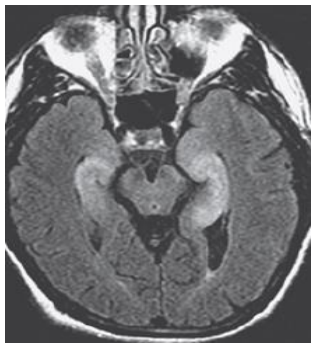
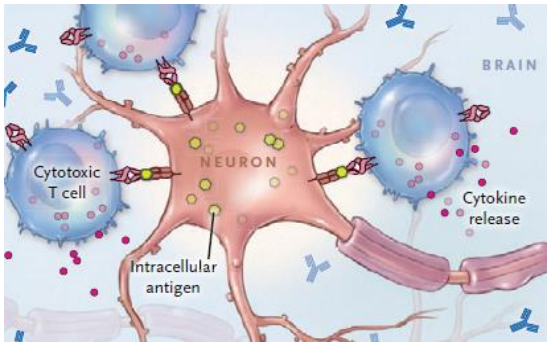
Sessão Clínica Hospital Prof. Doutor Fernando Fonseca
Serviço de Neurologia

Quadro consumptivo, dificuldade respiratória e rigidez – apresentação sistémica de doença neurológica imunomediada







Preletor: Dr. Francisco Bernardo
Responsável: Dra. Amélia Nogueira Pinto

CASO CLÍNICO

Homem, 49 anos
Leucodérmico

ANTECEDENTES PESSOAIS:

- Perturbação de ansiedade
- Sem outras doenças conhecidas

HÁBITOS:

- Tabagismo (30 UMA)
- Sem outros consumos tóxicos

MEDICAÇÃO HABITUAL:

- Fluoxetina 20 mg 1cp PA; cloxazolam 2 mg 1/2cp PA e ao deitar

CASO CLÍNICO

HISTÓRIA DA DOENÇA ATUAL

Janeiro 2018

Disfagia, odinofagia, dificuldade respiratória
Perda ponderal > 10% (60Kg » 45Kg) durante 1 mês

Endoscopia digestiva alta:
gastrite não erosiva, bulbite erosiva e refluxo biliar.
Inicia omeprazol 20mg 1cp jejum

20 Abril 2018

SU HFF

29 Maio 2018

Consulta de Medicina Interna
"estrabismo de novo?"

3 Junho 2018

SU HFF
2 semanas de diarreia
(> 3 dejeções diárias)

12 Junho 2018

Internamento eletivo
Medicina Interna

CASO CLÍNICO

INTERNAMENTO SERVIÇO MEDICINA INTERNA

12 Junho a 3 Agosto 2018

Exame objetivo geral:

- Vígil e orientado.
- Hemodinamicamente estável.
- Apirético.
- Mucosas pálidas
- Muito emagrecido. Peso: 43 Kg.
- Pescoço: sem adenopatias palpáveis; palpação tiroideia sem aumento do volume e sem nódulos palpáveis.
- AC: tons rítmicos, sem sopros ou extrassons.
- AP: MV mantido e simétrico, sem ruídos adventícios.
- Abdómen: emagrecido, mole, depressível, indolor à palpação, sem massas ou organomegálias palpáveis.
- MIs sem edema ou sinais de TVP.

CASO CLÍNICO

INTERNAMENTO SERVIÇO MEDICINA INTERNA

12 Junho a 3 Agosto 2018

Exame neurológico:

- Esotropia OE. Limitação da abdução do OE. Sem diplopia.
- Sem ptose palpebral.
- Anisocoria (pupila esquerda > direita).
- Reflexos fotomotor direto e de acomodação esquerdos lentos.
- Força muscular segmentar grau 5/5 nos 4 membros.
- Hiperreflexia membros inferiores +++/+++.
- Sinal de Babinski bilateral.

CASO CLÍNICO

INTERNAMENTO SERVIÇO MEDICINA INTERNA

12 Junho a 3 Agosto 2018

Exames complementares de diagnóstico:

- **Analiticamente:**

  Hemograma: Hemoglobina 10.9 g/dL, VGM 81 fL, HGM 26.5 pg, CHGM 32.7 g/dL

  Leucócitos 8.7 $x10^9$/L, Plaquetas 540 $x10^9$/L.

  VS 22 mm. PCR 24 mg/dL

  Função hepática, renal e tiroideia sem alterações.

  Ionograma: Na^+ 127 mmol/L; K^+ 4.73 mmol/L.

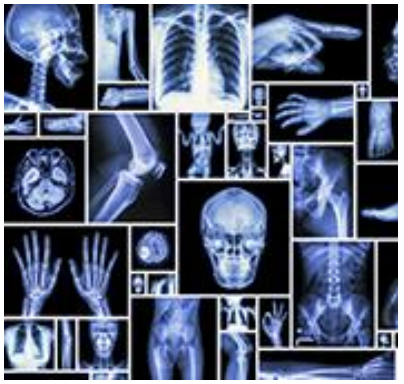
  Eletroforese de proteínas normal; imunofixação sem componente monoclonal.

  Ácido fólico diminuído, vitB12 e ferritina normais

  IGRA, HIV, serologias hepatites negativos

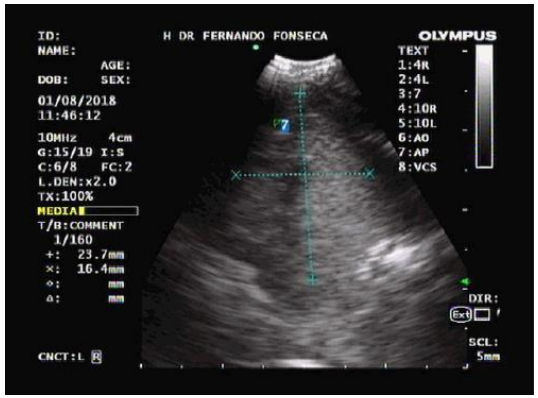
CASO CLÍNICO

INTERNAMENTO SERVIÇO MEDICINA INTERNA



Exames complementares de diagnóstico:

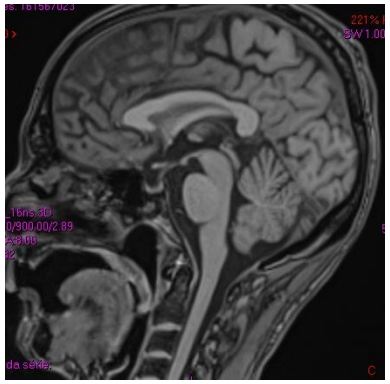
- **Estudo neoplasia oculta:**
  - ✓ **TC pescoço:** sem alterações, sem adenopatias cervicais.
  - ✓ **TC toraco-abdomino-pélvica:** adenopatias mediastínicas; alterações enfisematosas centrilobulares e parasseptais; bronquiectasias tubulares; sem alterações significativas na avaliação dos órgãos da cavidade abdominal e pélvica
  - ✓ **Broncofibroscopia:** sem alterações.
  - ✓ **EBUS:** Adenopatia na estação 7 (23.7X16.4 mm).
  - ✓ **Secreções brônquicas:** BAAR e exame cultural negativos.
  - ✓ **Anatomia patológica:** biópsia de adenopatia inconclusiva.
  - ✓ **Colonoscopia total:** sem alterações
  - ✓ **Analiticamente:** marcadores tumorais negativos; imunofenotipagem tipo B sem características de monoclonalidade.

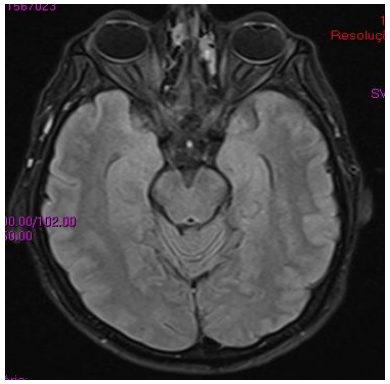


CASO CLÍNICO

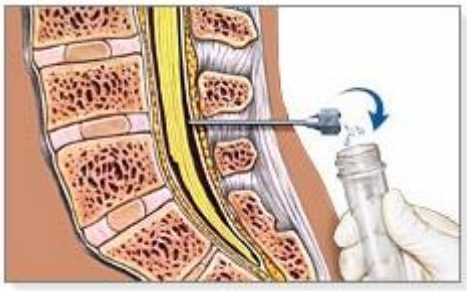
INTERNAMENTO SERVIÇO MEDICINA INTERNA

Exames complementares de diagnóstico:



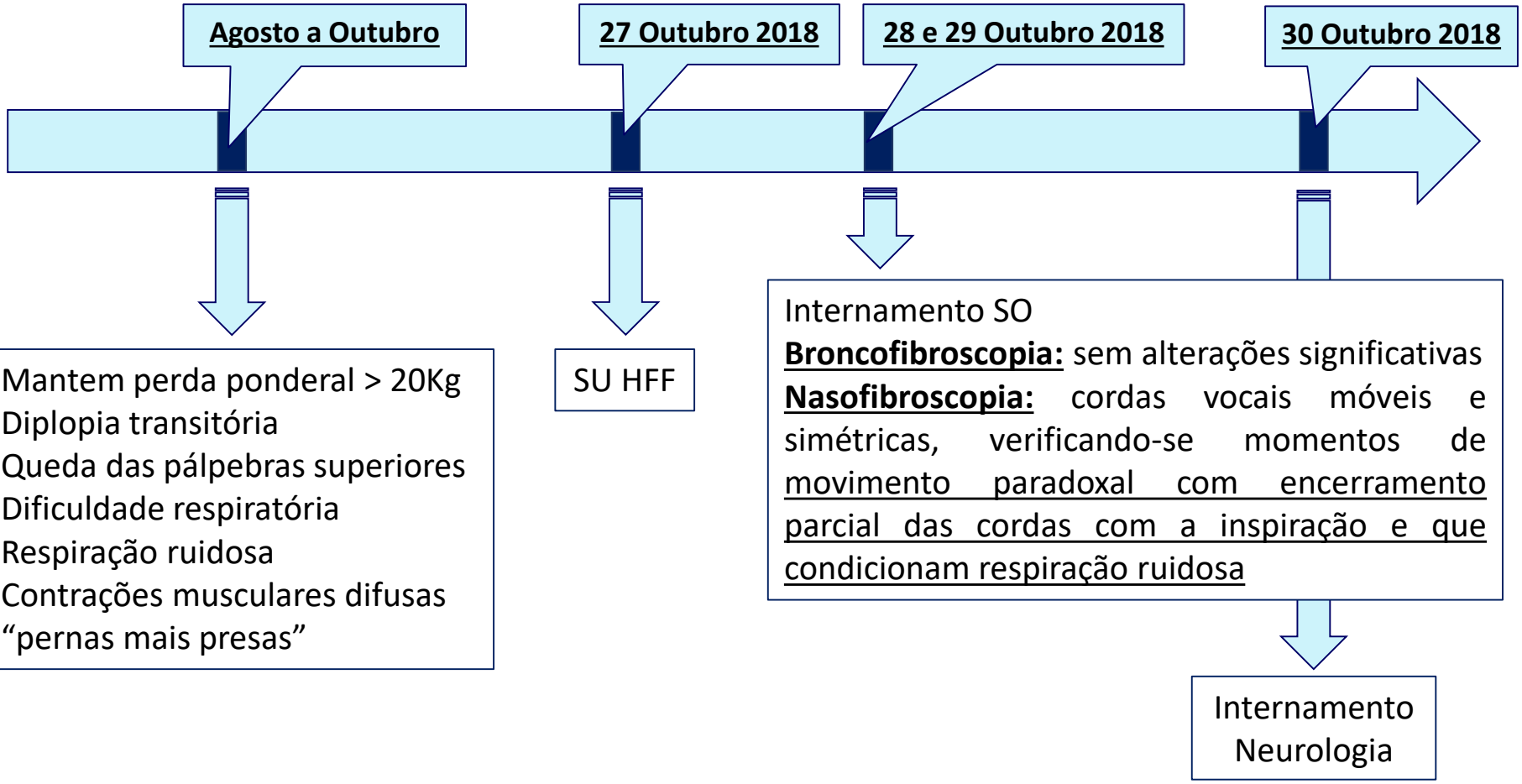


- **Estudo patologia SNC:**
  - ✓ **TC-CE:** sem alterações.
  - ✓ **TC órbitas:** sem alterações.
  - ✓ **RM neuroeixo:** sem alterações de sinal do parênquima cerebral e da medula espinhal; alterações osteodegenerativas da coluna cervical.
  - ✓ **Punção lombar:** LCR límpido, 1 célula, proteínas 19, glicose 50, ADA <0.5, Ag capsulares, VDRL, Borrelia, CMV, BAAR direto e exame cultural negativos.



CASO CLÍNICO

EVOLUÇÃO DO QUADRO CLÍNICO



CASO CLÍNICO

INTERNAMENTO SERVIÇO NEUROLOGIA

27 Outubro a 21 Novembro 2018

Exame neurológico:

- Vígil e orientado. Hipomimia facial.
- Disartria espástica moderada.
- FNS sem alterações de relevo.
- Desconjugação transitória dos movimentos oculares de perseguição.
- Sacadas horizontais lentas.
- Espasmo do orbicular dos olhos. Apraxia da abertura das pálpebras. Encerramento das pálpebras superiores com espasmos transitórios.
- PBE e Mingazzini sem quedas. FM segmentar grau 5/5 nos 4 membros.
- Hipertonia generalizada (MIs>>MSs)
- Hiperreflexia miotática generalizada: MIs ++++/++++, MSs +++/+++.
- Clónus aquiliano inextinguível. Sinal Babinski bilateralmente.
- Contração mantida da parede abdominal. Mioquimias face externa das coxas. Mioclonias dos membros superiores. Startle ligeiro.
- Marcha com hiperlordose lombar, tronco rígido, lentificada, instabilidade postural

CASO CLÍNICO

INTERNAMENTO SERVIÇO NEUROLOGIA

27 Outubro a 21 Novembro 2018

RESUMO

- Homem, 49 anos, sem antecedentes pessoais de relevo
- Perda ponderal > 10%, quadro de diarreia
- Alterações da oculomotricidade
- Ptose palpebral e espasmo laríngeo
- Rigidez generalizada
- Sinais piramidais
- Espasmos musculares

DIAGNÓSTICO DIFERENCIAL

- Síndrome stiff-person
- Síndrome de hiperexcitabilidade do nervo periférico (sínd Morvan; sínd Isaac)
- Parkinsonismo atípico
- Doença do neurónio motor + Miastenia Gravis

CASO CLÍNICO

INTERNAMENTO SERVIÇO NEUROLOGIA

27 Outubro a 21 Novembro 2018

Exames complementares de diagnóstico:

- **Analiticamente:**

  Hemograma: Hemoglobina 9.9 g/dL, VGM 81 fL, HGM 26.5 pg, CHGM 32.7 g/dL

  Leucócitos 8.7 $x10^9$/L, Plaquetas 460 $x10^9$/L.

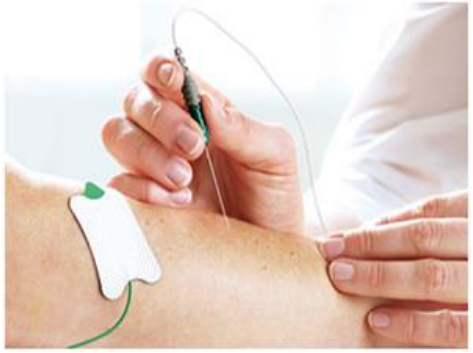
  VS 22 mm. PCR 5 mg/dL

  Função hepática, renal e tiroideia sem alterações.

  Ionograma: Na^+ 129 mmol/L; K^+ 4.73 mmol/L.

CASO CLÍNICO

INTERNAMENTO SERVIÇO NEUROLOGIA

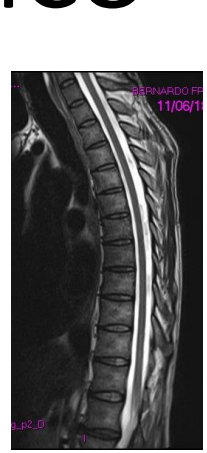
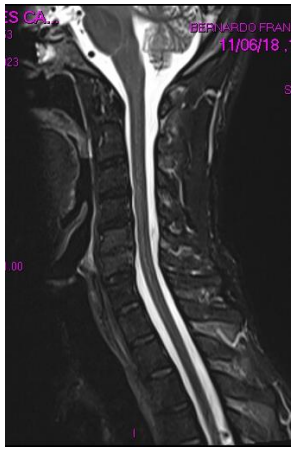
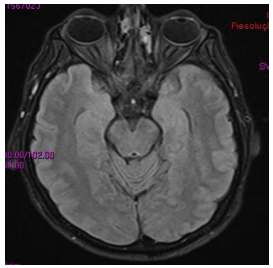


Exames complementares de diagnóstico:

- **Estudo patologia SNC:**
  - ✓ **Eletromiograma:** atividade de unidade motora contínua em repouso, que cedeu após administração de diazepam EV.

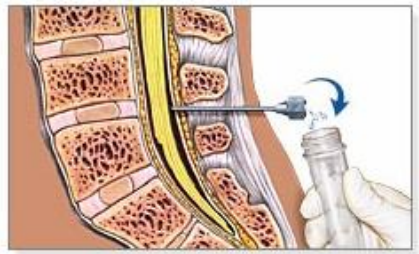
CASO CLÍNICO

INTERNAMENTO SERVIÇO NEUROLOGIA

Exames complementares de diagnóstico:

- **Estudo patologia SNC:**
  - ✓ **RM neuroeixo:** sem alterações de sinal do parênquima cerebral e da medula espinhal; alterações osteodegenerativas da coluna cervical.
  - ✓ **Punção lombar:** LCR límpido, 4 células, proteínas 15 mg/dL, glicose 89 mg/dL, ADA <0.5, lactato normal, BAAR direto e exame cultural negativos. Sem bandas oligoclonais. Imunoglobulinas normais.
  - ✓ **Anticorpos antineuronais:** NMDAr, DPPX, GAD, anfifisina, GlyR, ANNA3, Ma1, Ma2, GABA, CASPR2, LGI1, AchR, Canais de Ca^{2+} negativos
  - ✓ **Eletroencefalograma:** sem atividade patológica.

CASO CLÍNICO

INTERNAMENTO SERVIÇO NEUROLOGIA

Exames complementares de diagnóstico:

- **Estudo neoplasia oculta:**
  - ✓ **Ecografia tiroide:** sem alterações.
  - ✓ **Ecografia testicular:** sem alterações.
  - ✓ **PET FDG corpo inteiro:** Sem alterações sugestivas de doença metabolicamente ativa
  - ✓ **Analiticamente:** eletroforese de proteínas normal, imunofixação sem componente monoclonal; beta2-microglobulina e LDH normais; marcadores tumorais negativos.

