Encefalites autoimunes e vasculites do sistema nervoso

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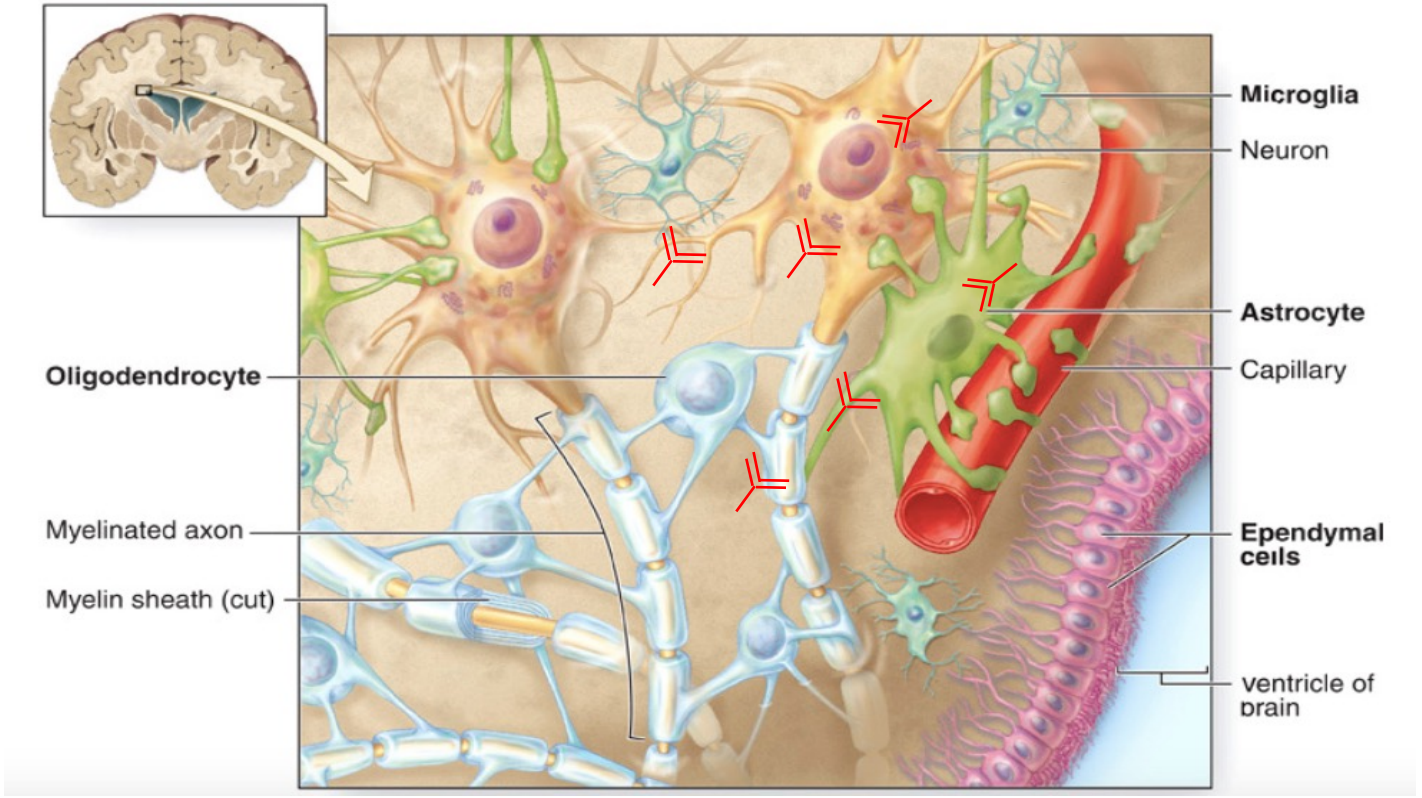
Conflitos de interesse

* Grant from Fleury Laboratory – BrAIN Project
* Grant from Fleury Laboratory - BrAIN Registry
* Grant Academia Brasileira de Neurologia – Consenso Brasileiro de Encefalites Autoimunes
- Fee Advisory Board Educational Technology Sanofi-Genzyme

O novo mundo da neuroimunologia



Microambiente neuronal

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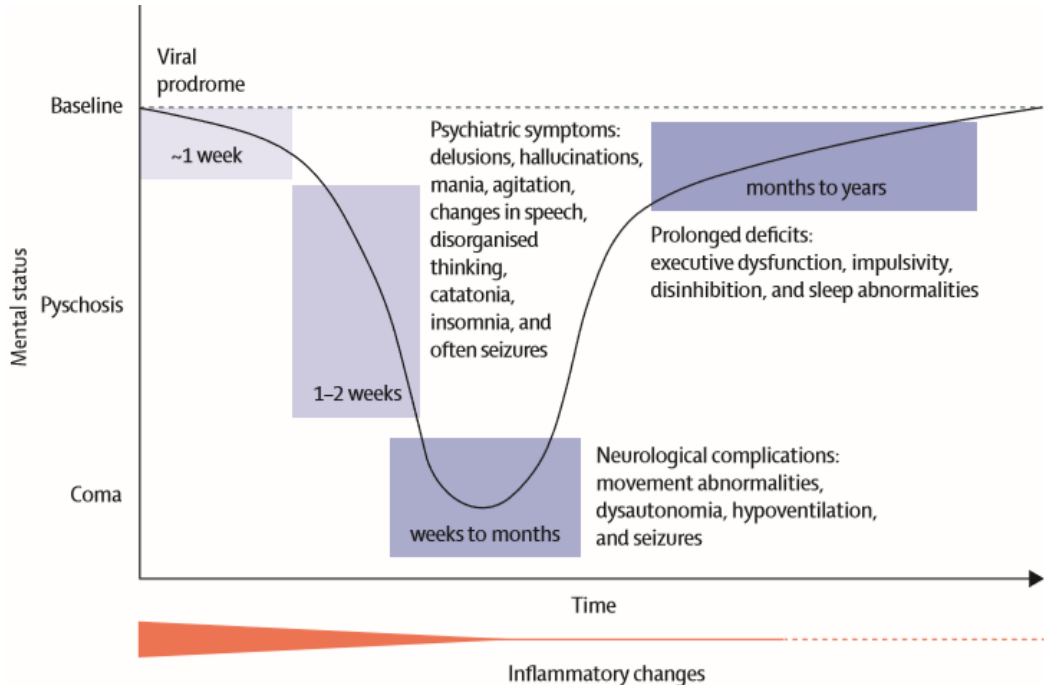
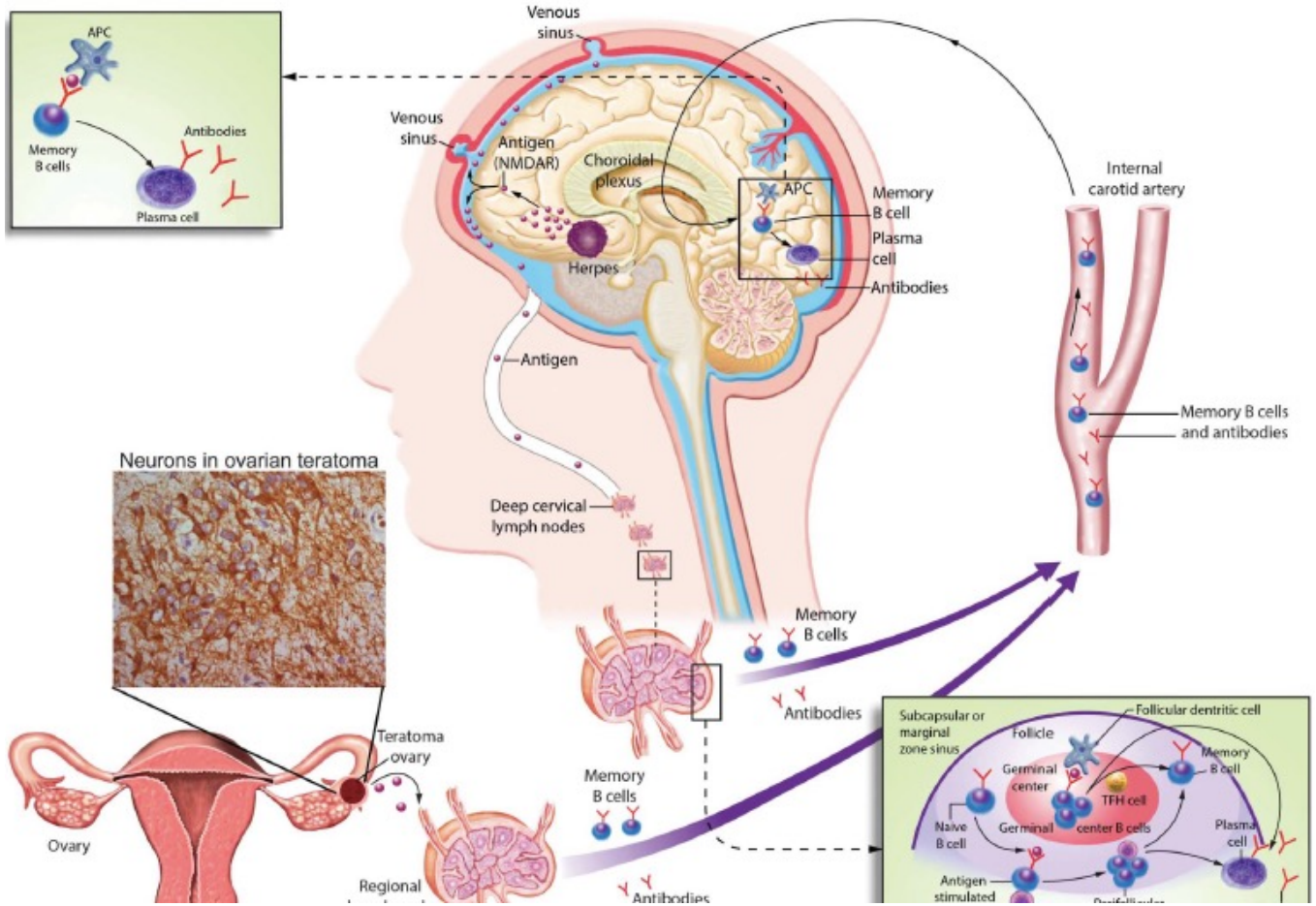
AIE : clinical manifestations

- AIE is not unfrequent, estimated prevalence 7-13/100.000
- Viral prodrome in 50% of children
- Multifocal symptoms: seizures, developmental regression, language impairments, hyperkinetic movements
- Irritability, hyperactivity, hypersexuality, insomnia and anger outbursts.
- Psychiatric symptoms from mood swings to psychosis in over 50% of AE pediatric patients



Florence, 2009; Titulaer, 2014; Goldbeerg,2014; Dalmau, 2020

EAI fisiopatologia



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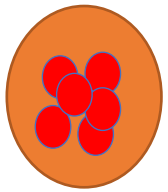
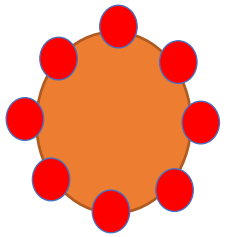
Brazilian AutoImmune encephalitis Network

Dalmau, 2016

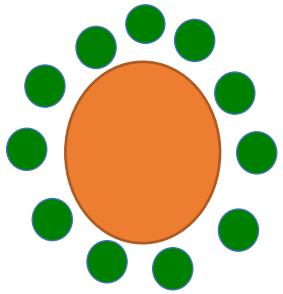
Antígenos antineuronais



HIGH RISK (antigos onconeurais)