Diagnóstico: Síndrome Stiff-person

CASO CLÍNICO

EVOLUÇÃO DO QUADRO CLÍNICO DURANTE O INTERNAMENTO

5 dias **Metilprednisolona** 1g/dia

5 dias **Imunoglobulina humana** 400mg/Kg/dia

Diazepam 5 mg PO 8/8h

Prednisolona 1mg/Kg durante 1 mês e desmame progressivo ao longo de 6 meses

Azatioprina 1-2mg/Kg/dia

<u>Melhoria clínica significativa durante o internamento, apresentando à data de alta:</u>

- Ptose palpebral bilateral.
- Sacadas lentificadas, sem desconjugação ocular evidente, sem diplopia.
- Hipomimia facial discreta.
- Melhoria da rigidez axial, mantendo rigidez ligeira MIs. Sem mioquimias.
- Hiperreflexia generalizada e sinal de Babinski bilateral.

CASO CLÍNICO

EVOLUÇÃO DO QUADRO CLÍNICO APÓS O INTERNAMENTO

1ª Consulta após Internamento

- **Exame neurológico:**

  Expressão facial mantida.
  Sem alterações oculomotricidade.
  Sem anisocoria.
  Sem disfagia. Sem disartria.
  Sem respiração ruidosa.
  Sem startle. Sem mioclonias.
  Discreta hiperreflexia generalizada.
  RCP em flexão bilateralmente.
  Discreta rigidez MI direito.
  Sem rigidez axial.
  Marcha normal.

Síndrome Stiff-person

- Doença neurológica incomum, frequentemente mediada por anticorpos, provavelmente subdiagnosticada.
- **Prevalência estimada:** 1-2 casos por milhão de habitantes.
- **Incidência:** 1 caso por milhão por ano.
- Idade de apresentação 20-50 anos
- Mais frequente no sexo feminino 3:1
- Rigidez e espasmos musculares progressivos (tronco » membros)

Table 1 Main features of stiff-person syndrome

Diagnostic criteria*
Major criteria
1. Stiffness in the axial and limb muscles, prominently in the abdominal and thoracolumbar paraspinal muscles leading to a fixed deformity (hyperlordosis)
2. Superimposed painful spasms precipitated by unexpected noises, emotional stress, or tactile stimuli
3. EMG: confirmation of continuous motor unit activity in agonist and antagonist muscles.
4. Absence of other neurological disorders or cognitive impairment that could explain the stiffness
Minor criteria
5. Positive anti-GAD65 (or antiamphiphysin) antibodies in serum, assessed by immunocytochemistry, Western blot or radioimmunoassay
6. Clinical response to benzodiazepines†

Síndrome Stiff-person

Perspetiva histórica

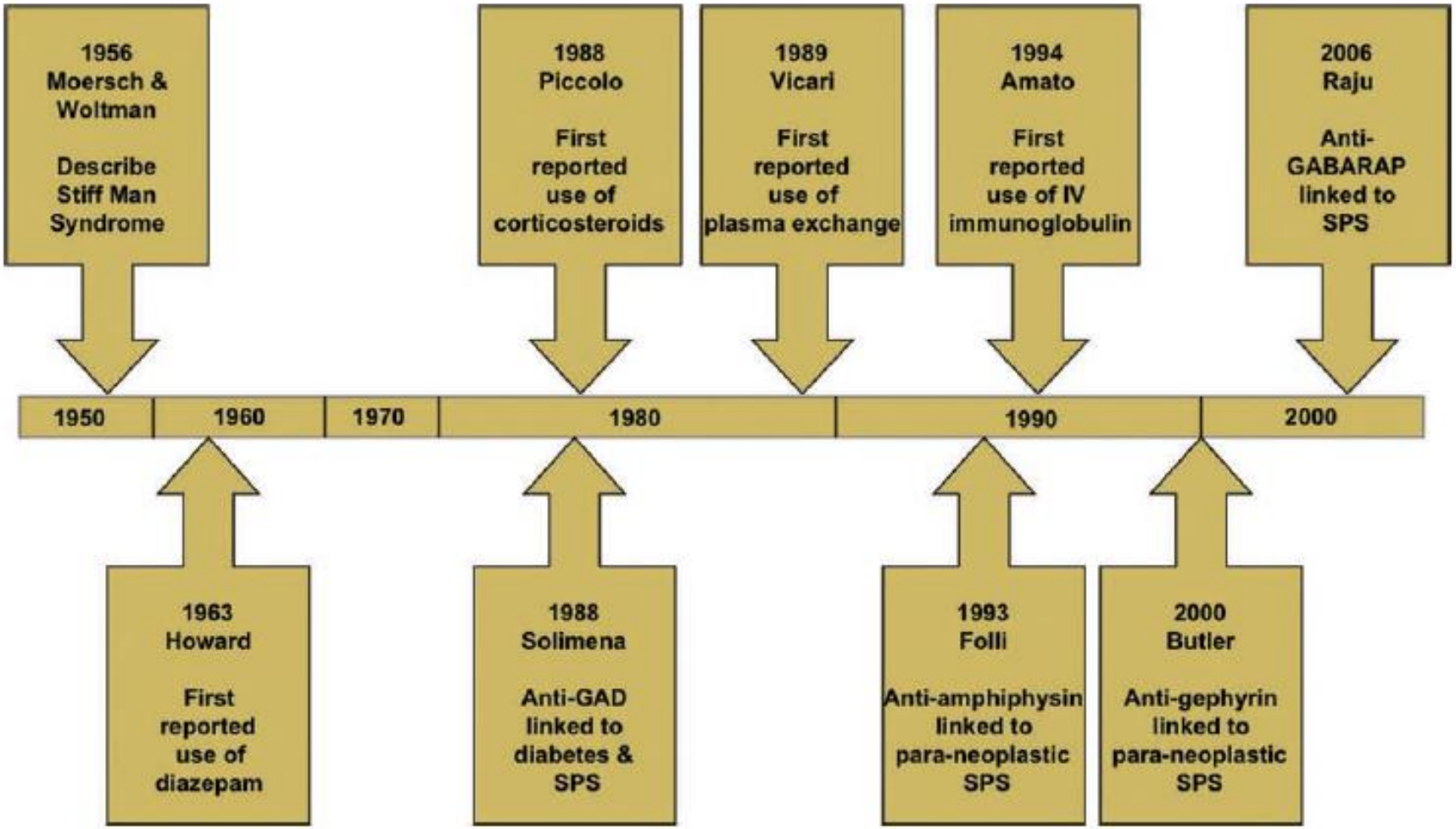
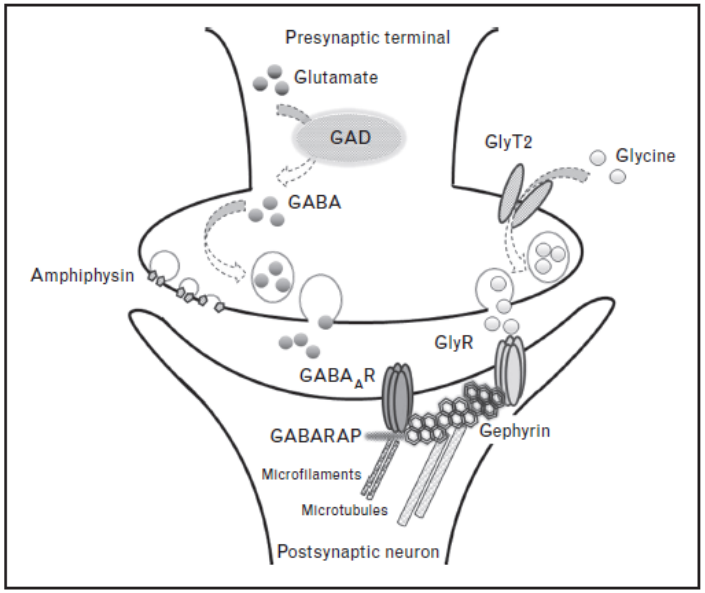


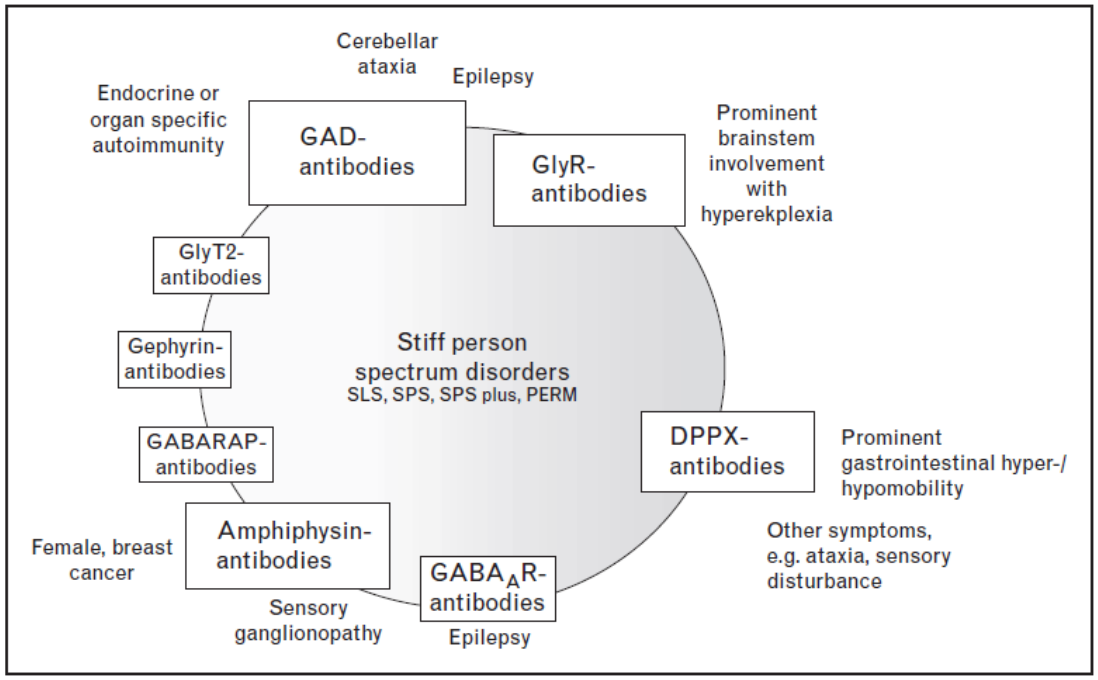
Figure 1 The timeline of significant dates in the history of SPS.[2,5–12] GABARAP, γ-aminobutyric acid (A) receptor-associated protein; GAD, glutamic acid decarboxylase; SPS, stiff person syndrome