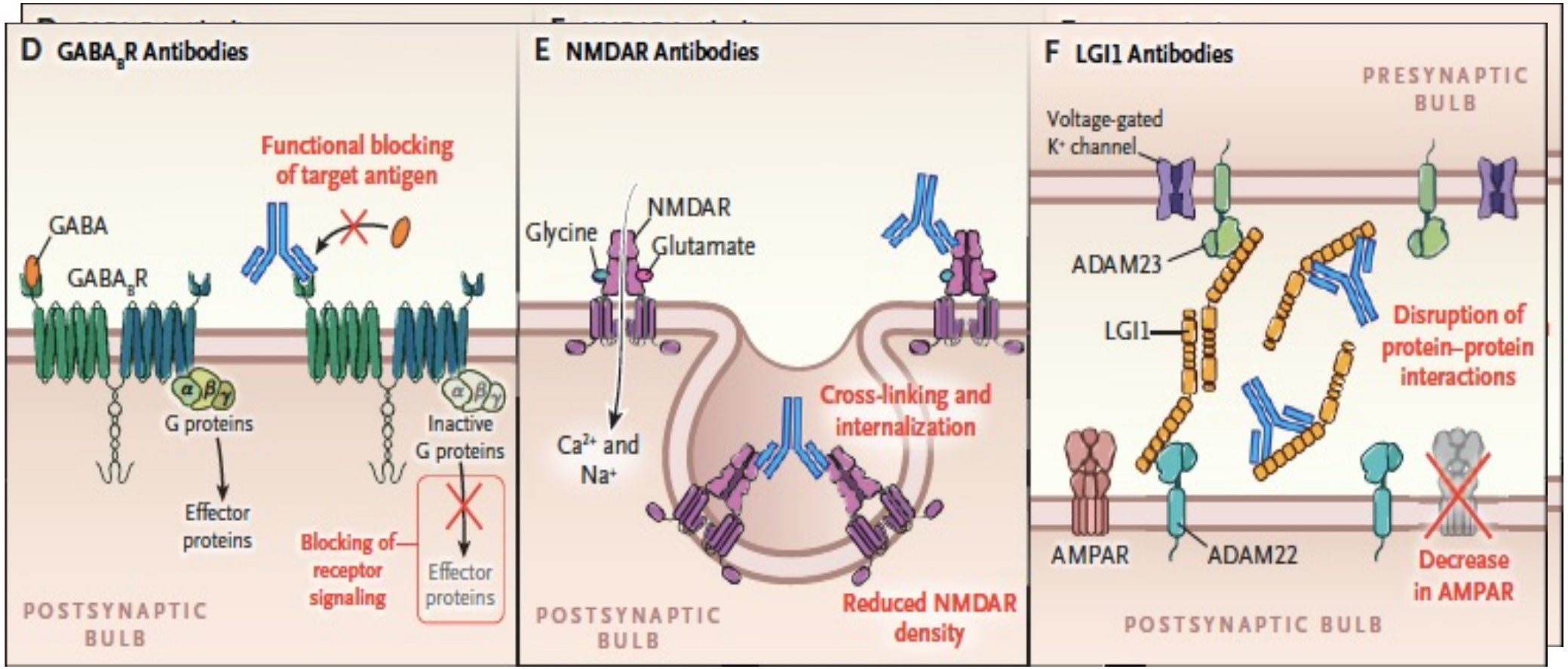


SUPERFÍCIE CELULAR



SINÁPTICOS

Anticorpos: diferentes efeitos fisiológicos



NEJM, 2018

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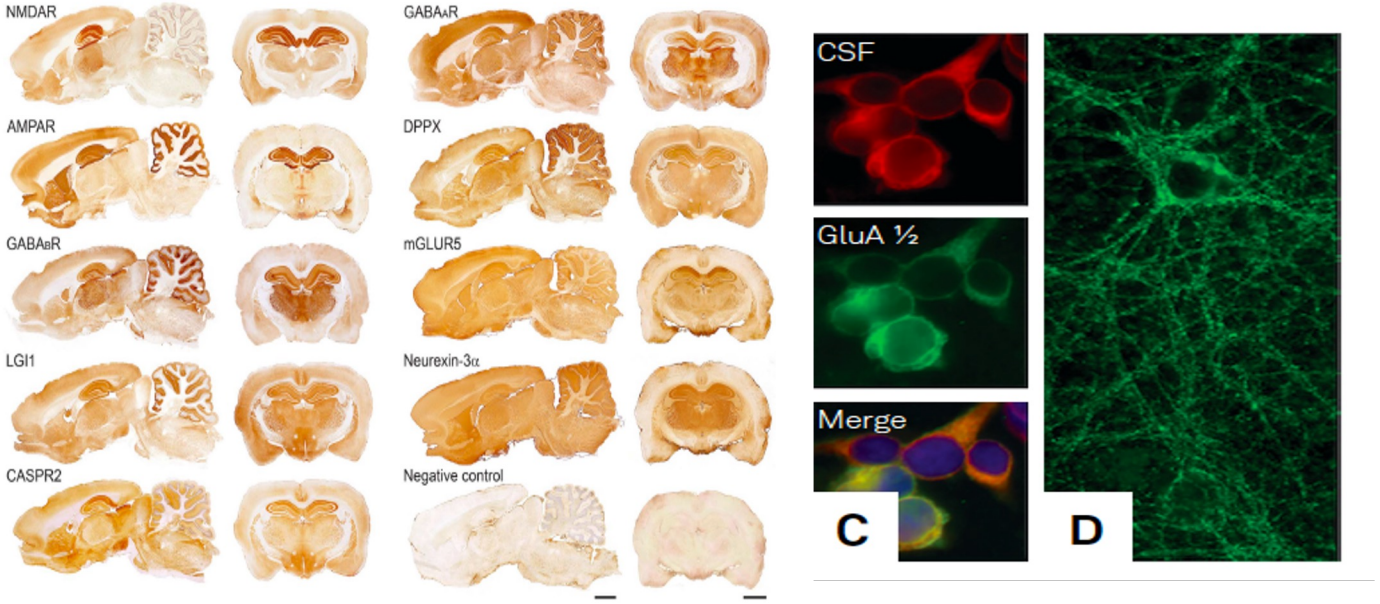
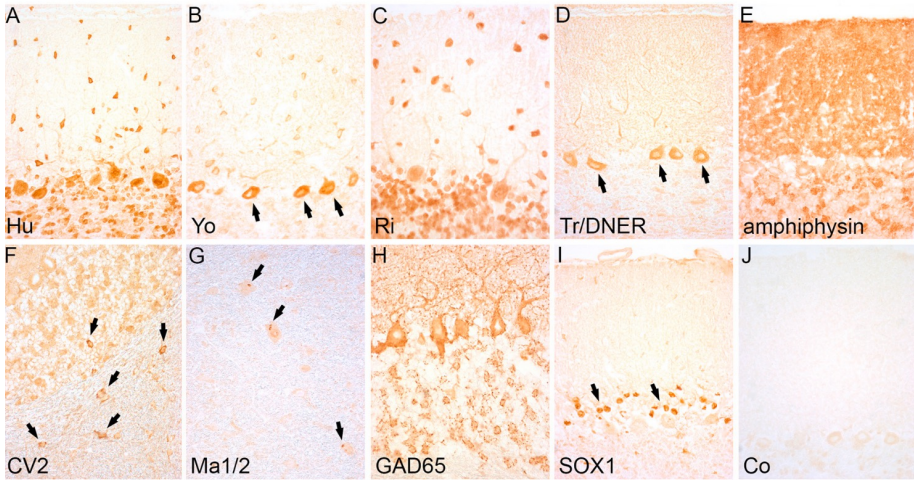
Técnicas para detecção de anticorpos antineuronais

TBA e CBA para Ac sinápticos



TBA para Ac intraneuronais



BrAIN
Brazilian AutoImmune encephalitis Network

McCraken, 2017; Dutra, 2018; Ricken 2018

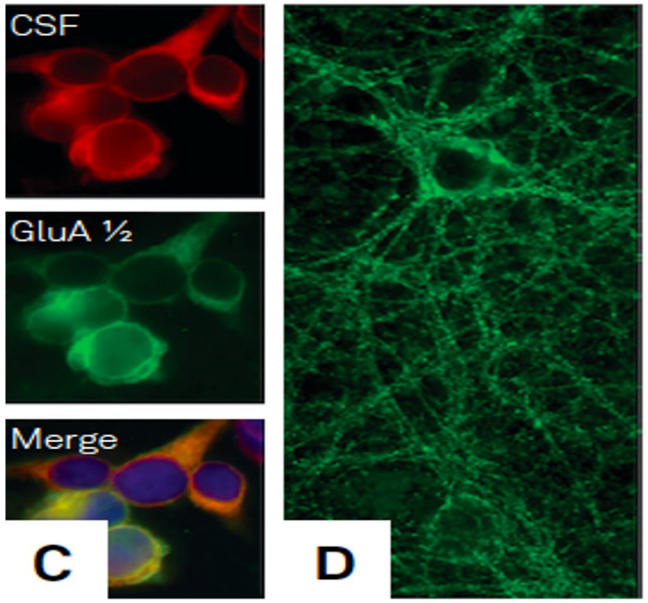
TBA: tissue-based assay

- TBA 2 subtipos: Não fixado (EAI) e pós-fixado (onconeurais)
- TBA detecta a maioria dos anticorpos nas EAI
  - NMDAR, AMPAR, LGI1, CASPR-2, GABA(B)R, GABA(A)R, mGluR1, mGluR5, DPPX, Tr/DNER, Neurexin3alpha e IgLON5, anti-GAD, e novos anticorpos
  - Detecta anti-AQP4
  - **Não detectam anti-MOG (epitopo humano), anti-Gly**

Gresa- Arribas, 2014; Ricken, 2018

CBA: cell-based assay

- CBA isolado: 2-14% falso positivo ou falso negativo
- CBA negativo pode ocorrer em kits comerciais (proteínas danificadas na fixação)



Cell-based assay

Cultura de neurônios

Table 2 Number of true-positive and true-negative cases (as determined by the clinical testing kits and research laboratory, or research laboratory alone) along with corresponding sensitivity and specificity measures of the commercial testing kits

	True positive	True negative	Sensitivity	Specificity
NMDAR serum	50	240	86% (n = 43)	99.2% (n = 238)
NMDAR CSF	38	399	92.1% (n = 35)	99.8% (n = 398)
LGI1 CSF	8	237	62.5% (n = 5)	100% (n = 237)
Caspr2 CSF	3	242	66.7% (n = 2)	100% (n = 242)
AMPA CSF	1	422	0% (n = 0)	100% (n = 244)
$GABA_B$	4	241	100% (n = 4)	100% (n = 241)
GAD65	7	238	100% (n = 7)	100% (n = 238)

Abbreviations: AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; Caspr2 = contactin-associated protein-like 2; LGI1 = leucine-rich glioma-inactivated 1; GABA= γ-aminobutyric acid; GAD65 = glutamic acid decarboxylase 65 kDa; NMDAR = NMDA receptor.

McKraken, 2017

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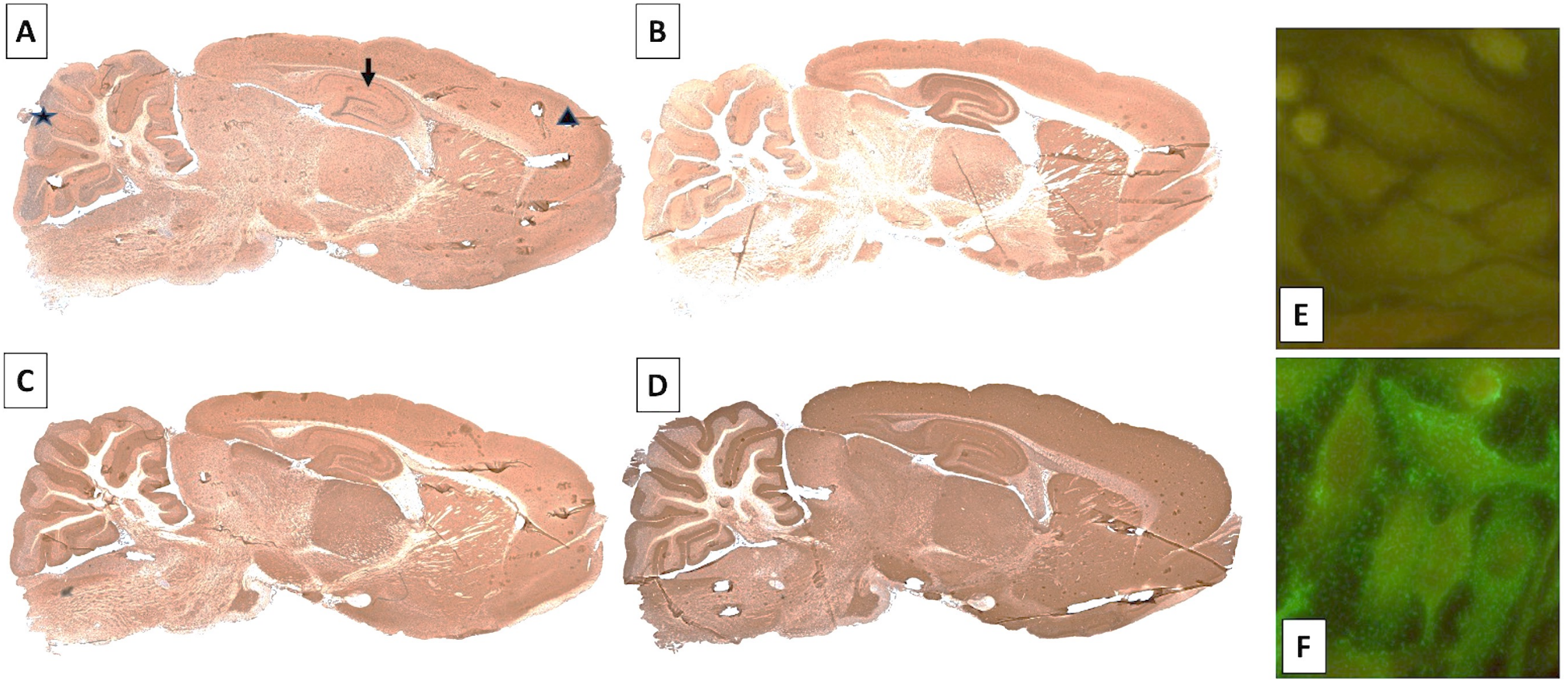
Brazilian AutoImmune encephalitis Network



PRIMEIRO TBA / CBA NO BRASIL

Por quais motivos não testar apenas no LCR?

- Na encefalite associada a anticorpos anti-CASPR-2
  - 38 pacientes, 100% soro, 10% neg LCR

- Na encefalite associada a anticorpos anti-LGI1
  - Sensibilidade CSF menor do que no soro (100% soro, 57% LCR)

- Na encefalite associada a anticorpos anti-Glicina
  - 52 pacientes, 11% apenas soro

- Na encefalite associada a anticorpos anti-MOG
  - Sensibilidade maior no soro

BrAIN
Brazilian AutoImmune encephalitis Network

Carvajal-Gonzalez, 2014; McCraken, 2017, van Sonderen 2016

Com quais técnicas testar?

- Sensibilidade dos métodos (TBA + CBA) para encefalite anti-NMDA no soro 85%
- **Falso positivo na testagem sérica CBA:**
  - CBA sérico positivo em esquizofrenia, CJD, Doença de Parkinson, e individuos saudáveis.
  - Tais amostras testadas de forma pareada com CBA+ TBA eram negativas.
- Não usar CBA sem confirmação de segunda técnica em soro
- **Falso positivo na testagem LCR CBA: 11%**

Zandi MS, 2011; Mackay, 2012; Gresa- Arribas, 2014; Ricken, 2018; Bastianseen, 2022

Hiperexcitabilidade

THELANCET-D-16-02270

S0140-6736(16)31459-3

Morvan syndrome as a paraneoplastic disorder of thymoma with anti-CASPR2 antibodies

Thiago Cardoso Vale, José Luiz Pedroso*, Lívia Almeida Dutra, Lyamara Azevedo, Lucio Huebra Pimentel Filho, Lucila B F Prado, Romana Hoftberger, Gilmar F Prado, Orlando G Barsottini*

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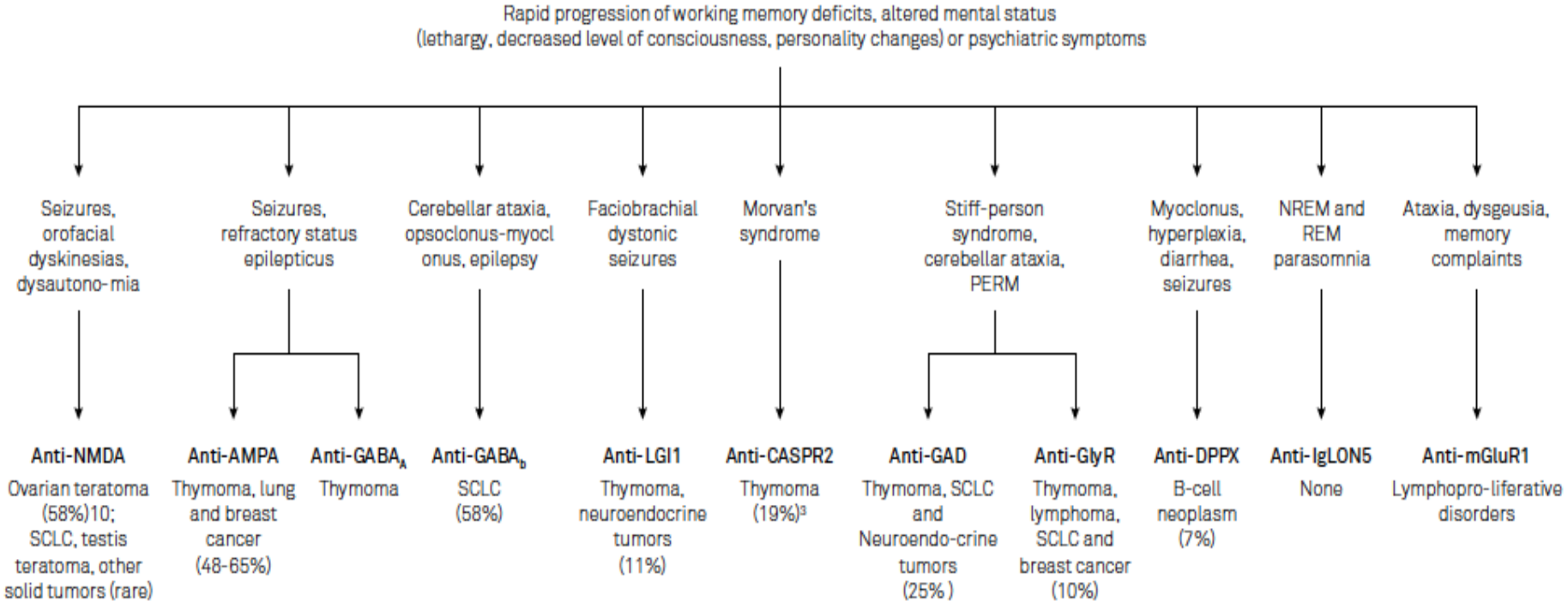
EAI fisiopatologia: anticorpos

- Anticorpos **neurogliais**
- Correlação anticorpo-fenótipo



BrAIN
Brazilian AutoImmune encephalitis Network

Dutra, 2018

BrAIN
Brazilian AutoImmune encephalitis Network

Brazilian autoimmune encephalitis network (BrAIN): antibody profile and clinical characteristics from a multicenter study

Bruna de Freitas Dias[1], Fabio Fieni Toso[1], Maria Eduarda Slhessarenko Fraife Barreto[1], René de Araújo Gleizer[1], Alessandra Dellavance[2], Pedro André Kowacs[3], Helio Teive[4], Mariana Spitz[5], Aline Freire Borges Juliano[6], Letícia Januzi de Almeida Rocha[7], Pedro Braga-Neto[8], Paulo Ribeiro Nóbrega[8], Jamary Oliveira-Filho[9], Ronaldo Maciel Dias[10], Clécio de Oliveira Godeiro Júnior[11], Fernanda Martins Maia[12], Rodrigo Barbosa Thomaz[1], Mara Lúcia Santos[13], Eduardo Sousa de Melo[14], Adaucto Wanderley da Nóbrega Júnior[15], Katia Lin[15], Orlando Graziani Povoas Barsottini[16], Verena Endmayr[17,18], Luís Eduardo Coelho Andrade[19], Romana Höftberger[17,18] and Lívia Almeida Dutra[1*]

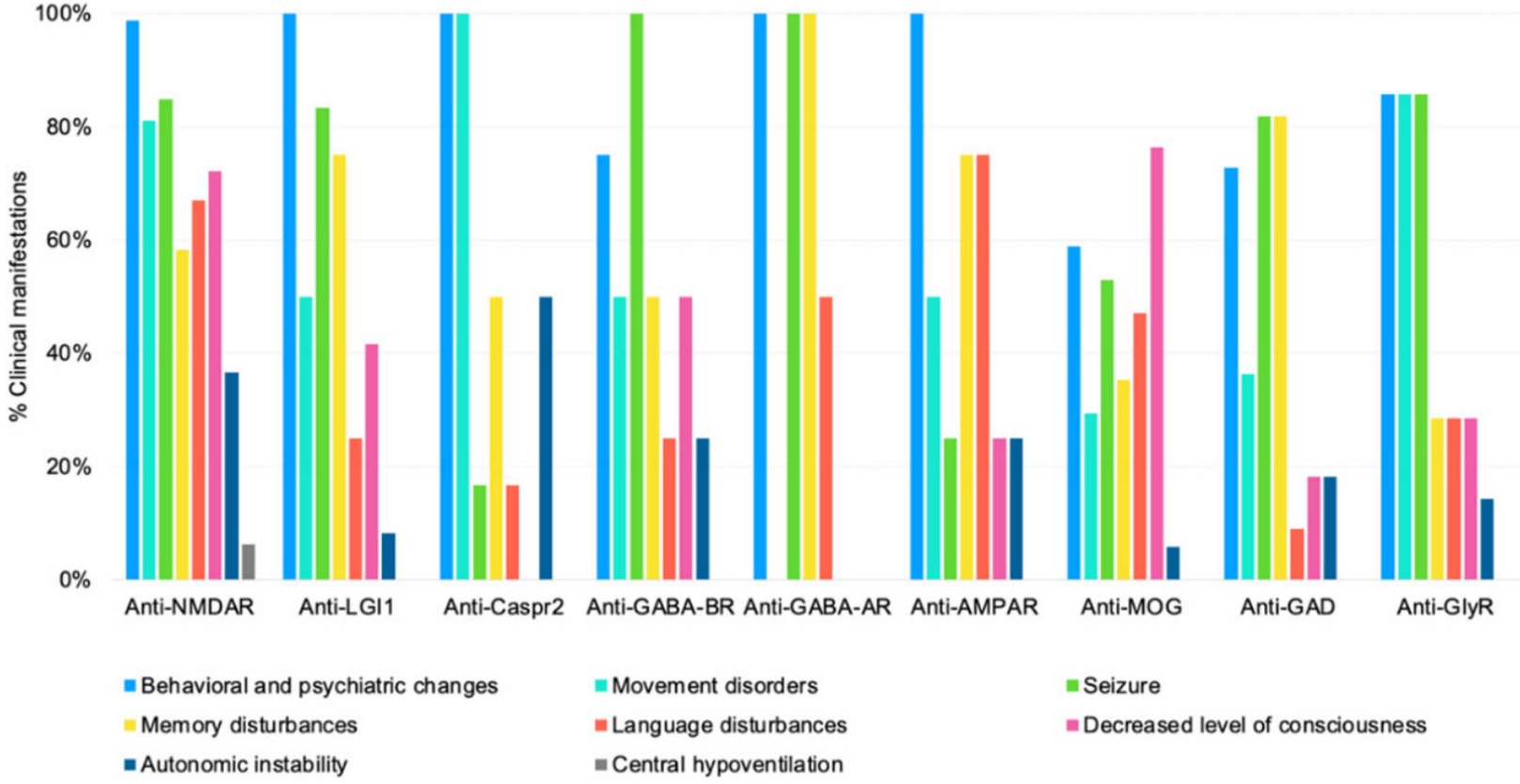
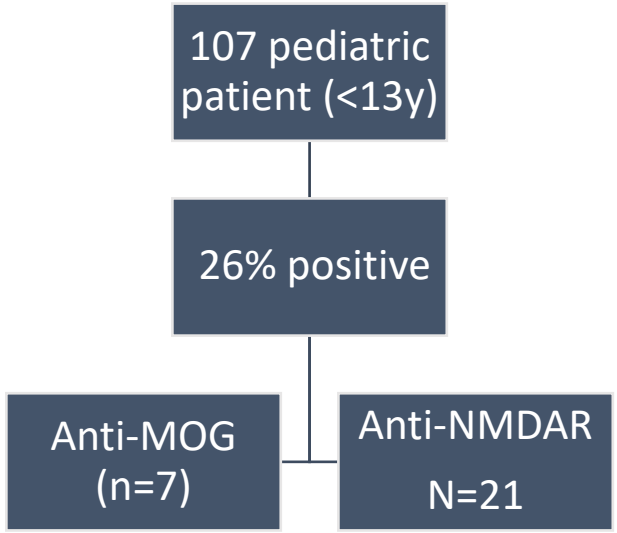


FIGURE 2
Clinical manifestations by the antineuronal antibody. NMDAR, N-methyl-D-Aspartate receptor; LGI1, Leucine-rich glioma inactivated 1; CASPR2, Contactin-associated protein 2; GABA-BR, Gamma-aminobutyric acid-B receptor; GABA-AR, Gamma-aminobutyric acid-A receptor; AMPAR, a-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor; MOG, Myelin oligodendrocyte glycoprotein; GAD, Glutamic acid decarboxylase; GlyR, Glycine receptor.

Front. Immunol. 14:1256480. doi: 10.3389/fimmu.2023.1256480

AIE in children is different when compared to adults

* Most common antibodies are anti-NMDAR, anti-MOG, anti-GAD (Spain, Denmark, China)
  * Other antibodies rarely reported in children (anti-GABA A, anti-AMPA, anti-LGI1, anti-Glyc)
  * Clinical phenotype was consistent with and clinical criteria for possible AIE was met

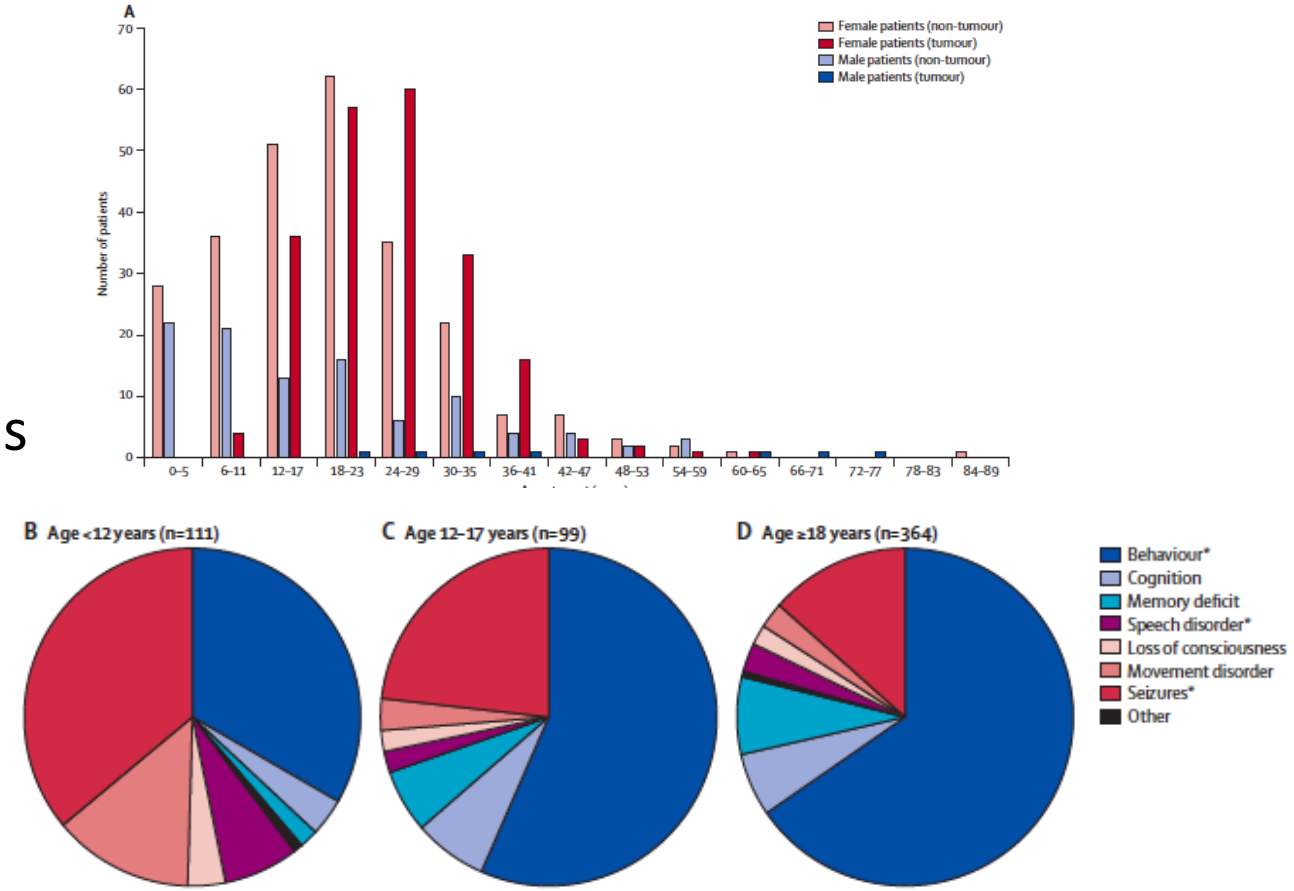


Dutra, *in preparation*

Armangue, 2020; Cellutti 2020, deBrujin 2020, Han 2022

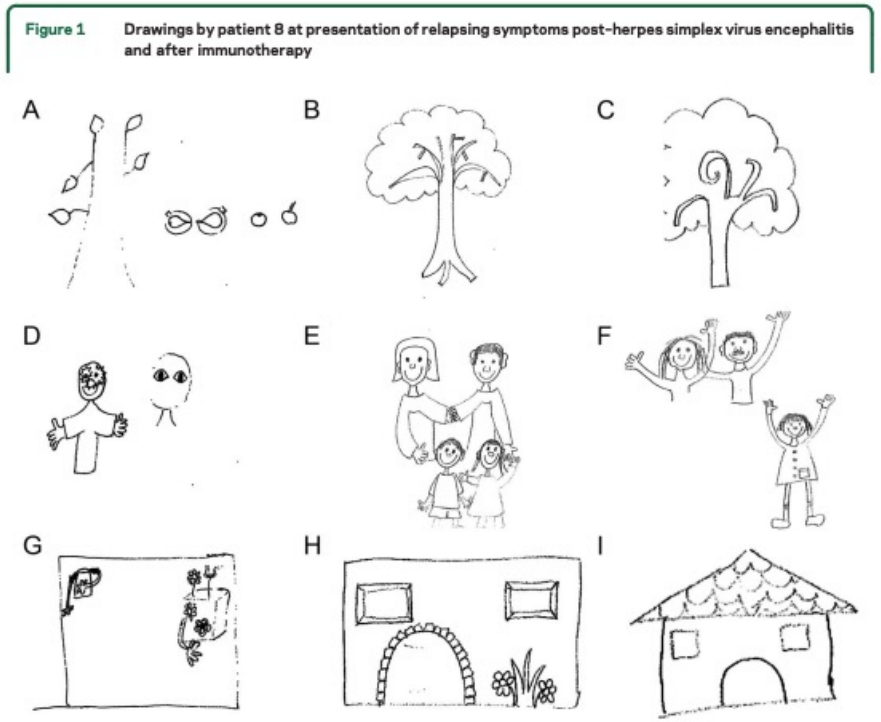
AIE in children is different when compared to adults

* Tumor association in children is lower
* Viral trigger more consistently reported (EBV, VZV)
* Seizures, movement disorders, hemiparesis very common



Danieli, 2017; Titulaer, 2014, Dalmau 2020

AIE in children is different when compared to adults



Drawings by patient 8 at the time of relapsing symptoms (tree, family, and house, A, D, and G), 3 weeks after immunotherapy (B, E, H), and at a 6 months follow-up (C, F, I). At presentation of relapsing symptoms, the patient had severe anterograde amnesia, confusion, disorganized thoughts, and disorientation to place, time, and person. After immunotherapy, her symptoms resolved except for amnesia and temporal orientation.

* 27% of HSV encephalitis develop anti-NMDAR encephalitis, usually in the first 2 months
* Some children presented 12 days after HSV symptoms, all had neg PCR
* ABS remain positive for over 1 year
* AIE after HSV in children > worse prognosis

Armangue, 2015

A clinical approach to diagnosis of autoimmune encephalitis

Francesc Graus, Maarten J Titulaer, Ramani Balu, Susanne Benseler, Christian G Bien, Tania Cellucci, Irene Cortese, Russell C Dale, Jeffrey M Gelfand, Michael Geschwind, Carol A Glaser, Jerome Honnorat, Romana Höftberger, Takahiro Iizuka, Sarosh R Irani, Eric Lancaster, Frank Leypoldt, Harald Prüss, Alexander Rae-Grant, Markus Reindl, Myrna R Rosenfeld, Kevin Rostásy, Albert Saiz, Arun Venkatesan, Angela Vincent, Klaus-Peter Wandinger, Patrick Waters, Josep Dalmau

Lancet Neurol 2016; 15: 391–404

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)