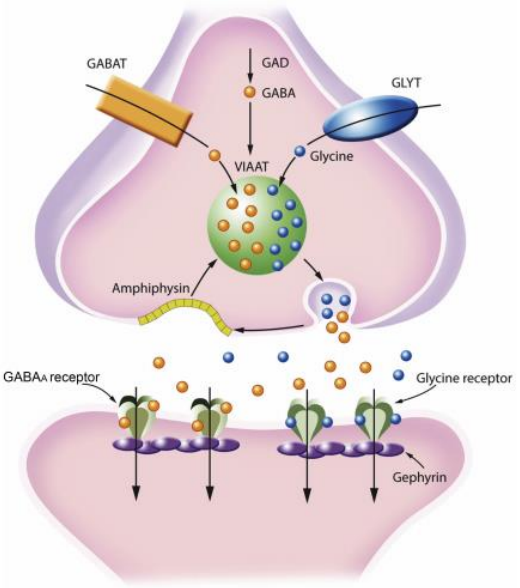
Síndrome Stiff-person

Subtypes of stiff-person syndrome

I Classic stiff-person syndrome
II Stiff person variants
Focal or segmental stiff-person syndrome
Jerky stiff-person syndrome
PERM
Stiff-person syndrome plus (ataxia, epilepsy, etc)
Paraneoplastic stiff-person syndrome







Síndrome Stiff-person

Associated autoimmune disorders	Associated neoplasia
Diabetes mellitus type 1	Breast cancer‡
Hashimoto's thyroiditis	Pulmonary cancer
Grave's disease	Renal cell carcinoma
Pernicious anemia	Thyroid carcinoma
Anti-NMDAR encephalitis	Colon cancer
Limbic encephalitis	Neuroendocrine neoplasm
Refractory epilepsy	Thymoma
Polyendocrine autoimmune syndrome	Hodgkin lymphoma
Vitiligo	Non-Hodgkin lymphoma
Caeliac disease	Cholangiocarcinoma
Myasthenia gravis	
Autoimmune retinopathy and scleritis	
Systemic lupus erythematosus	

Major complications

- Severe dysautonomic and painful muscle spasms crises
- Oesophageal obstruction from cricopharyngeal muscle spasm
- Hypoxemic respiratory failure
- Falls
- Fractures and joint dislocations
- Sudden death

Síndrome Stiff-person

BOX 3 DIFFERENTIAL DIAGNOSIS

- Clinical differential
  - Myelopathy: compressive, ischaemic, haemorrhagic and inflammatory (including multiple sclerosis and infectious causes)
  - Myopathy: channelopathies, inflammatory, myotonic dystrophy, paramyotonia
  - Neuropathic: neuromyotonia, Isaac's syndrome
  - Parkinson's disease or Parkinson-plus syndromes (eg, progressive supranuclear palsy, multiple system atrophy)
  - Primary lateral sclerosis
  - Dystonia (generalised and focal)
  - Ankylosing spondylitis
  - Neuroleptic malignant syndrome, malignant hyperthermia and serotonin syndrome
  - Tetanus
  - Psychogenic
  - Hereditary spastic paraparesis
  - Leukodystrophies
  - Drug-induced and toxicity: monoamine oxidase inhibitors, phenothiazines, amphetamines, 5,6-methylenedioxy-N-methyl-2-aminoindane, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, carbon monoxide
  - Spinal interneuronitis with rigidity
- Diseases associated with positive GAD autoantibodies
  - Cerebellar ataxia
  - Epilepsy
  - Limbic encephalitis
  - Myasthenia gravis
  - Myoclonus
  - Neuromyotonia
  - Batten's disease

Síndrome Stiff-person

Tratamento

Table 3 Main treatment options in stiff person syndrome

Agent	Action	Daily doses	Side effects
Drugs treating symptoms			
Benzodiazepines, eg, diazepam, clonazepam	GABA-A agonist	Diazepam 5–100 mg (divided doses) Clonazepam 1–6 mg (divided doses) (though often doses are far higher)	Drowsiness, vertigo, dysarthria, respiratory depression
Baclofen	GABA-B agonist	Oral 5–60 mg (divided doses) Intrathecal 50–800 μg/day	Drowsiness, vertigo
Antiepileptics, eg, levetiracetam, gabapentin	GABA-ergic and other actions	Levetiracetam 2000 mg Gabapentin 3600 mg	Variable
Other options: tizanidine, dantrolene, botulinum toxin			
Drugs that modulate the immune process			
IVIG	Incompletely understood	2 g/kg	Infusion reactions including anaphylaxis, thrombotic events, headaches, aseptic meningitis
Plasma exchange	Incompletely understood	5–6 Exchanges	Hypotension, bleeding, allergic reaction, severe immune suppression
Rituximab	B cell depletion	2 g (Divided doses)	Breathing problems, arrhythmia and rarely skin reactions (Stevens–Johnson syndrome) and progressive multifocal leucoencephalopathy

Vinheta clínica 1

Encefalomielite Progressiva com Rigidez e Mioclonias (**PERM**) mediada pelo **anticorpo anti-recetor da glicina**

♂ 78 anos

Deterioração cognitiva

Rigidez axial e dos 4 membros

Mioclonias

Disfagia

LCR: citoquímico normal

RM-CE, RM medular e EMG sem alterações valorizáveis

EEG: lentificação marcada e difusa, sem atividade paroxística

PET-FDG cerebral: hipometabolismo focal

Encefalite Autoimune

Table 1 Clues to an autoimmune etiology

Change in baseline neurologic function
Subacute onset (days to weeks)
Fluctuating course
Personal or family history of organ- or non-organ-specific autoimmune disorder
Systemic markers of autoimmunity: e.g., elevated ANA or TPO antibodies
History of or concurrent malignancy
CSF studies: elevated WBC (<100 cells/ul), protein (<100 mg/dL), IgG index, oligoclonal bands, synthesis rate
EEG: focal abnormalities
MRI: T2/FLAIR hyperintensities, rarely enhancement
PET brain: areas of hyper/hypometabolism
Response to immunosuppression
Identification of a neural autoantibody

When to suspect an autoimmune etiology
Female gender
Subacute onset
Fluctuating course
Multifocal neurological disease
Personal or family history of autoimmunity
Personal history of cancer or suspicion of new cancer
Abnormal supportive tests, i.e., CSF, imaging
Response to immunotherapy

Encefalite Autoimune

Panel 1: Diagnostic criteria for possible autoimmune encephalitis

Diagnosis can be made when all three of the following criteria have been met:

1. Subacute onset (rapid progression of less than 3 months) of working memory deficits (short-term memory loss), altered mental status*, or psychiatric symptoms
2. At least one of the following:
   - New focal CNS findings
   - Seizures not explained by a previously known seizure disorder
   - CSF pleocytosis (white blood cell count of more than five cells per mm^3)
   - MRI features suggestive of encephalitis†
3. Reasonable exclusion of alternative causes (appendix)

*Altered mental status defined as decreased or altered level of consciousness, lethargy, or personality change. †Brain MRI hyperintense signal on T2-weighted fluid-attenuated inversion recovery sequences highly restricted to one or both medial temporal lobes (limbic encephalitis), or in multifocal areas involving grey matter, white matter, or both compatible with demyelination or inflammation.