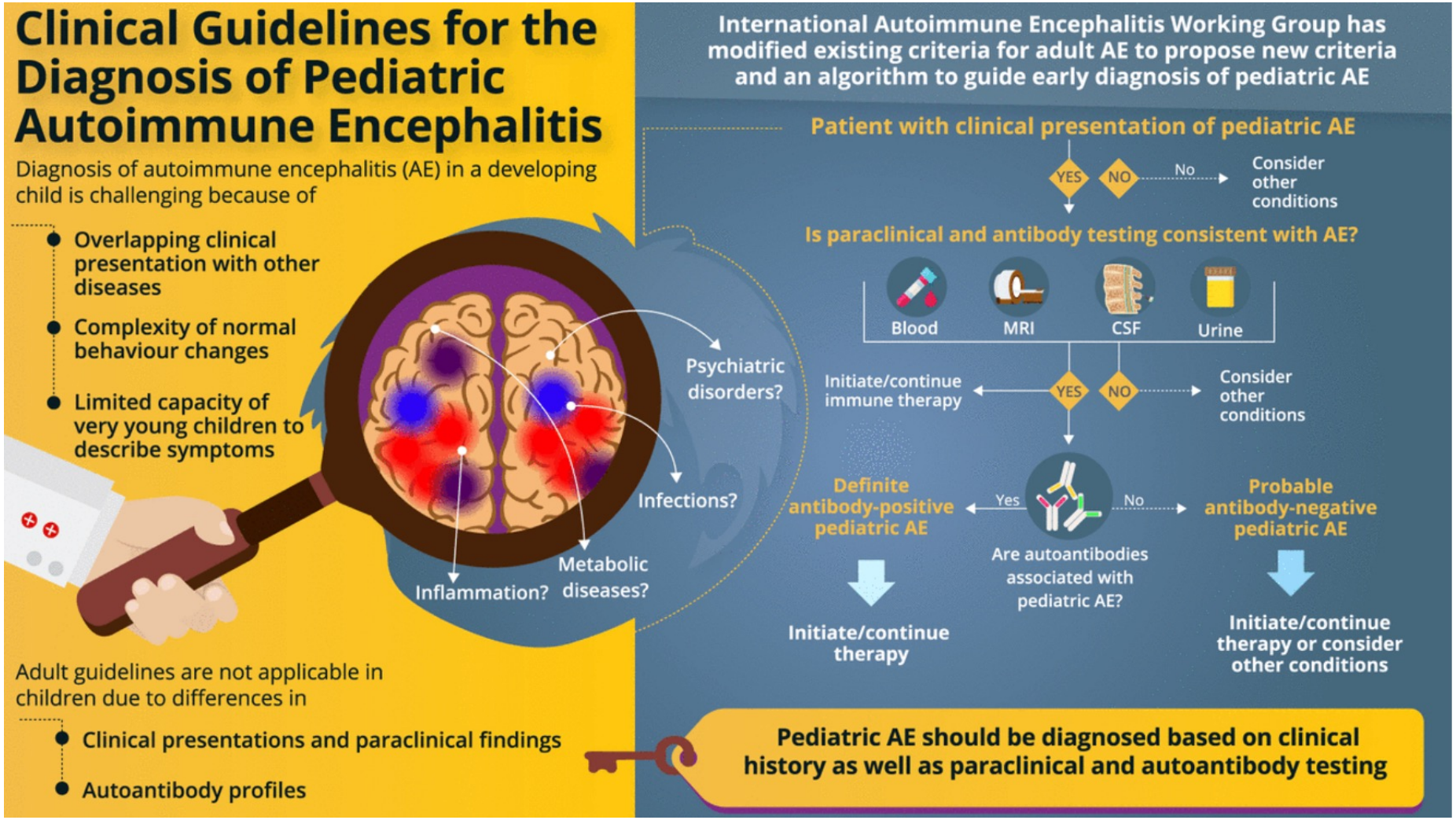
Panel 7: Criteria for autoantibody-negative but probable autoimmune encephalitis

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.[102]

AIE pediátrico: critérios diagnósticos



Celutti, 2020

O que esperar na fase aguda

- Coortes EAI anti-NMDAR
  - **30-77% dos pacientes necessitam de vaga de UTI**

Titulaer M., et al. *Lancet* 2013
Xu X., et al. Neurol N. Neuroinflamm 2020

- População em UTI - (85% com Ac contra antígenos de superfície)

  - Tempo de UTI: 24 dias (IIQ 7-45)
  - Ventilação mecânica (57%)
  - Sepse ou choque séptico (33%)
  - Status epilepticus (35%)
  - Disautonomia (45%)

Schubert J., et al. *Neurol N. Neuroinflamm* 2019

O que esperar na fase aguda

- **<u>Terapia de segunda linha: 7-46%</u>**

Xu X., et al. Neurol N. Neuroinflamm 2020
Thaler FS., et al., *Neurol N. Neuroinflamm 2021*

- Para inicio do tratamento de segunda linha, precisamos avaliar:
  - Gravidade da doença
  - Resposta ao tratamento de primeira linha
  - Prognóstico de longo prazo

NEOS score

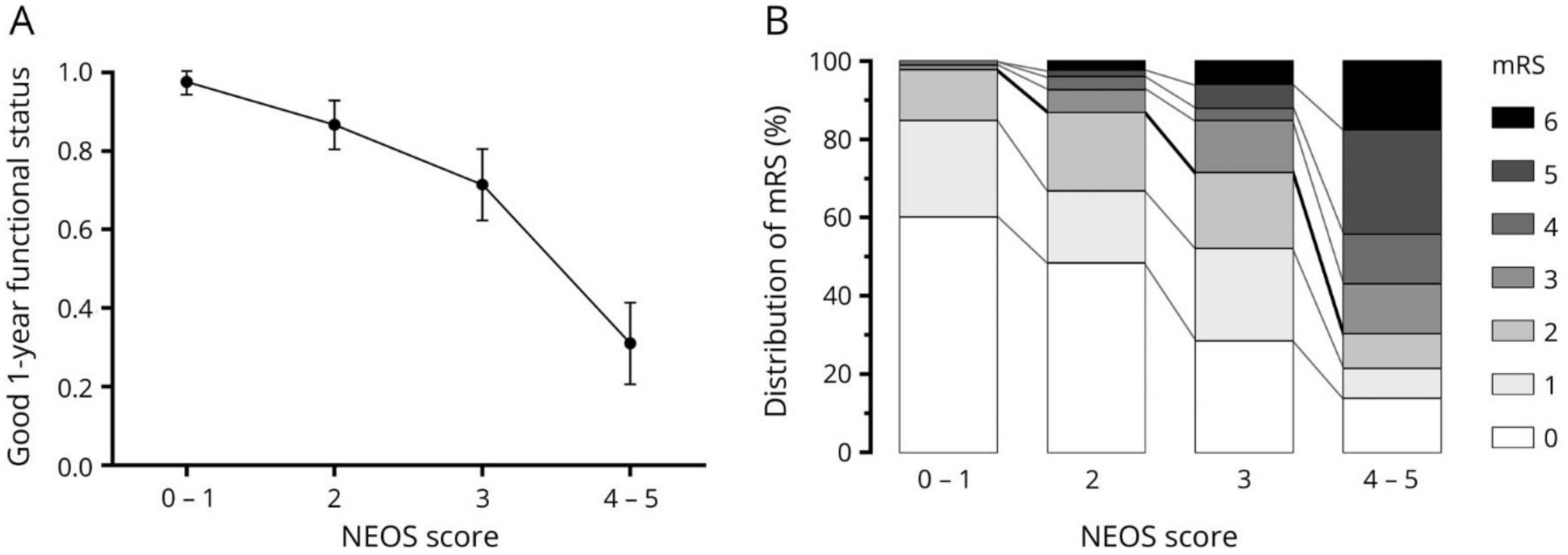
- 382 pacientes com EAI anti-NMDAR
  - Variáveis clínicas preditoras de gravidade e status funcional após 1 ano

Table 3 Multivariate regression model and point values used for the NEOS score

Patient characteristic	Odds ratio (95% CI)	*p*	NEOS score points
ICU admission required	5.89 (2.17–15.99)	0.001	1
No clinical improvement after 4 wk of treatment	12.10 (6.38–22.93)	<0.001	1
No treatment within 4 wk of symptom onset	2.52 (1.39–4.55)	0.002	1
Abnormal MRI	2.20 (1.21–3.98)	0.009	1
CSF WBC count >20 cells/μL	2.10 (1.13–3.91)	0.019	1

Balu R., et al. *Neurology* 2019

NEOS score


A
Good 1-year functional status
1.0
0.8
0.6
0.4
0.2
0.0
0 – 1
2
3
4 – 5
NEOS score
B
Distribution of mRS (%)
100
80
60
40
20
0
0 – 1
2
3
4 – 5
NEOS score
mRS
6
5
4
3
2
1
0

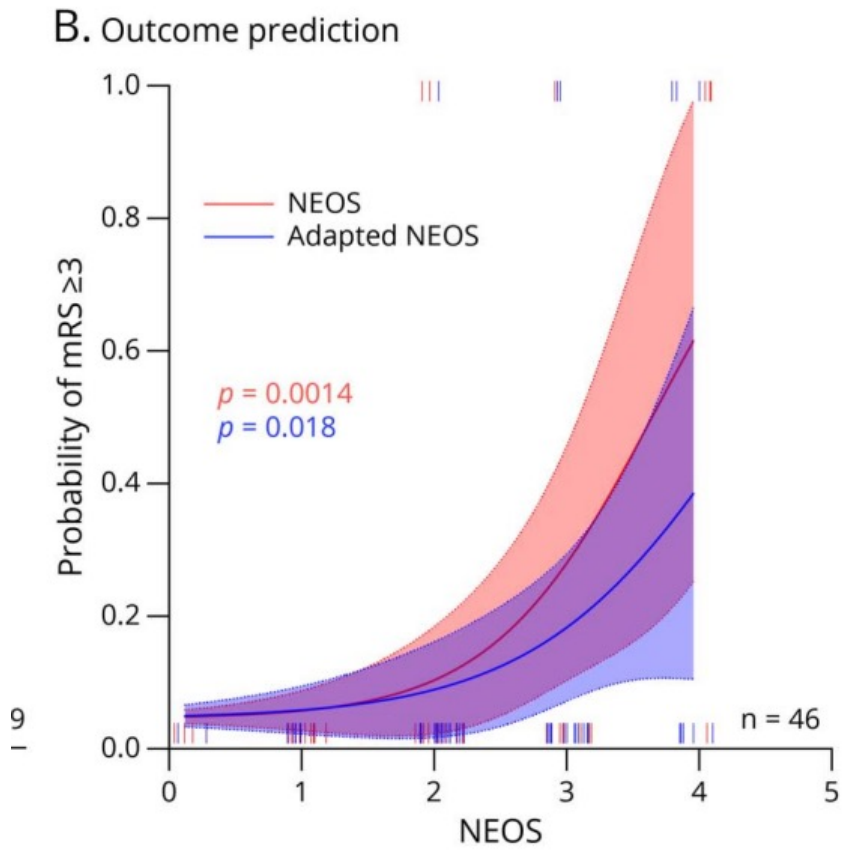
AIE in children: prognosis

* NEOS score validated for children, in a pediatric cohort of 59 patients, mean age 8 years. Inferior intervals for ICU and treatment for children

* Adapted NEOS = NEOS

* **NEOS = 3 predicts mRs ≥3, deficits of executive function (p = 0.048) and memory (p = 0.043) in 1 year**

Patients with anti-NMDAR after HSV and those younger were at higher risk, confirming prior data from Arrmangue 2018



Nicolaus, 2023

Escalas clínicas, quais utilizar?

- 501 pacientes - EAI anti-NMDAR seguidos por pelo menos 4 meses:
  - Critério para início de terapia de segunda-linha: **mRS ≥4 após 4 semanas**
  - 203/252 80% dos pacientes apresentaram desfecho favorável (mRS 0-2)
- mRS foi utilizada inicialmente para avaliar resposta ao tratamento e prognóstico de longo prazo

Titulaer M., et al. *Lancet* 2013

Escalas clínicas, quais utilizar?

- CASE
  - Capaz estratificar gravidade de pacientes dentro da mesma mRS
  - 9 domínios, com score total 0-27
  - Pode ser utilizada para avaliação de resposta a imunoterapia e acompanhamento

1. **Crises epilépticas**
2. **Memória**
3. **Sintomas psiquiátricos**
4. **Nível de consciência**
5. **Linguagem**
6. **Discinesia/distonia**
7. **Instabilidade de marcha/ataxia**
8. **Disfunção tronco cerebral**
9. **Fraqueza**

Lim J., *et al. Ann. Of Neurol.* 2019

ESCALA CASE – exemplo prático

JDS, 32 anos

Diagnóstico de EAI anti-NMDAR

30 dias após tratamento de primeira linha

- mRS = 5
- CASE = 21

crises controladas, abre os olhos ao estímulo doloroso, não se comunica, discinesia leve, restrita ao leito, IOT

1. **Crises epilépticas (1)**
2. **Memória (3)**
3. **Sintomas psiquiátricos (3)**
4. **Nível de consciência (2)**
5. **Linguagem (3)**
6. **Discinesia/distonia (1)**
7. **Instabilidade de marcha/ataxia (3)**
8. **Disfunção tronco cerebral (2)**
9. **Fraqueza (3)**

ESCALA CASE – exemplo prático

Reavaliação após 30 dias:

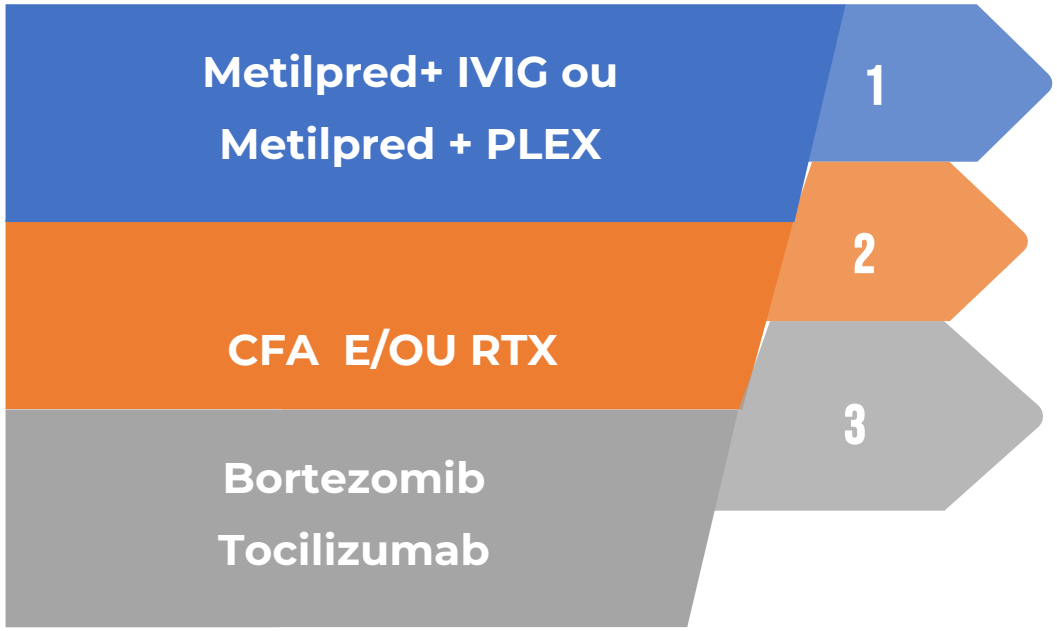
- mRS = 5
- CASE = 14

(crises controladas, mutismo, restrita ao leito, gastrostomia, mobiliza os 4 membros)

→ Melhora do nível de consciência e das discinesias, extubação

1. **Crises epilépticas (1)**
2. **Memória (3)**
3. **Sintomas psiquiátricos (3)**
4. **Nível de consciência (0)**
5. **Linguagem (3)**
6. **Discinesia/distonia (0)**
7. **Instabilidade de marcha/ataxia (3)**
8. **Disfunção tronco cerebral (1)**
9. **Fraqueza (1)**

Tratamento das encefalites autoimunes



ARTICLE OPEN ACCESS

Rituximab Treatment and Long-term Outcome of Patients With Autoimmune Encephalitis

Real-world Evidence From the GENERATE Registry

Neurol Neuroimmunol Neuroinflamm 2021;8:e1088. doi:10.1212/NXI.0000000000001088

- 358 pacientes, 46% receberam rituximab
- Media de início de tratamento 16 dias após inicio da doença
- Recorrência: NMDAR 19%, LGI1 20%, CASPR2- 11%)

Tratamento das encefalites autoimunes

- Séries de casos: poucos pacientes tratados com **imunossupressores orais**
  - NMDAR 8,9% / LGI1 13%
  - Consenso Delphi pediátrico: não recomenda
  - Meta-análise pactes pediátricos: sem benefício
- Evidências favoráveis a demais tratamentos
  - Rituximab – grande experiência e evidência Real-World disponível
  - Bortezomib – em ascensão

Avaliando a resposta ao tratamento

→ Na prática, a resposta ao tratamento de primeira linha pode ser avaliada após os **primeiros 14 dias**

- A estratificação de gravidade e resposta ao tratamento pode ser realizada utilizando as ferramentas **NEOS, mRS e CASE**

- Avaliação cognitiva seriada (MOCA ou MEEM)

AIE in children: rituximab

Rituximab Treatment and Long-term Outcome of Patients With Autoimmune Encephalitis

Real-world Evidence From the GENERATE Registry

* German Network for Research on Autoimmune Encephalitis (GENERATE) included only adults
* Real-world evidence (classe IV) + follow-up 41 meses
* 149 pacientes (NMDA = 81 / GAD = 31 / LGI1 = 26 / CASPR2 = 11)
* Functional recovery in 91% (NMDAR), 80% (LGI1), 63% (CASPR2)

-

- Média de início de tratamento 16 dias após inicio da doença
- Recorrência: NMDAR 19%, LGI1 20%, CASPR2- 11%)

Efficacy and Safety of Rituximab in Chinese Children With Refractory Anti-NMDAR Encephalitis

* 8 patients with refractory anti-NMDAR

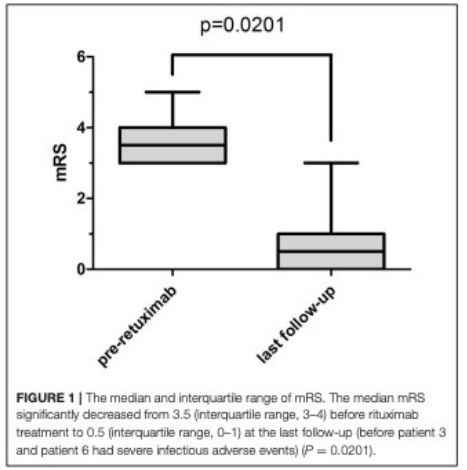


FIGURE 1 | The median and interquartile range of mRS. The median mRS significantly decreased from 3.5 (interquartile range, 3–4) before rituximab treatment to 0.5 (interquartile range, 0–1) at the last follow-up (before patient 3 and patient 6 had severe infectious adverse events) ($P = 0.0201$).