Panel 7: Criteria for autoantibody-negative but probable autoimmune encephalitis

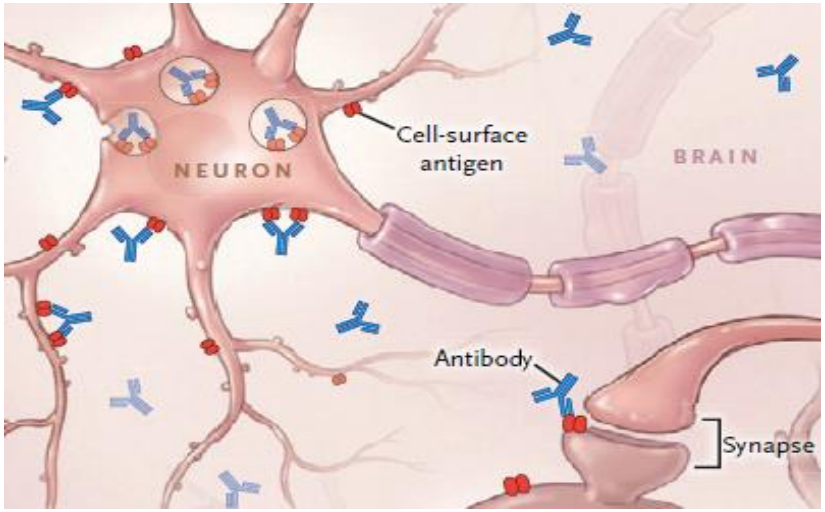
Diagnosis can be made when all four of the following criteria have been met:

1. Rapid progression (less than 3 months) of working memory deficits (short-term memory loss), altered mental status, or psychiatric symptoms
2. Exclusion of well defined syndromes of autoimmune encephalitis (eg, typical limbic encephalitis, Bickerstaff's brainstem encephalitis, acute disseminated encephalomyelitis)
3. Absence of well characterised autoantibodies in serum and CSF, and at least two of the following criteria:
   - MRI abnormalities suggestive of autoimmune encephalitis*
   - CSF pleocytosis, CSF-specific oligoclonal bands or elevated CSF IgG index, or both*
   - Brain biopsy showing inflammatory infiltrates and excluding other disorders (eg, tumour)
4. Reasonable exclusion of alternative causes

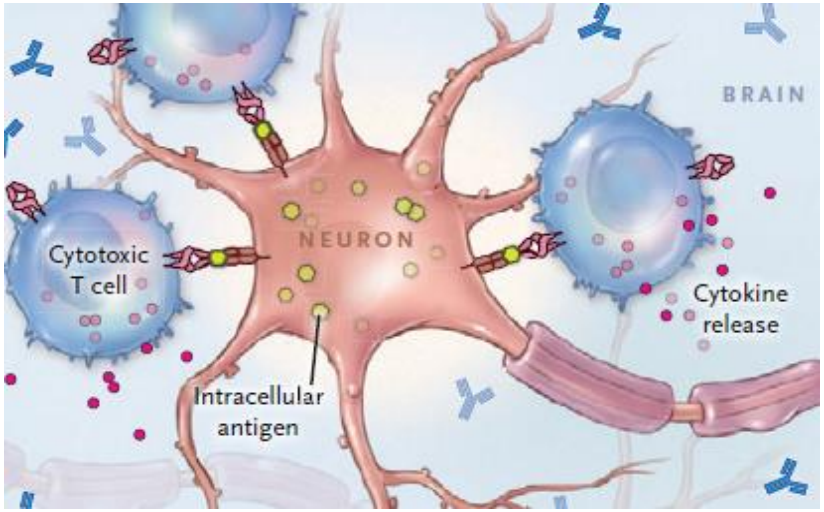
*Some inherited mitochondrial and metabolic disorders can present with symmetric or asymmetric MRI abnormalities and CSF inflammatory changes resembling an acquired autoimmune disorder.[302]

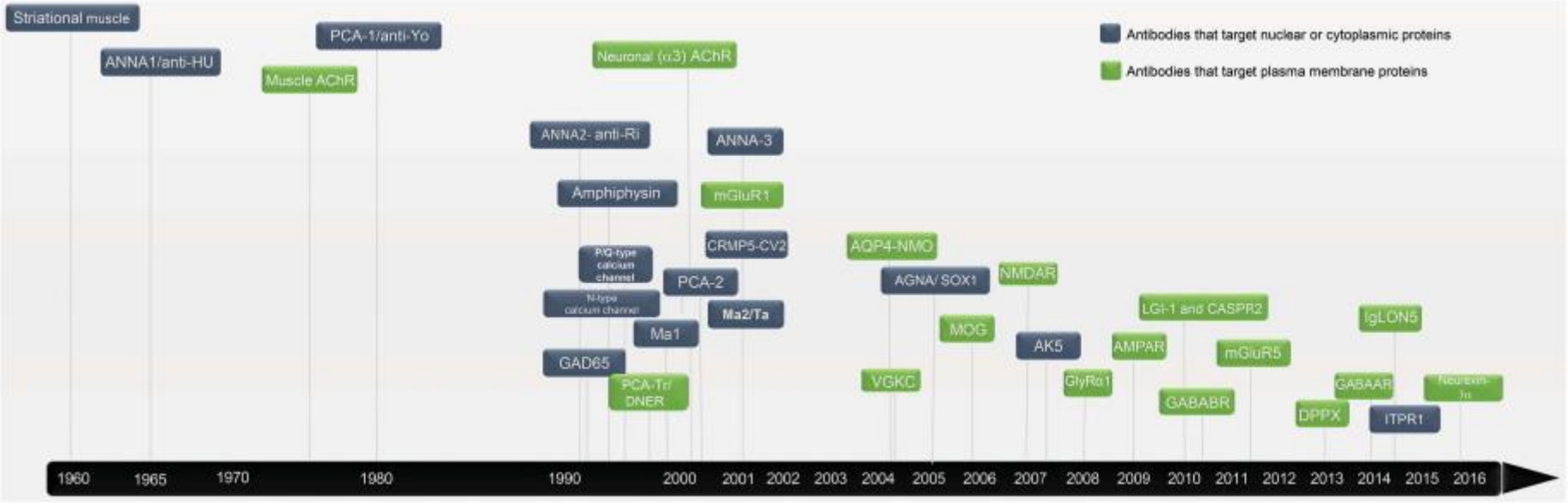
Encefalite Autoimune

Anticorpos anti-antigénios de superfície



Anticorpos anti-antigénios intracelulares





Encefalite Autoimune

Table 1. Clinical and Immunologic Features and Antibody Effects of Antibody-Mediated Encephalitis.*

Antibody (No. of Patients)†	Median Age (Range); Male:Female Ratio	Main Clinical Features on Presentation	Main Syndrome	Findings on MRI (% of Patients)‡	Frequency of Cancer (% of Patients)	Predominant IgG Class	In Vitro Antibody Effects
NMDAR (>1500)	21 yr (2 mo–85 yr); 1:4	Children: seizures, dyskinesias; adults: behavioral changes, psychiatric symptoms	NMDAR encephalitis	Normal findings (70) or nonspecific changes	Varies with age and sex; ovarian teratoma in women 18–45 yr old (58)§	IgG1	Internalization of NMDAR, disruption of NMDAR interaction with ephrin-B2 receptor
AMPAR (80)	56 yr (23–81); 1:2.3	Confusion, memory loss; in rare cases, psychiatric symptoms	Limbic encephalitis	Increased signal in medial temporal lobes (67)	SCLC, thymoma, or breast cancer (56)	IgG1	Internalization of AMPARs
$GABA_BR$ (80)	61 yr (16–77); 1.5:1	Seizures, memory loss, confusion	Limbic encephalitis, prominent seizures	Increased signal in medial temporal lobes (45)	SCLC (50)	IgG1	Blocking of agonist effect of baclofen on $GABA_BR$
LGI1 (400)	64 yr (31–84); 2:1	Memory loss, faciobrachial dystonic seizures, hyponatremia	Limbic encephalitis	Increased signal in medial temporal lobes (83)	Thymoma (<5)	IgG4	Inhibition of LGI1 interaction with ADAM22 and ADAM23; decrease in postsynaptic AMPAR
CASPR2 (120)	66 yr (25–77); 9:1	Memory loss, insomnia, dysautonomia, ataxia, peripheral-nerve hyperexcitability, neuropathic pain	Limbic encephalitis¶‖	Increased signal in medial temporal lobes (67)	Varies with the syndrome (<5 overall)**	IgG4	Alteration of gephyrin clusters in inhibitory synapses
mGluR5 (11)	29 yr (6–75); 1.5:1	Confusion, psychiatric symptoms	Encephalitis	Normal findings in 5 of 11 patients	Hodgkin's lymphoma in 6 of 11 patients	IgG1	Decrease in density of surface mGluR5
D2R (25)	6 yr (2–15); 1:1	Parkinsonism, dystonia, psychiatric symptoms	Basal ganglia encephalitis	Increased signal in basal ganglia (50)	No associated cancer	Unknown	Receptor internalization and decrease in D2R surface density
DPPX (45)	52 yr (13–76); 2.3:1	Confusion, diarrhea, weight loss	Encephalitis, myoclonus, tremors, hyperekplexia¶	Normal findings or nonspecific changes (100)	B-cell neoplasms (<10)	IgG4	Decrease in density of surface DPPX and Kv4.2
$GABA_AR$ (70)	40 yr (2 mo–88 yr); 1:1	Seizures, confusion, behavioral changes	Encephalitis, frequent status epilepticus	Cortical and subcortical FLAIR signal abnormalities involving two or more brain regions (77)	Thymoma (27)	IgG1	Selective reduction of $GABA_AR$ at synapses
Neurexin-3α (6)	44 yr (23–57); 2:4	Confusion, seizures	Encephalitis	Normal findings in 4 of 6 patients	No associated cancer	Unknown	Decrease in density of surface neurexin-3α and total number of synapses in neurons undergoing development

Encefalite Autoimune

Anticorpos anti-antigénios intracelulares

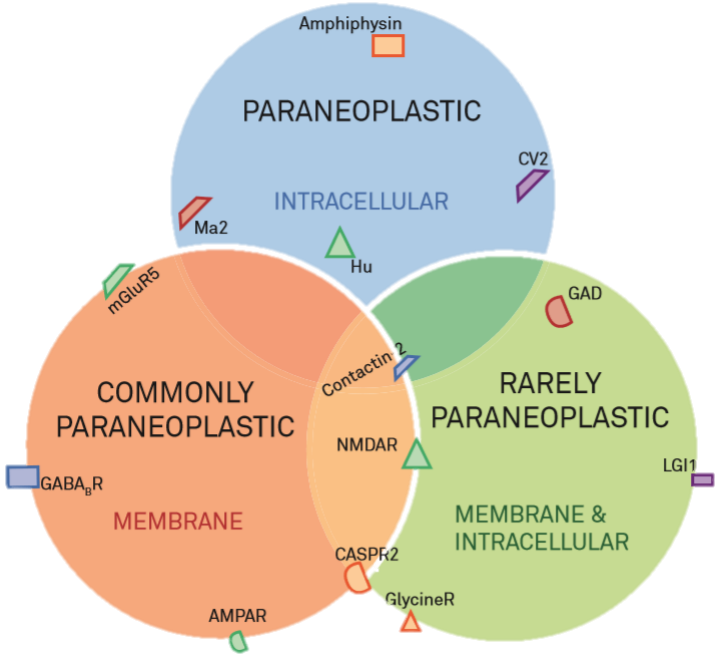
Nuclear and cytoplasmic targets
AK5: limbic encephalitis
ANNA-1: limbic encephalitis, sensory neuronopathy, GI dysmotility
ANNA-2: brainstem encephalitis, opsoclonus-myoclonus, laryngospasm, jaw dystonia
ANNA-3: sensory/sensorimotor neuropathies, cerebellar ataxia, myelopathy, brain stem, and limbic encephalopathy
Amphiphysin: SPS, encephalopathy, myelopathy
AGNA: LES, cerebellar degeneration
CRMP-5: chorea, optic neuropathy, peripheral and autonomic neuropathy, retinitis, myelopathy, cerebellar ataxia
GAD65: multifocal, SPS, cerebellar ataxia, encephalitis, autoimmune epilepsy, myelopathy, neuropathy
GFAP: meningoencephalitis, myelitis, bilateral optic disc edema, tremor
GRAF1: cerebellar ataxia
ITPR1: cerebellar ataxia, neuropathy
Ma1 Ma2: limbic encephalitis, diencephalic syndrome, brainstem encephalitis, ataxia
PCA-1: cerebellar degeneration
PCA-2: peripheral neuropathy, cerebellar ataxia, encephalopathy
ZIC4: cerebellar ataxia

Encefalite Autoimune

Associações a patologia oncológica

Table 2 Antibodies that target nuclear or antibodies that target plasma membrane proteins/cytoplasmic proteins

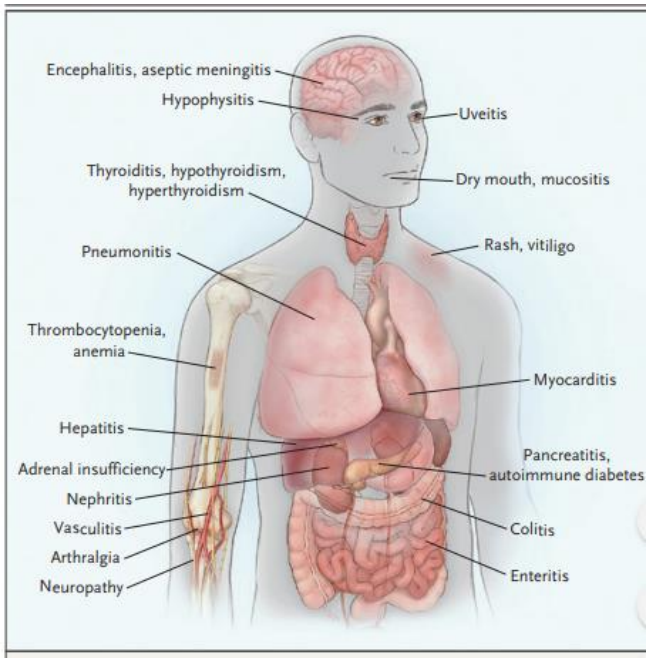
Antibody	Oncologic association	Antibody	Oncologic association
AGNA (SOX1)	Small-cell carcinoma	Ganglionic AChR	adenocarcinomas
Amphiphysin	Small-cell carcinoma, breast adenocarcinoma	Muscle AChR	Thymoma
ANNA-1 (anti-Hu)	Small-cell carcinoma, neuroblastoma (pediatric)	AMPAR	Thymic tumors, lung carcinoma, breast adenocarcinoma
ANNA-2 (anti-Ri)	Small-cell carcinoma, breast adenocarcinoma	DPPX	Lymphoproliferative disorders
ANNA-3	Aerodigestive carcinomas	$GABA_AR$	Hodgkin'slymphoma, ovarian
CRMP-5 (anti-CV2)	Small-cell carcinoma, thymoma	$GABA_BR$	Small-cell lung
GAD65	Rare thymoma, breast adenocarcinoma	mGluR1	Hodgkin's lymphoma
GFAP	Ovarian teratoma, adenocarcinomas	mGluR5	Hodgkin's lymphoma
ITPR	Lung adenocarcinoma	Glycine receptor	Thymoma, lymphoma, ovarian
Anti-Ma1-Anti-Ma2 (anti-Ta)	Testicular germ cell tumors, lung cancer, other solid neoplasms	NMDA-R	Ovarian teratoma, others[a]
PCA-1 (anti-Yo)	Mullerian, adenocarcinomas, breast	NMO (AQP4)	Rare[a] thymoma and breast adenocarcinoma
PCA-2 (MAP1B)	Small-cell carcinoma	P/Q- and N-type VGCC	Small-cell carcinoma
ROCK2	bladder carcinoma	PCA-Tr (DNER)	Hodgkin's lymphoma
Zic 4	Small-cell carcinoma	LGI-1/CASPR2	Small-cell lung carcinoma, thymoma, or adenocarcinomas

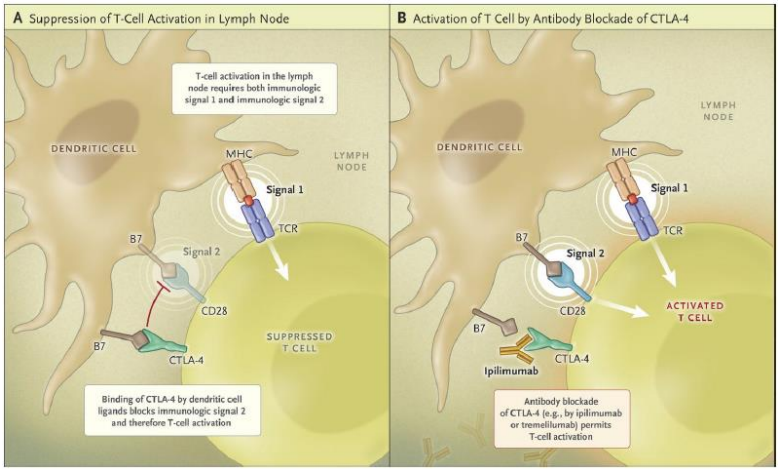


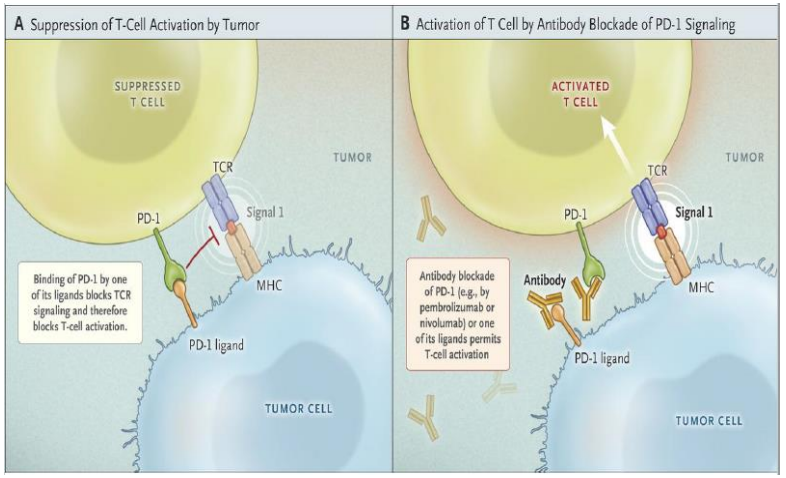
Encefalites iatrogénicas – Tx oncológicos

Table 1 | Neurological toxicities of currently approved ICIs

Drug	Target	Cancer indications	Frequency of grade 3–4 nirAEs in clinical trials (%)[a]	Main nirAEs described in case reports	Classical PNSs described as nirAEs
Ipilimumab	CTLA-4	Melanoma	0.8	Polyneuropathy, Guillain–Barré syndrome, myasthenia, myelitis and myositis, encephalitis and aseptic meningitis	Enteric neuropathy
Nivolumab	PD-1	Melanoma, NSCLC, Hodgkin lymphoma, MSI-H/dMMR colorectal cancer and hepatocellular, kidney, bladder and head and neck cancers	0.4	Encephalitis, Guillain–Barré syndrome, vasculitis, myasthenia, polyneuropathy, myositis, aseptic meningitis and cerebellar ataxia	Limbic encephalitis
Pembrolizumab	PD-1	Melanoma, NSCLC, Hodgkin lymphoma, MSI-H/dMMR solid tumours and bladder, gastric and head and neck cancers	0.2	Myasthenia, motor neuropathy, polyneuropathy, myelitis, myositis, cerebellar ataxia and encephalitis	Limbic encephalitis
Cemiplimab	PD-1	Cutaneous squamous cell carcinoma	0	Limbic encephalitis	Limbic encephalitis
Atezolizumab	PD-L1	NSCLC and bladder cancer	<0.1[b]	Encephalitis, aseptic meningitis, neuropathy and myositis	None
Avelumab	PD-L1	Merkel cell and bladder cancers	0.3[c]	None	None
Durvalumab	PD-L1	NSCLC and bladder cancer	<0.2[d]	Myositis	None