Thaler, 2021; Dou.2020

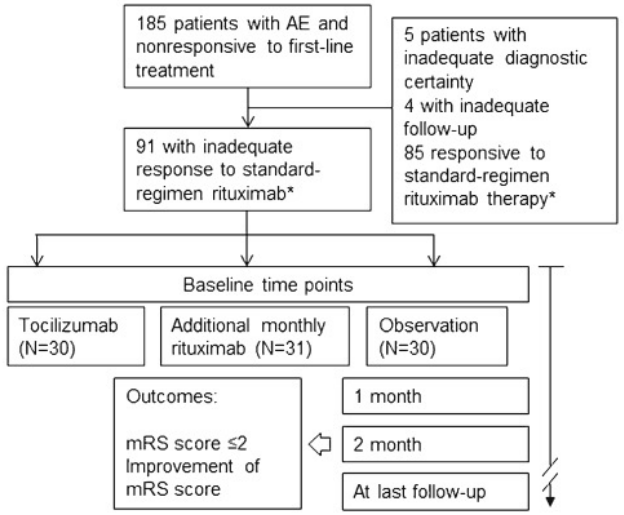
AIE in children: bortezomib and tocilizumabe

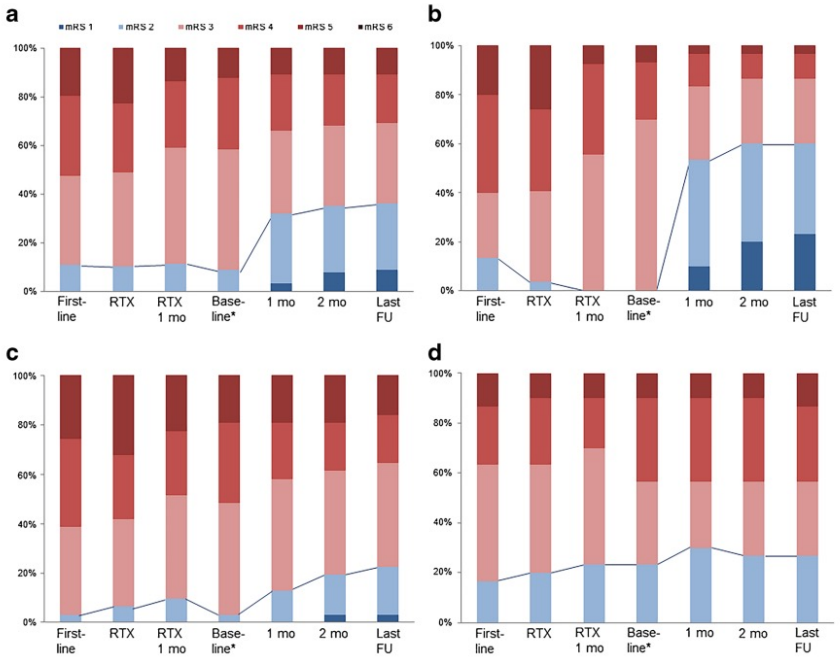
Neurotherapeutics (2016) 13:824–832
DOI 10.1007/s13311-016-0442-6

ORIGINAL ARTICLE

Tocilizumab in Autoimmune Encephalitis Refractory to Rituximab: An Institutional Cohort Study

Woo-Jin Lee [1,2] · Soon-Tae Lee [1,2] · Jangsup Moon [1,2] · Jun-Sang Sunwoo [1,2] ·





Contents lists available at ScienceDirect
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journal homepage: www.elsevier.com/locate/pnu

Clinical Observations

Tocilizumab in Refractory Autoimmune Encephalitis: A Series of Pediatric Cases

Rachel L. Randell, MD [a,*], Ashley V. Adams, BA [b], Heather Van Mater, MD [c]
[a] Department of Pediatrics, Duke University School of Medicine, Durham, North Carolina
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[c] Division of Pediatric Rheumatology, Department of Pediatrics, Duke University, Durham, North Carolina

Review > J Neurol. 2020 Aug;267(8):2462-2468. doi: 10.1007/s00415-020-09988-w. Epub 2020 Jun 13.

Refractory anti-NMDAR encephalitis successfully treated with bortezomib and associated movements disorders controlled with tramadol: a case report with literature review

Serena Marita Lazzarin [1 2], Marco Vabanesi [# 1 2], Giordano Cecchetti [1 2], Raffaella Fazio [1], Giovanna Franca Fanelli [2], Maria Antonietta Volonté [1], Angela Genchi [1], Antonino Giordano [1], Vittorio Martinelli [1], Sergio Colombo [3], Paolo Beccaria [3], Milena Mucci [3], Jacopo Peccatori [4], Massimo Filippi [5 6 7 8], Fabio Minicucci [2]

Case Reports > J Neuroimmunol. 2021 Jun 15;355:577565. doi: 10.1016/j.jneuroim.2021.577565. Epub 2021 Mar 31.

Refractory NMDA-receptor encephalitis in a teenager: A novel use of Bortezomib

Tratamento das EAI no Brasil

Brazilian autoimmune encephalitis network (BrAIN): antibody profile and clinical characteristics from a multicenter study

Bruna de Freitas Dias[1], Fabio Fieni Toso[1], Maria Eduarda Slhessarenko Fraife Barreto[1], René de Araújo Gleizer[1], Alessandra Dellavance[2], Pedro André Kowacs[3], Helio Teive[4], Mariana Spitz[5], Aline Freire Borges Juliano[6], Letícia Januzi de Almeida Rocha[7], Pedro Braga-Neto[8], Paulo Ribeiro Nóbrega[8], Jamary Oliveira-Filho[9], Ronaldo Maciel Dias[10], Clécio de Oliveira Godeiro Júnior[11], Fernanda Martins Maia[12], Rodrigo Barbosa Thomaz[1], Mara Lúcia Santos[13], Eduardo Sousa de Melo[14], Adaucto Wanderley da Nóbrega Júnior[15], Katia Lin[15], Orlando Graziani Povoas Barsottini[16], Verena Endmayr[17,18], Luís Eduardo Coelho Andrade[19], Romana Höftberger[17,18] and Lívia Almeida Dutra[1]*

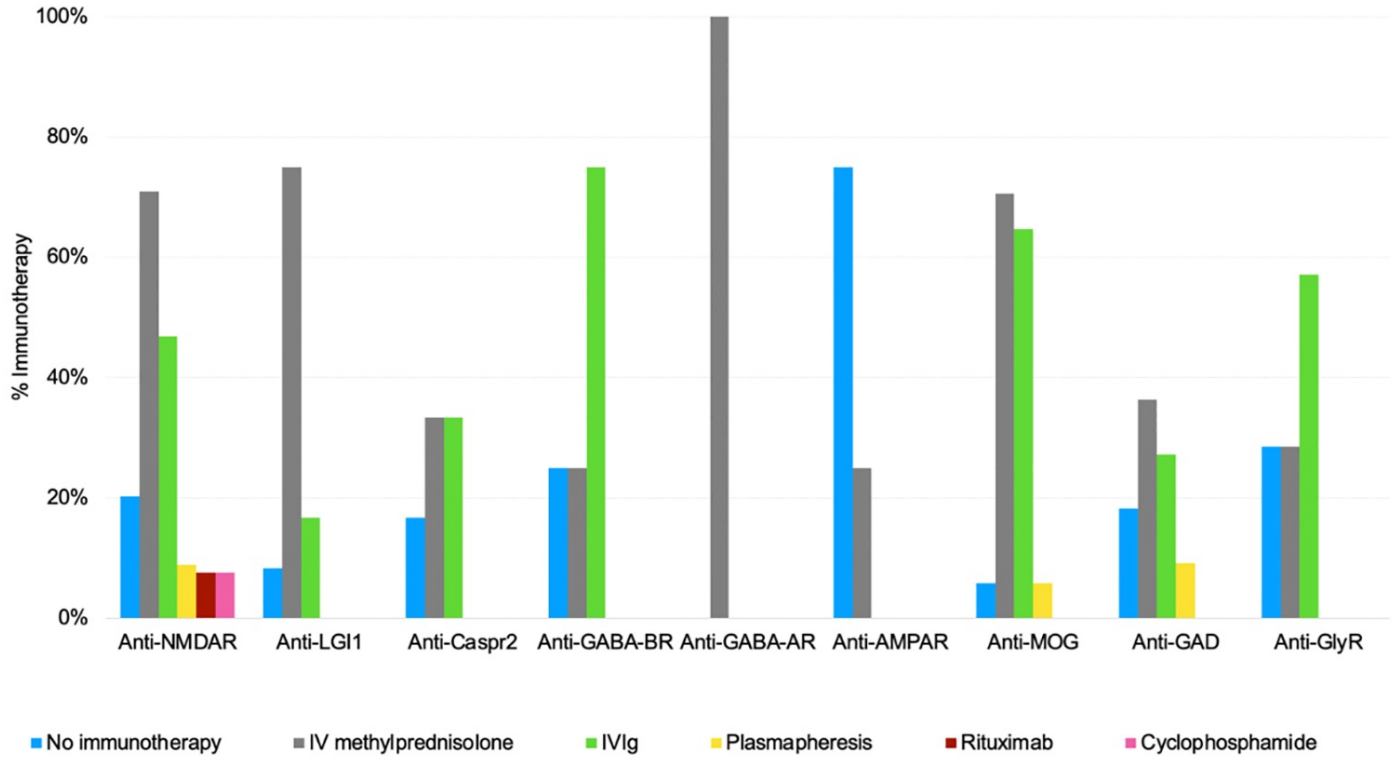


FIGURE 3
The treatment protocol used by each AIE phenotype. NMDAR, N-methyl-D-Aspartate receptor; LGI1, Leucine-rich glioma inactivated 1; CASPR2, Contactin-associated protein 2; GABA-BR, Gamma-aminobutyric acid-B receptor; GABA-AR, Gamma-aminobutyric acid-A receptor; AMPAR, a-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor; MOG, Myelin oligodendrocyte glycoprotein; IgLON5, Immunoglobulin-like cell adhesion molecule 5; GAD, Glutamic acid decarboxylase; GlyR, Glycine receptor; IVIg, Intravenous immunoglobulin; IV, intravenous.

Front. Immunol. 14:1256480.

Tratamento das EAI no Brasil

Diagnosis and treatment of autoimmune encephalitis in Brazil: an urgent call to action

Tratamento e diagnóstico das encefalites autoimunes no Brasil: um apelo urgente à ação

Lívia Almeida Dutra[1]

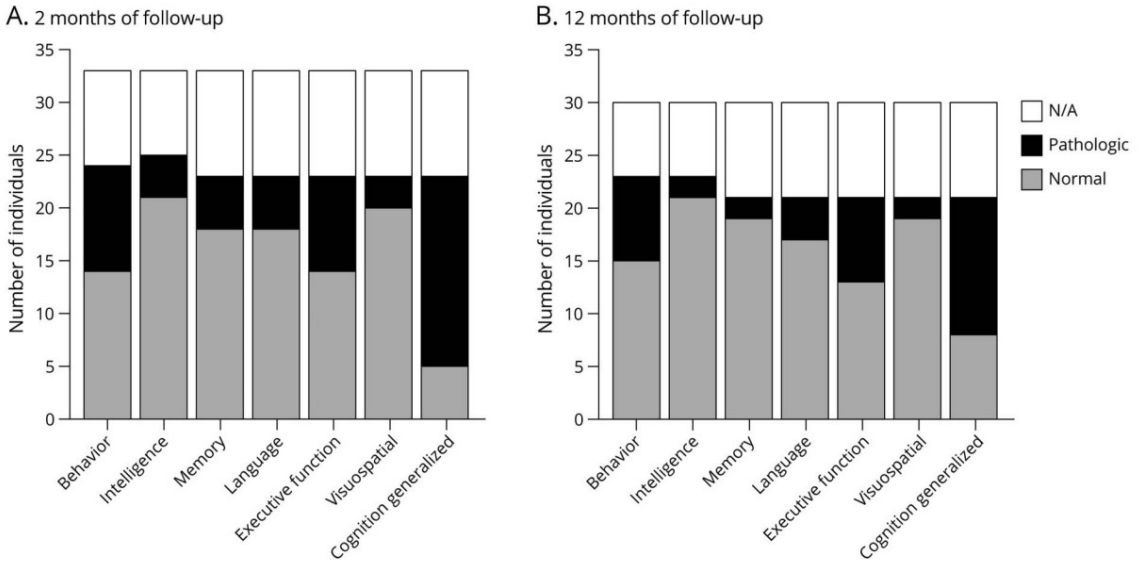
[1] Faculdade Israelita de Ciências da Saúde Albert Einstein, Instituto do Cérebro do Hospital Israelita Albert Einstein, São Paulo SP, Brazil.

Arq. Neuropsiquiatr. 2024;82(2):s00441781442.