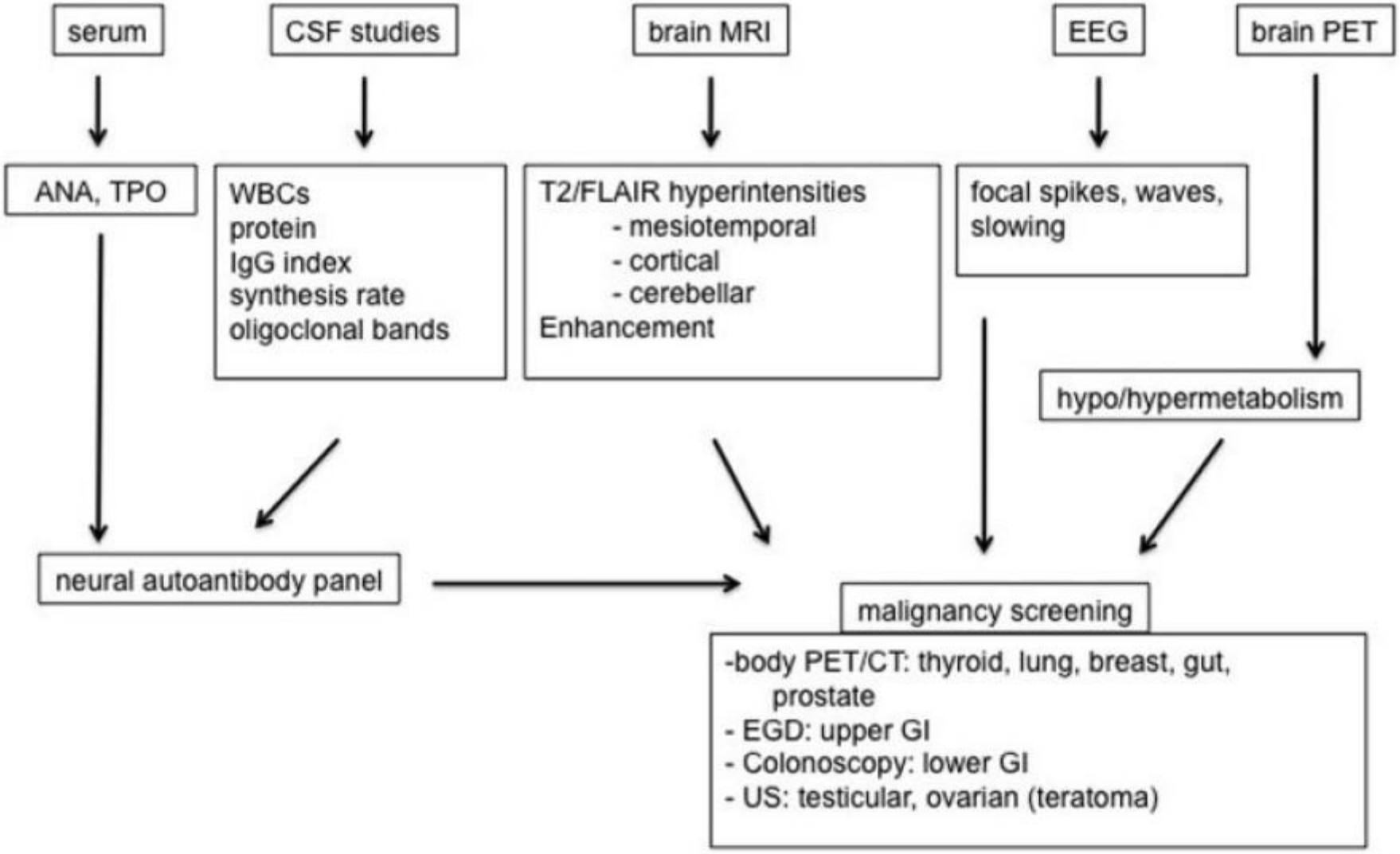






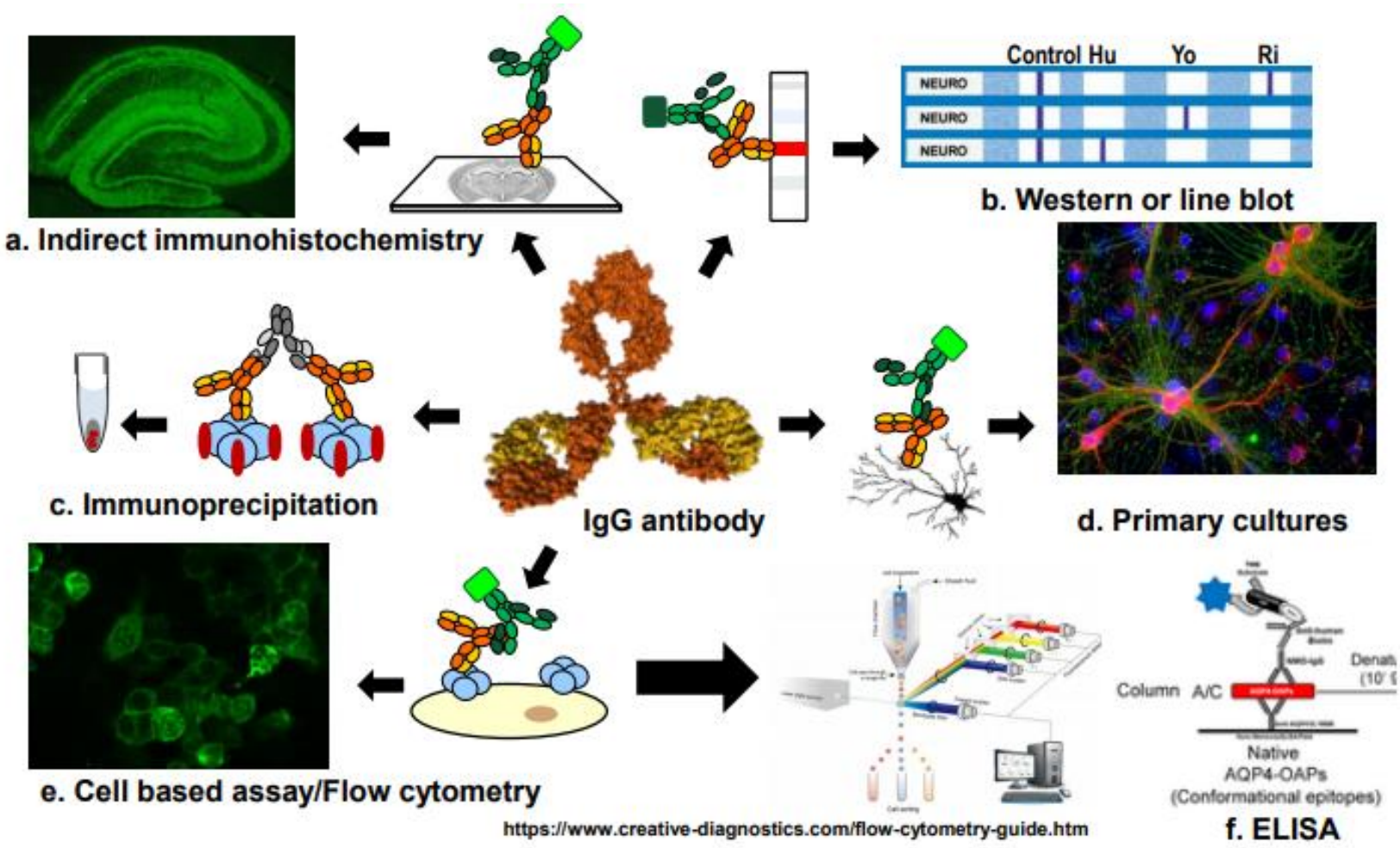
Encefalite Autoimune

Diagnóstico



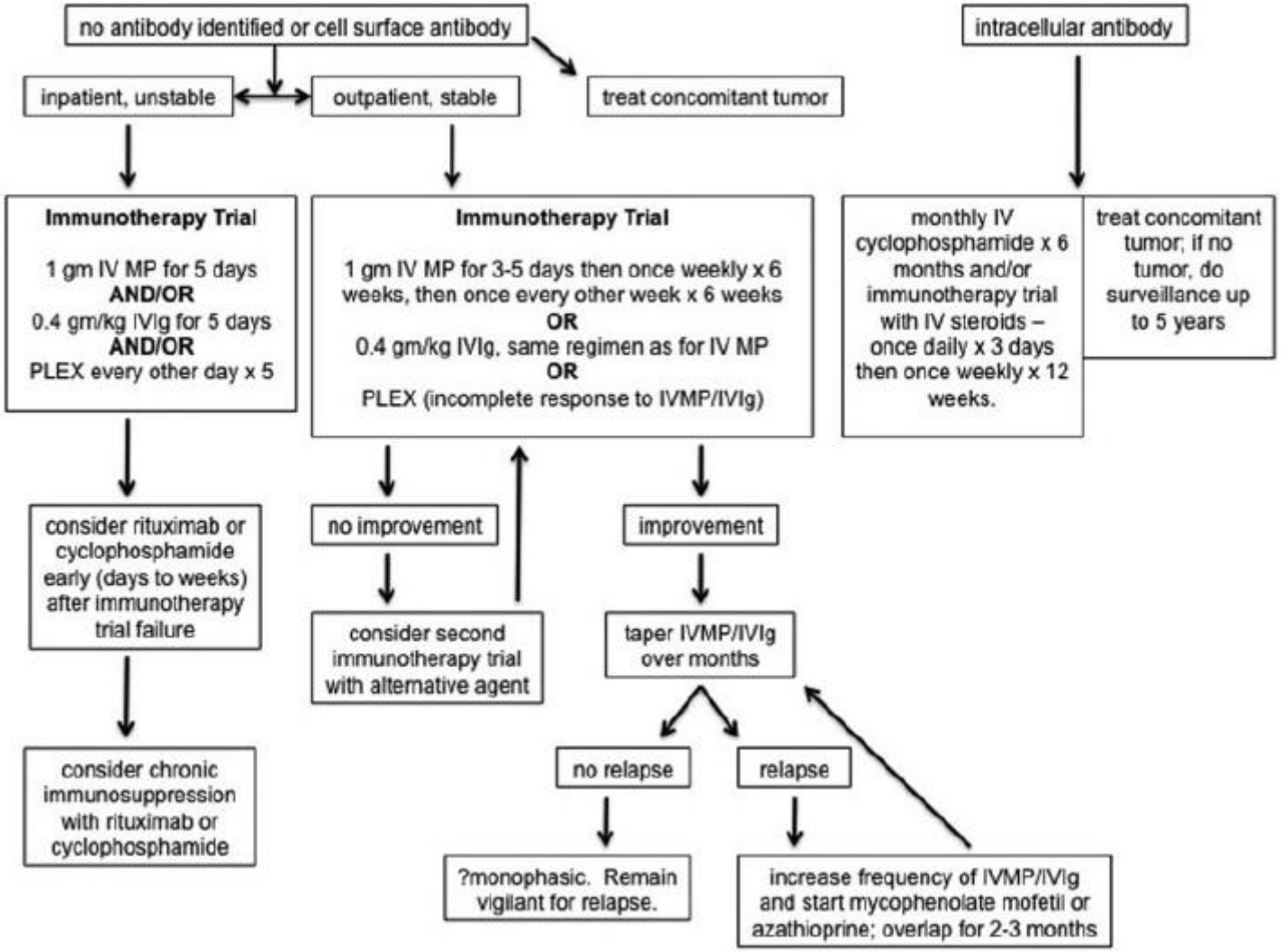
Encefalite Autoimune

Métodos de identificação do anticorpo



Encefalite Autoimune

Tratamento



Vinheta clínica 2

Encefalite autoimune com anticorpos anti-NMDAr

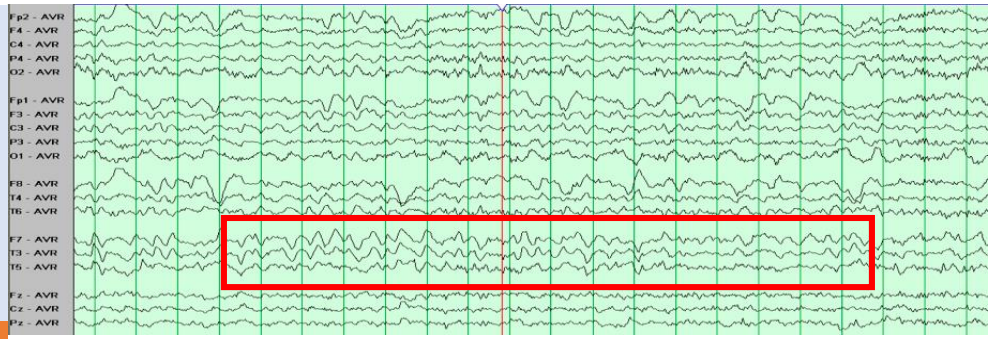
2014 | **31a**

Internamento Psiquiatria: sintomas depressivos e psicóticos, palilalia (1mês)

UCIP: depressão do estado de consciência discinésias oro-linguais, mandibulares, clonias e distonia MSD

- RM-CE e PL normais
- EEG <u>lentificação temporal esquerda</u>
- **Gravidez evolutiva**
- **Estudo neoplasia oculta neg**

Ac anti-NMDAr+ (LCR e sangue)

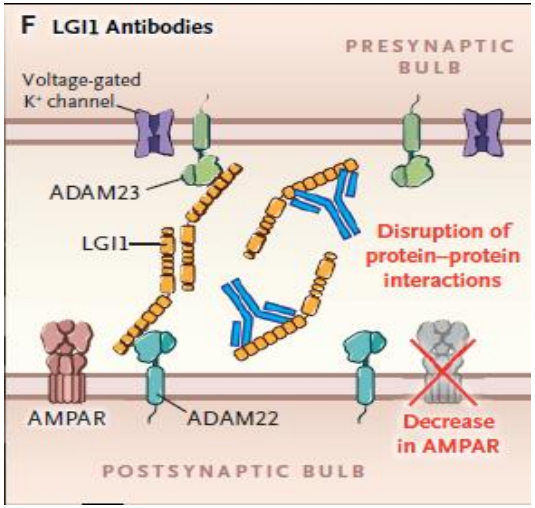


IVIG + metilprednisolona 1g/d x 10d --» interrupção gravidez --» melhoria clínica

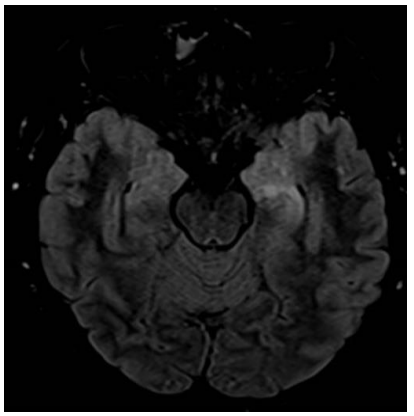
Em remissão sob AZAT

Vinheta clínica 3 e 4