AIE in children: prognosis

BCTRIMS 2023
24th ANNUAL MEETING
XXIV Congresso Brasileiro de Esclerose Múltipla e Neuromielite Óptica
June 14th to 17th, 2023
Tivoli Mofarrej São Paulo - SP

* Most children and adolescents return to their daily life and previous activities
* Low quality of life, low executive function
* On the other hand, some cognitive skills, such as general intelligence, show good overall recovery over time



Tarantino, 2021; Nicolaus, 2023

Fase crônica – prognóstico

- Cerca de 80% retornam para mRS ≤ 2 em uma mediana de 24 meses, após tratamento adequado

Titulaer M., et al. *Lancet* 2013

- No entanto… estudos de follow-up mostram:
  - Disfunção cognitiva
  - Sintomas psiquiátricos
  - Distúrbios do sono
  - Impacto negativo na função psicosocial
  - Ausência de retorno a atividades previas

Blum RA., et al. *Epilepsy Behav* 2020
Yeshokumar A., et al. *Neurol N. Neuroinflamm 2020*
De Bruijn, M.A.A.M., et al. *Neurology* 2018

AIE in children: prognosis

* Danish series, 28 cases reported deficits in attention, quality of life, cognition and fatigue
* 64% returned to schoool, all had lower attention spam
* 12% hadd impulsivity
* 20% schoool dropput
* No correlation with treatment
* Pos-acute NMDAR syndrome

de Brujin, 2018

Escalas clínicas – quais utilizar

- Avaliação cognitiva
  - Na fase aguda e para o monitoramento de longo prazo

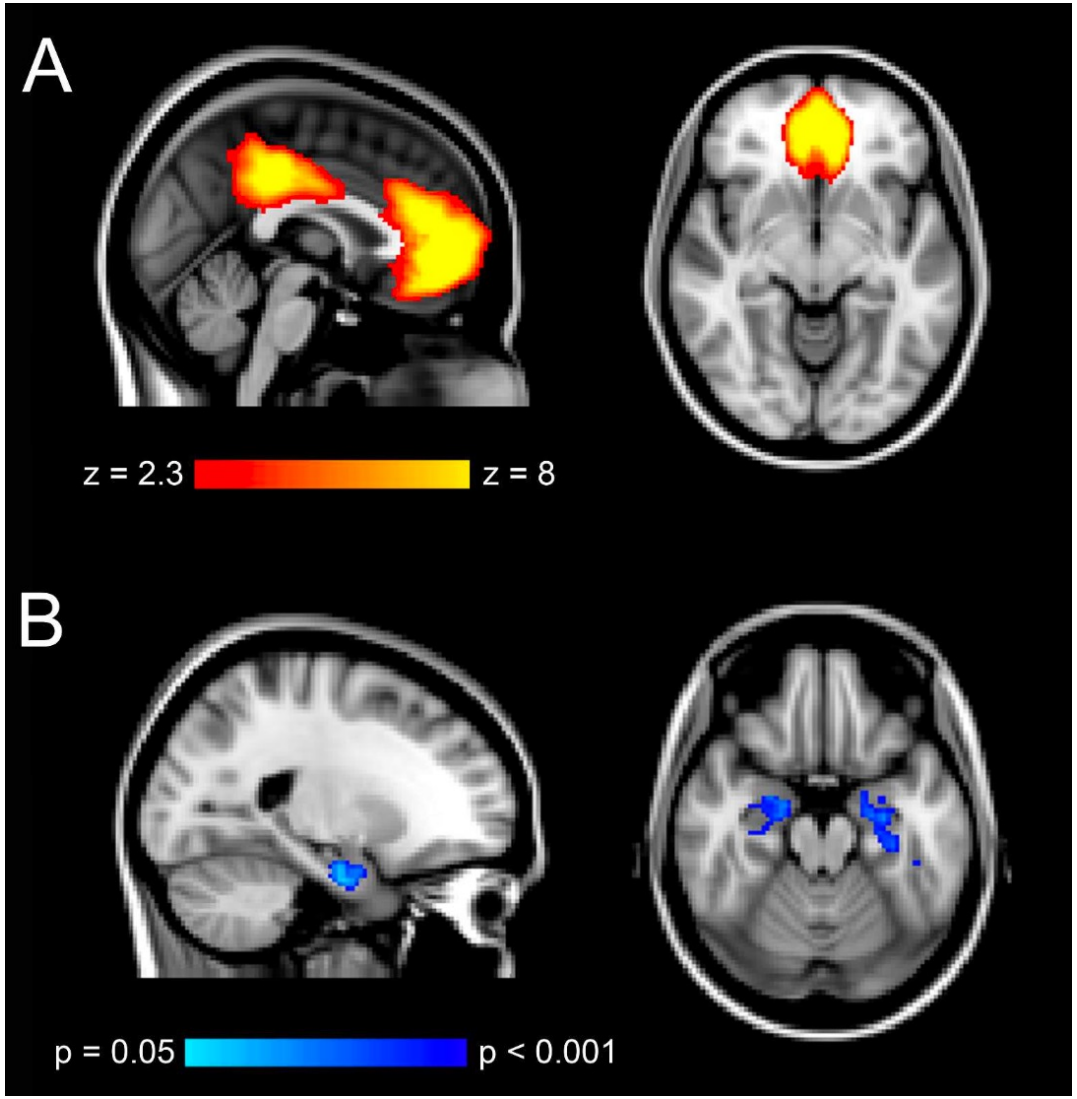
- Ferramentas utilizadas na literatura:
  - MEEM – (limitado para avaliação de memória e função executiva)
  - MOCA

Dalmau J., et al. *Lancet Neurol.* 2008
Morgan A., et al. *Neurology 2024*

Fase crônica – cognição

EAI anti-NMDAR

- Sequências avançadas RM crânio
  - Alterações volumétricas e da integridade microestrutural
  - RMf: redução de conectividade entre hipocampo e córtex pré-frontal medial (DMN)



Finke C., et al. Ann Neurol. 2013

Fase crônica

- Distúrbios do sono e humor
  - Hipersonolência (78%)
  - Despertar confusional (33%)
  - Depressão (HAM-D) (33%)
  - Hiperfagia (78%) e hipersexualidade (33%)

Ariño, H., et al. *Neurology* 2020

- Crianças com EA NMDAR:
  - apenas 64% retornaram a escola com desemprenho semelhante ao anterior
  - Alta pontuação em escalas de fadiga (PedsQL-MFS)

De Bruijn, M.A.A.M., et al. *Neurology* 2018

Fase crônica – o que monitoriar?

- Escalas de mRS e CASE

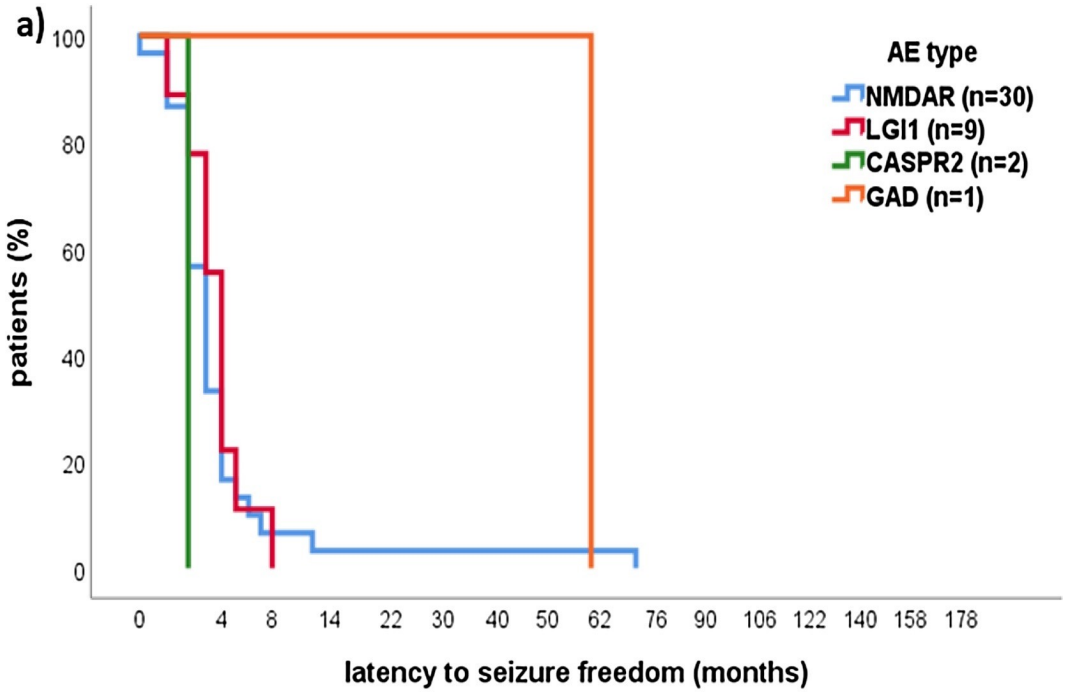
- Cognição
  - MOCA
  - MEEM
  - Avaliação neuropsicológica

- Sintomas psiquiátricos, fagida e alterações do sono

- Retorno para atividadades previamente desempenhadas
  - Em crianças, acompanhar marcos do desenvolvimento e retorno escolar

AIE: Mangement of seizures

* Overall adult and children do not develop epilepsy, rather seizures should be considered as symptomatic
* 110 Danish patients (43 NMDAR, 46 LGI1, 21 GABA-B) 89% seizure-free
* 320 patients, adult and children (NMDAR = 234 / LGI1 = 37 / CASPR2 = 12 /GABA-BR = 37) 3,1% had persistent seizures
* 83 chinese pediatric anti-NMDAR patietns, 8% had persistent seizures



deBrujin 2019; Qu, 2019; lyas-Feldmann 2021; Liu 2021

AIE in children do’s and dont’s

- Do search for anti-NMDAR in patients with HSV that recur or fail to improve
- Do consider tapper anticonvulsant as AIE remits
- Do order serum anti-MOG
- Do order autoimmune panel in CSF and sérum in patient with compatible clinical picture
- Do not use routineely oral immunussupressants in anti-NMDARE
- Do use NEOS score
- Do try to escalate therapy fast – 14 days
- Do monitor school dropout and cognitive domains after acute phase.
- Do search for tumors in children – increase interval for every two years, up to five years
- Do not insist in AIE diagnosis with clinical criteria is not met
- Remember post-acute NMDAR syndrome

Diagnostic criteria for autoimmune encephalitis: utility and pitfalls for antibody-negative disease

Josep Dalmau, Francesc Graus

- **Aplicar critério de EAI possível para testagem**
Misdiagnoses evitados se descartássemos AIE em pacientes com sintomas>3 meses sem sinais inflamatórios em RNM e LCR

- **Testar CSF e soro com duas técnicas.**
Casos clássicos como discinesia orofacial e FBDS podem ser testados com uma única técnica

- **Correta interpretação dos anticorpos** (títulos baixos, apenas em soro, correta interpretação do anti-GAD, anti-VGKC e anti-TPO não devem ser valorizados.

***Panel 2:* Criteria for probable antibody-negative autoimmune encephalitis**

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

Panel adapted from reference 9. *For paediatric patients, only one feature is required.[13] †Some inherited mitochondrial and metabolic disorders can present with symmetrical or asymmetrical MRI abnormalities, and with CSF inflammatory changes resembling an acquired autoimmune disorder.[14]

Diagnostic criteria for autoimmune encephalitis: utility and pitfalls for antibody-negative disease

Josep Dalmau, Francesc Graus

- Anti-GABA-AR e anti-IgLON5 não são testados comercialmente de rotina

- Anti-MOG mais sensível no soro – considerar e checar o título

- PANDAS, PANS, NORSE não são encefalite autoimune soronegativa provável

Erros diagnósticos em encefalites autoimunes

- Estudo retrospectivo 2014-2020, multicêntrico,
- Review de prontuários de pacientes que foram encaminhados por suspeita de encefalites autoimunes, mas que não fecharam critério.

- N=107 (27,2%) do total de encaminhamentos

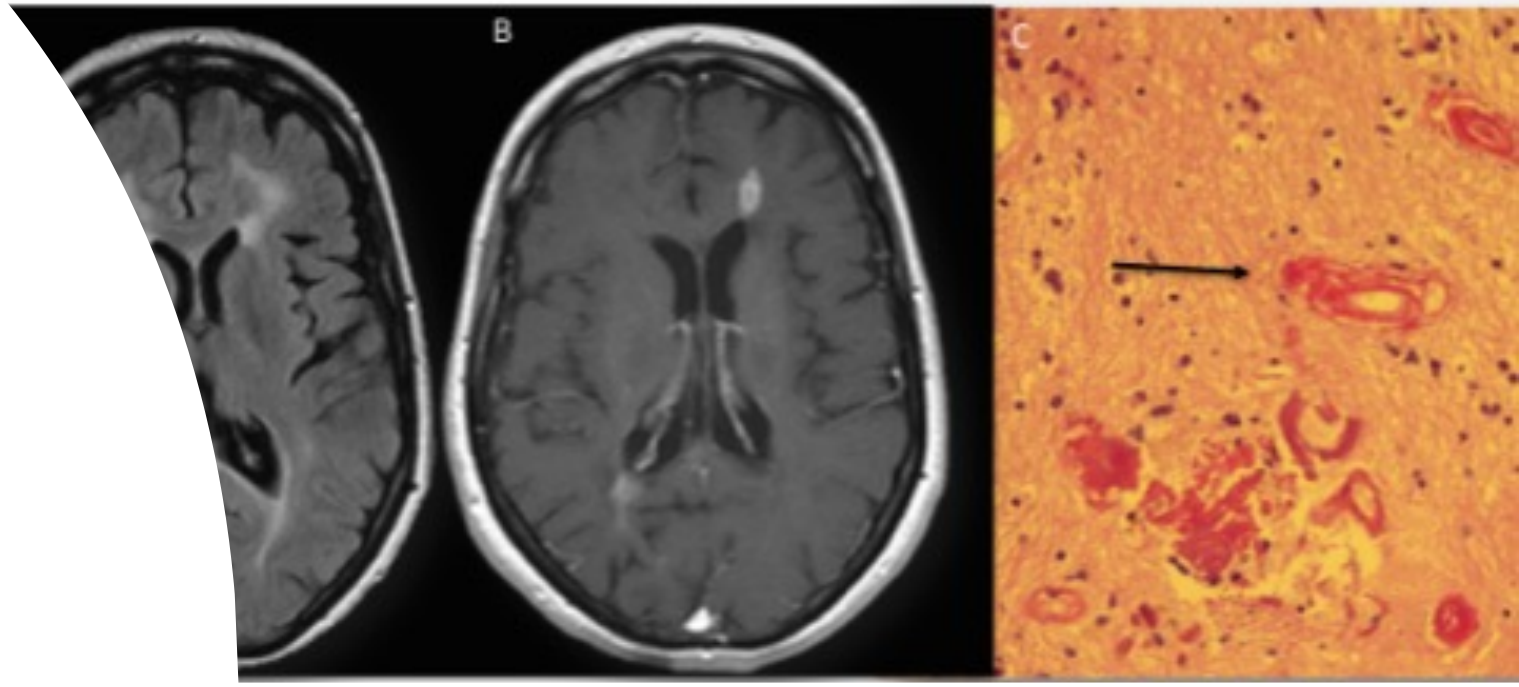
- 72% não preenchiam o critérios para EAI provável

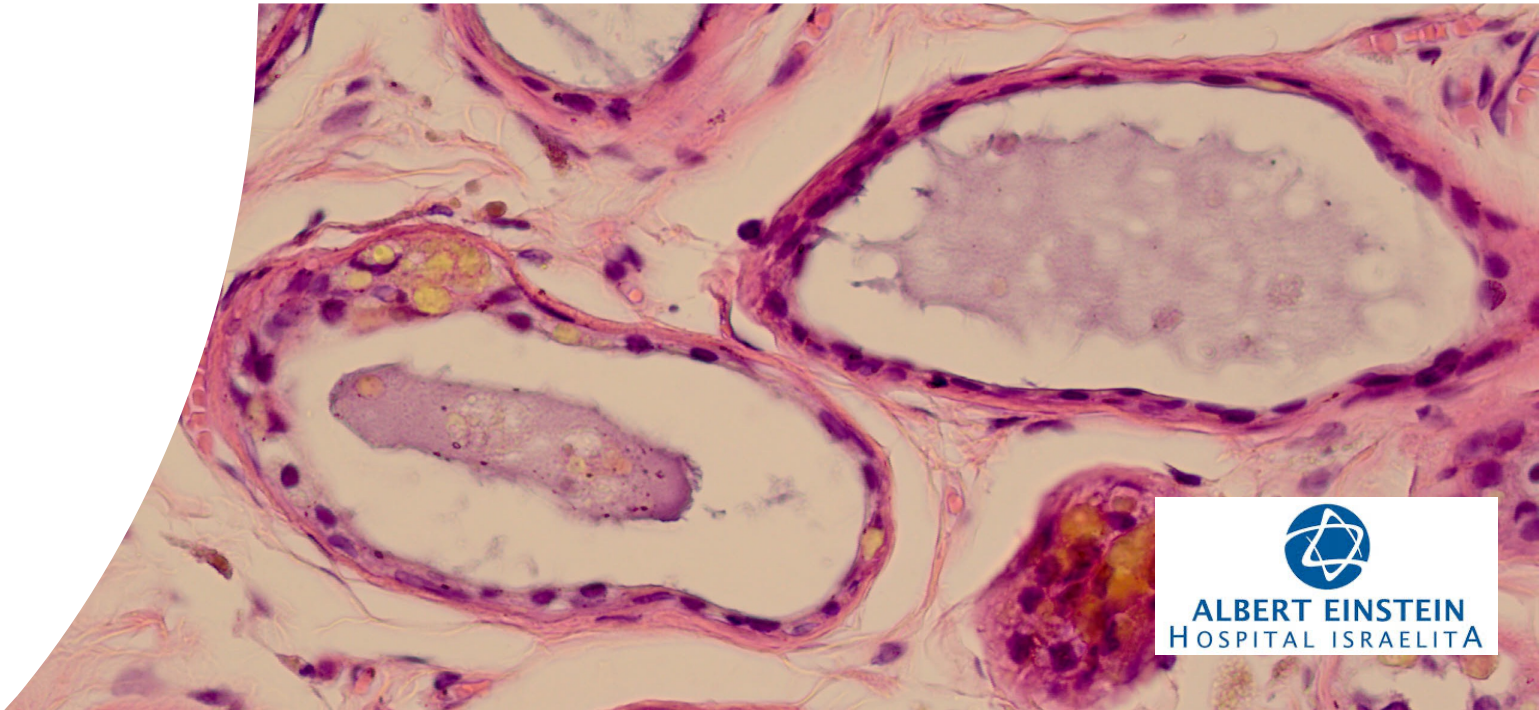
- Titulos baixos de vgkc, anti-receptor Ache gangliônico

Positive neural antibody	No.[a]	Assay detection method
Serum		
GAD65	14	RIA
Voltage-gated potassium-channel-complex (negative for LGI1 & CASPR2)	10	RIA
NMDAR[d]	10	CBA
Ganglionic acetylcholine receptor	5	RIA
CASPR2[f]	2	CBA
LGI1[f]	2	CBA
Muscle acetylcholine receptor	2	RIA
Voltage-gated calcium channel (N type)	2	RIA
Striated muscle	2	ELISA
Glycine receptor	1	CBA
Amphiphysin[d]	1	WB
Multiple positive neural antibodies in noncertified laboratory	1	Uncertain
CSF		
NMDAR[d]	4	CBA
Voltage-gated potassium-channel-complex (Negative for LGI1,	1	RIA

Flanagan, et al JAMA Neurol 2023 Jan 1;80(1):30-39.

Diagnóstico diferencial





AIE in children: differential diagnosis

* FIRES/NORSE
* Rasmussen
* Tics (Gilles de la Tourette)
* PANDAS
* SLE
* Narcolepsy
* Genetic epilepsy
* Mitochondrial disorders
* Functional disorders

- **If the AIE pediatric criteria is met and abs neg , check techniques done in both CSF and serum, consider sending to ref lab**
- **Check serum anti-MOG**
- **If the AIE pediatric criteria is not met, if seronegative criteria is not met, look for alternate diagnosis.**

Dalmau 2023, Flanagan 2022

Anti-MOG encephalitis in children: what to expect

- Second most common cause of AIE in children
- Patients may fulfill AIE and ADEM criteria
- Clinical picture: fever, reduced level of consciousness
- May not have demyelination
- Brain MRI: Many have cortical involvement, however 30% normal
  - Chinese series 50% with cortical involvement
  - One series report of 18 cases, 30% had normal MRI
  - Not only FLAMES
- Prognosis and response to treatment differs from anti-NMDAR

Armangue 2022, Han, 2022, Song, 2022

NORSE e FIRES

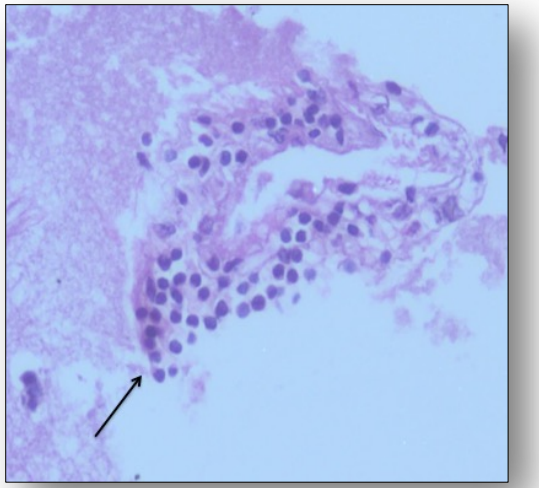
- NORSE (*New-onset refractory status epilepticus*) – apresentação clínica
    - Pacientes sem antecedentes relevantes e com investigação inicial negativa

- FIRES (*Febrile infection-related epilepsy syndrome*)
    - Febre 2 semanas à 24 horas antes do status

ALBERT EINSTEIN
HOSPITAL ISRAELITA

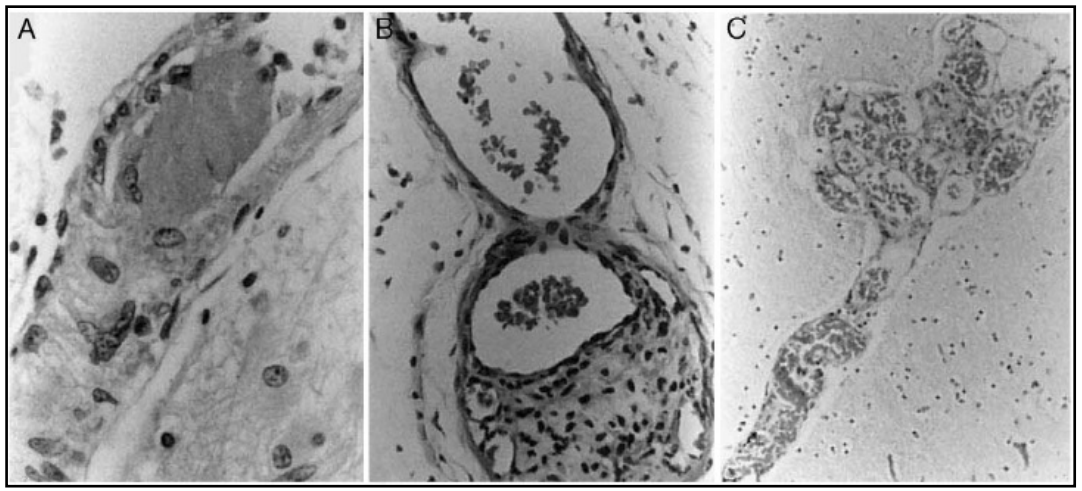
Vasculites do SNC

Vasculite



X

Vasculopatia



Mecanismo fisiopatológico

Dutra, 2017; Younger, 2003

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1933

Vasculites do SNC

Classificação a partir do calibre do vaso

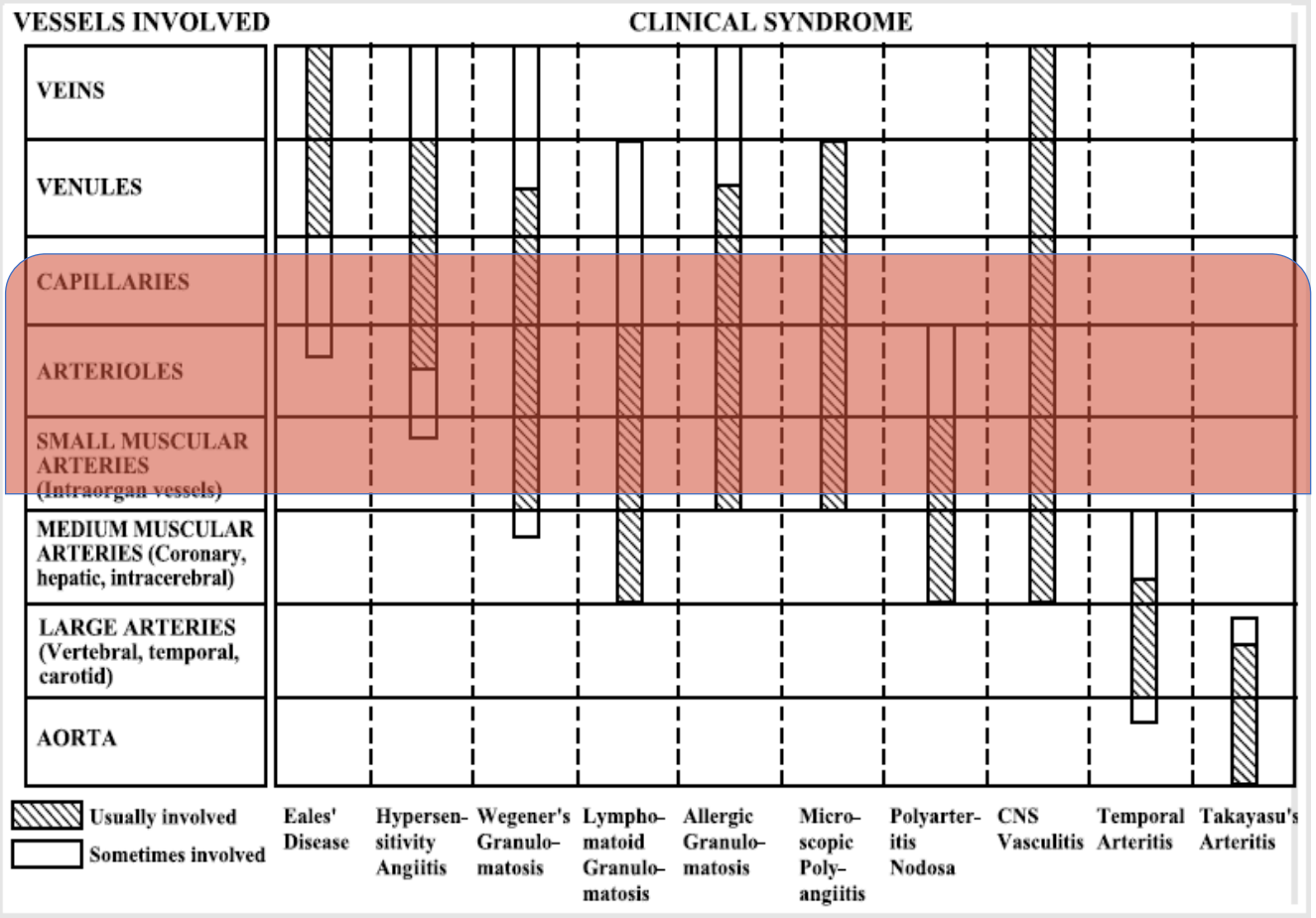
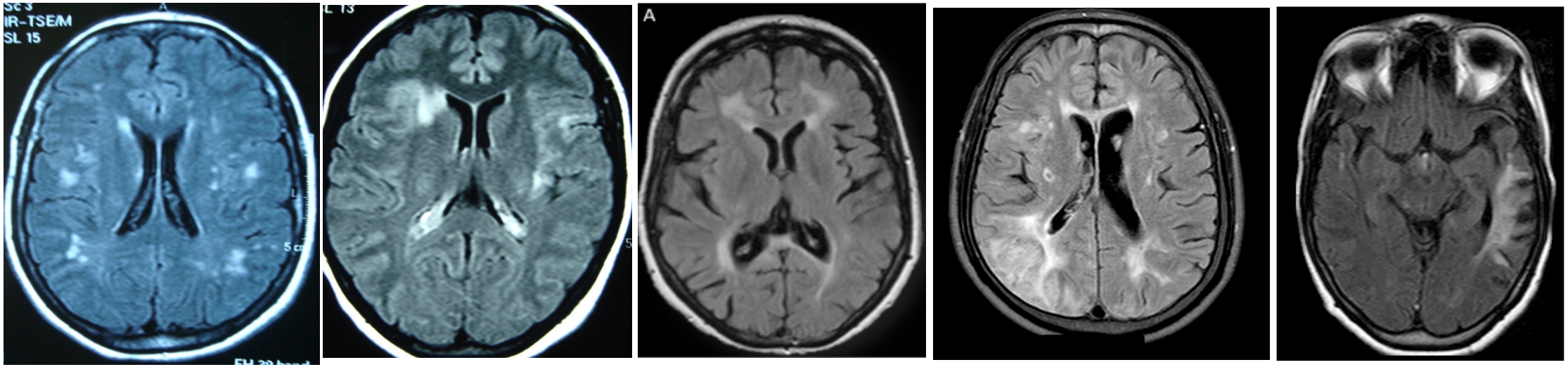


FIGURE 1-1 The pathological spectrum of the major vasculitides.

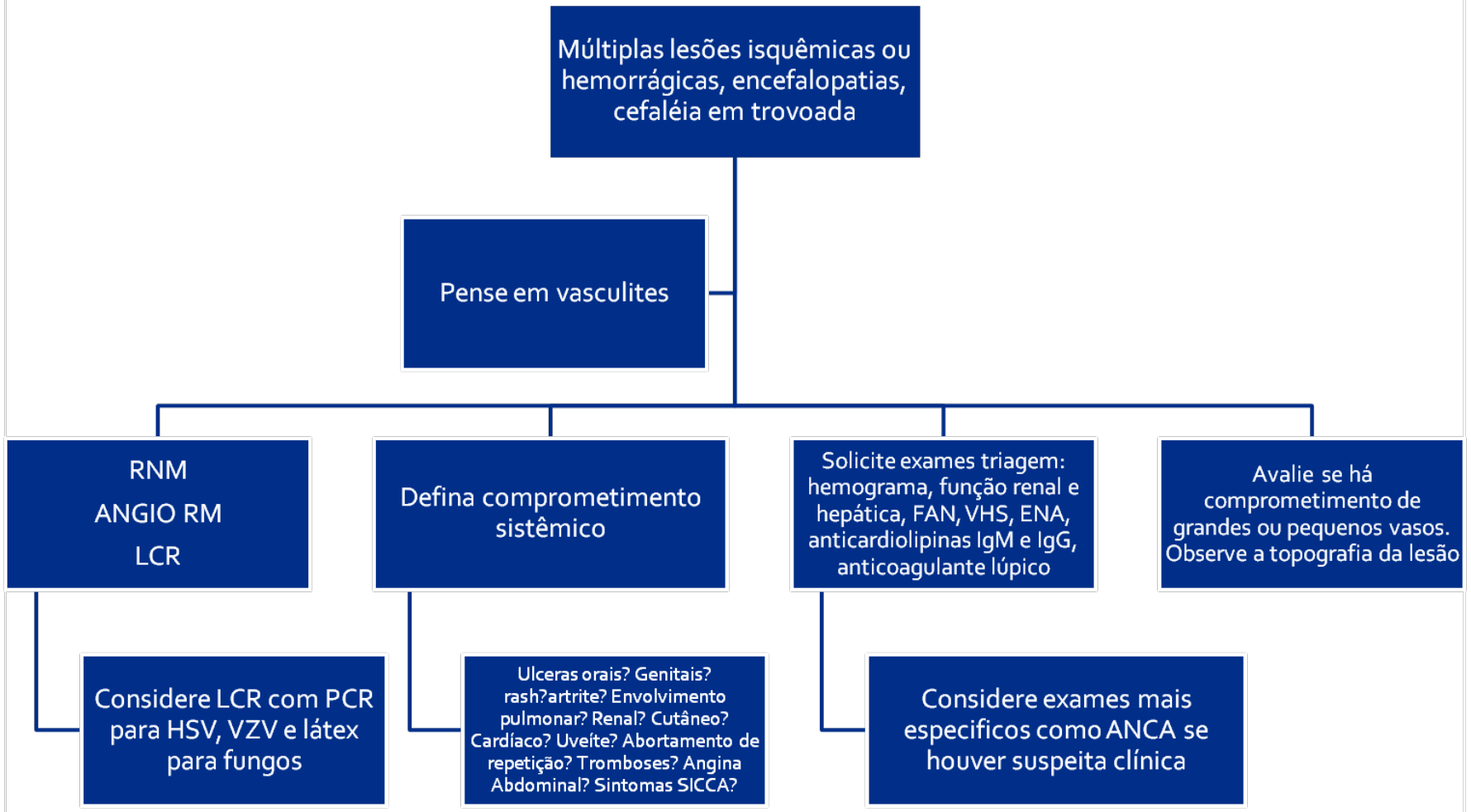
Vasculite do sistema nervoso central: não é possível inferir mecanismo pela imagem