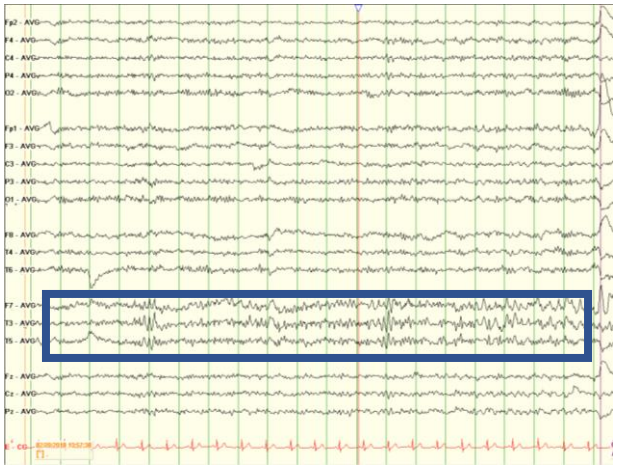
Encefalite autoimune com anticorpos anti-LGI1

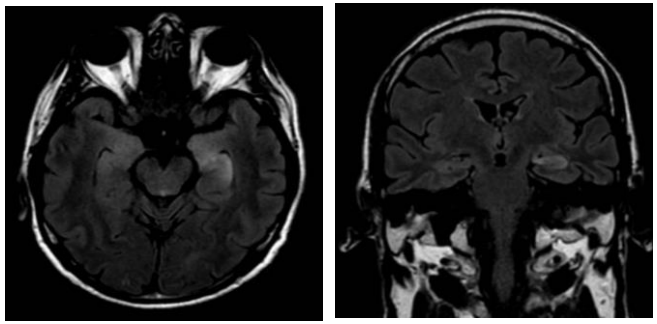


♀ 42 anos
Deterioração cognitiva
Movimentos involuntários
Alterações comportamentais
Hiponatrémia
LCR: citoquímico normal
EEG: atividade paroxística



♂ 64 anos
Deterioração cognitiva
Movimentos involuntários
Alterações comportamentais
LCR: citoquímico normal
EEG: atividade paroxística





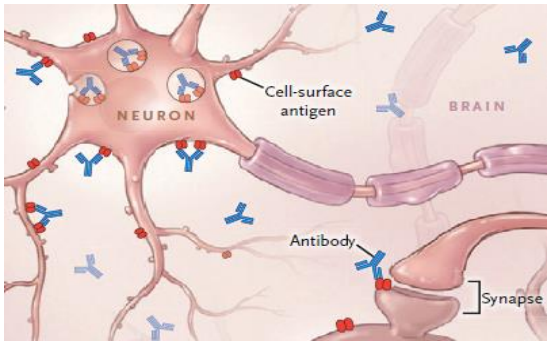
Vinheta clínica 5

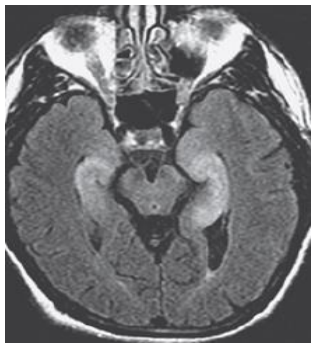
Síndrome Opsoclonus-mioclonus

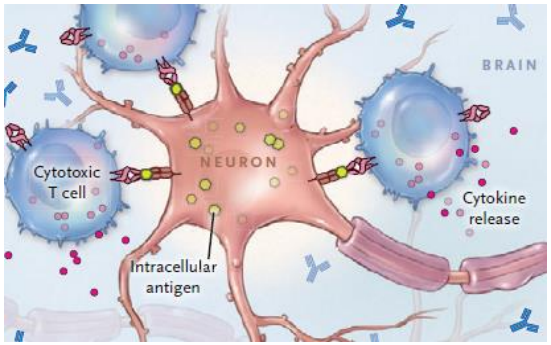
♀ 37a. **Carcinoma da mama**
diagnosticado 3 semanas antes.

Sessão Clínica Hospital Prof. Doutor Fernando Fonseca
Serviço de Neurologia

Quadro consumptivo, dificuldade respiratória e rigidez – apresentação sistémica de doença neurológica imunomediada







Preletor: Dr. Francisco Bernardo
Responsável: Dra. Amélia Nogueira Pinto