SVCR | SAAF | VPSNC | ABRA | PAN



Cuidado com bright spots
Vasculopatias x vasculite

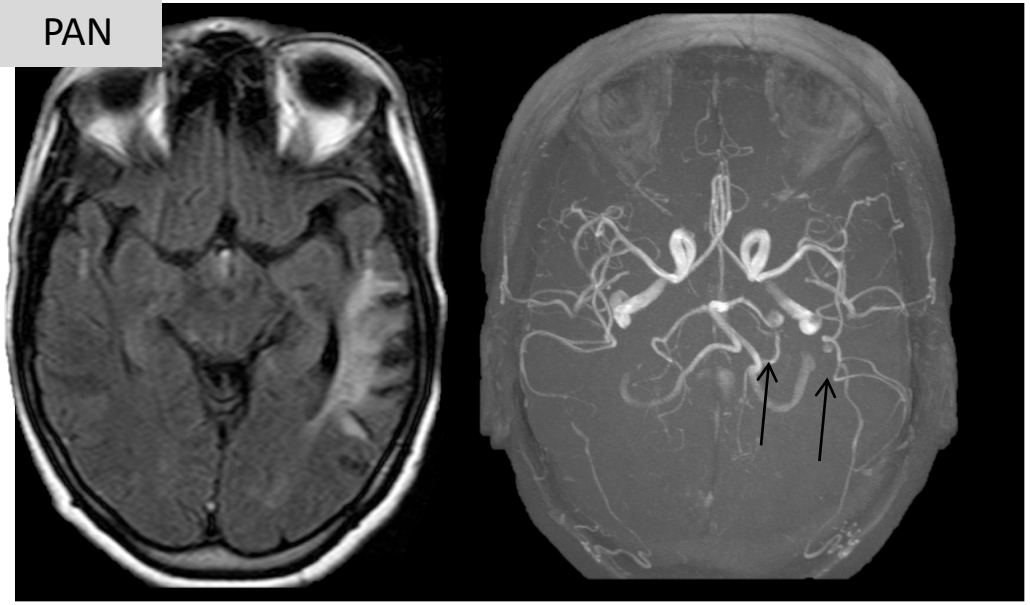
Vasculite do sistema nervoso central



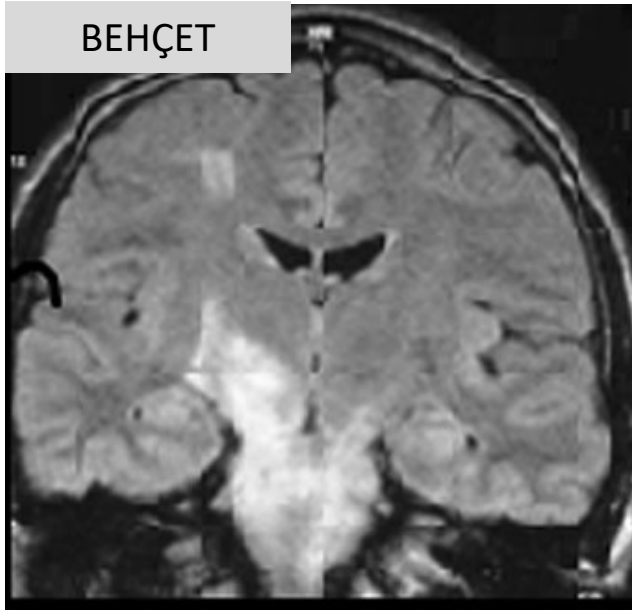
Dutra, LA; Souza AWS, Barsottini, OGP. Vasculites do Sistema Nervoso. In: Guia de Medicina Ambulatorial e Hospitalar: Neurologia, 2010

Vasculites do SNC em doenças sistêmicas

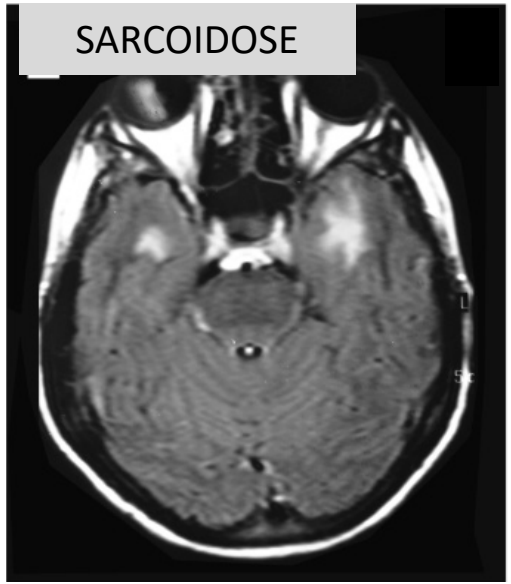
PAN

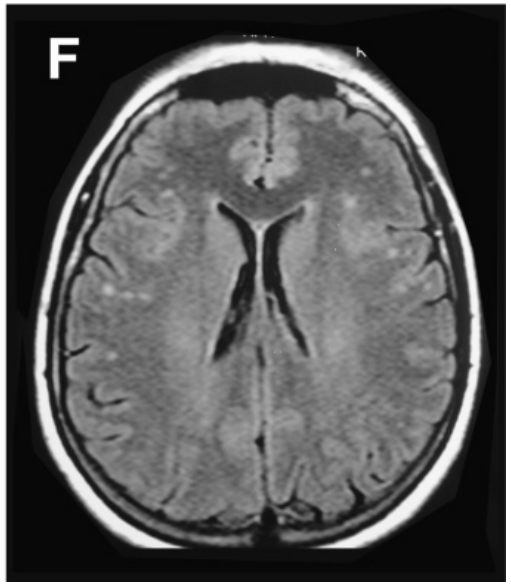


BEHÇET

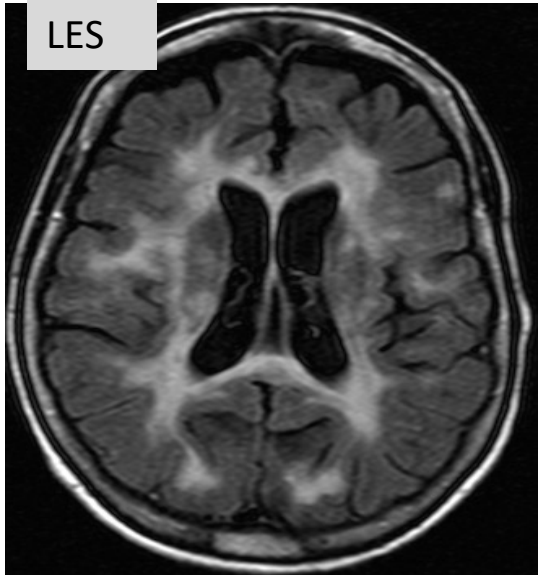


SARCOIDOSE



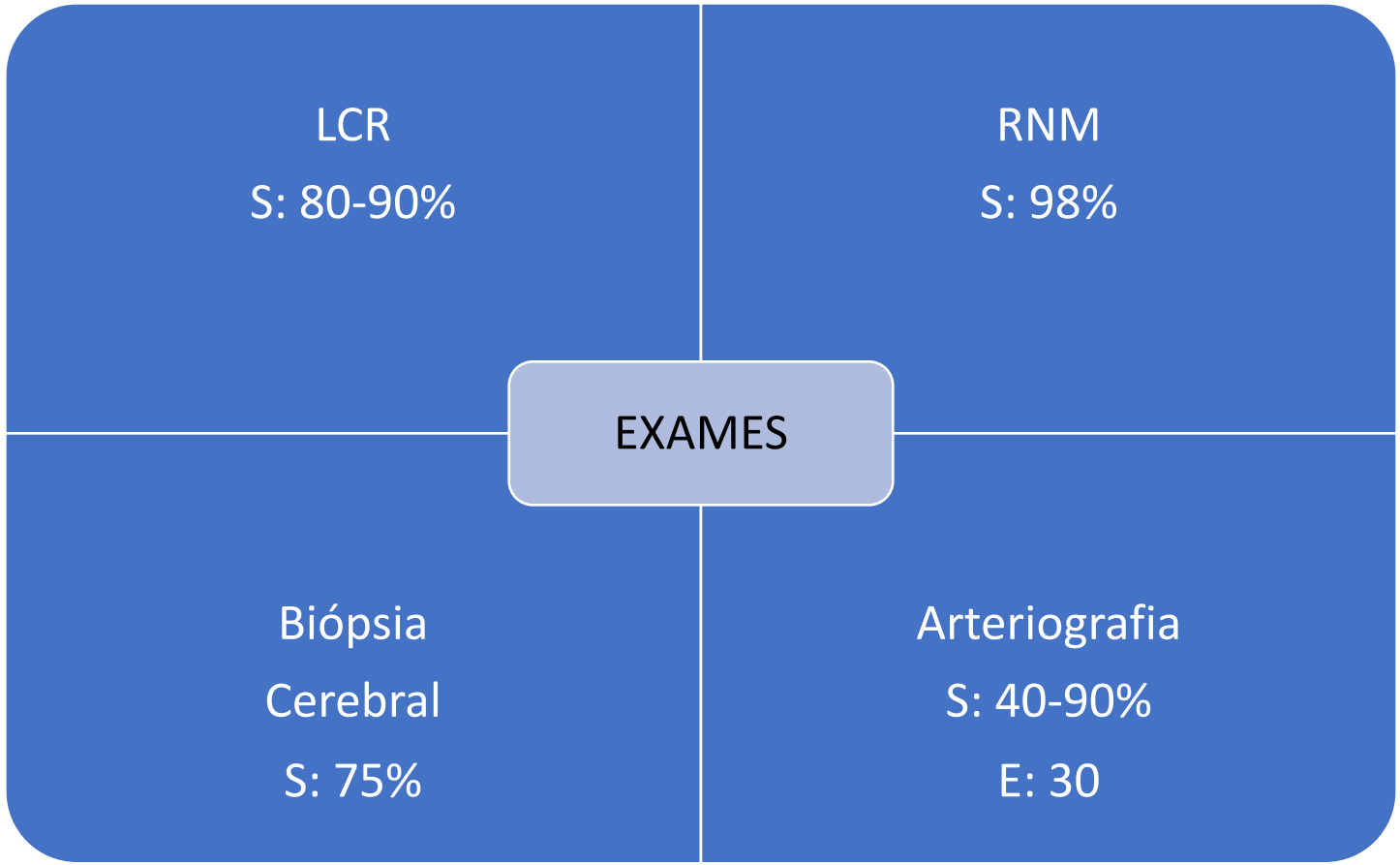


LES



Vasculite primária do SNC

Exames complementares



Vasculite do sistema nervoso central

Guideline

EUROPEAN STROKE JOURNAL

European Stroke Journal
2023, Vol. 8(4) 842–879

DOI: 10.1177/23969873231190431
journals.sagepub.com/home/eso
Sage

European Stroke Organisation (ESO) guidelines on Primary Angiitis of the Central Nervous System (PACNS)

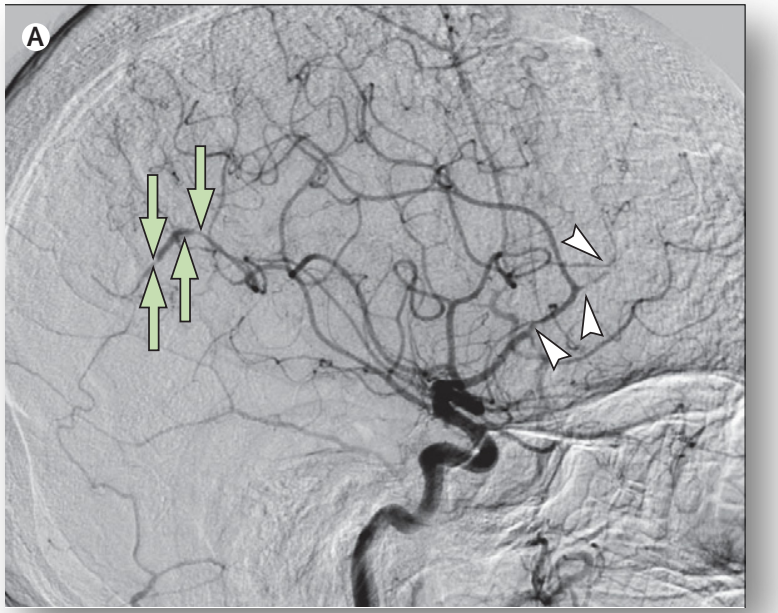
Rosario Pascarella[1], Katherina Antonenko[2], Grégoire Boulouis[3], Hubert De Boysson[4], Caterina Giannini[5], Mirjam R Heldner[2], Odysseas Kargiotis[6], Thanh N Nguyen[7], Claire M Rice[8,9], Carlo Salvarani[10], Antje Schmidt-Pogoda[11], Daniel Strbian[12], Salman Hussain[13] and Marialuisa Zedde[14]

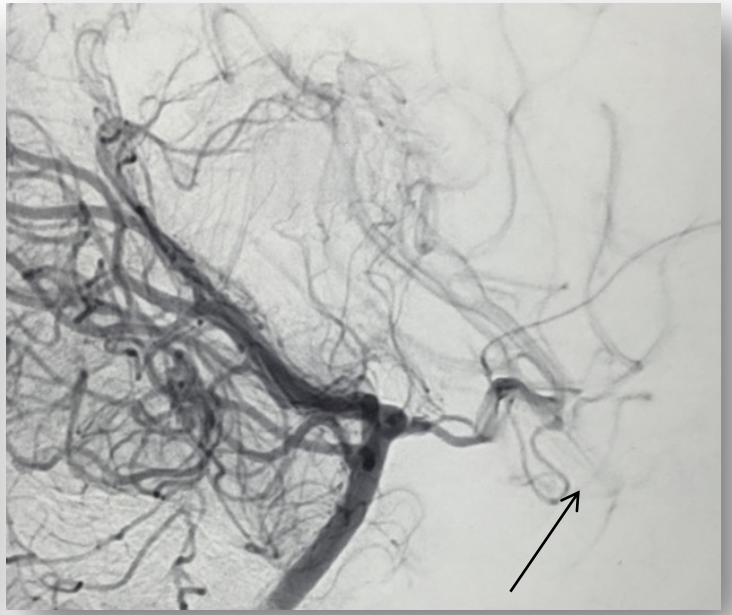
Abstract

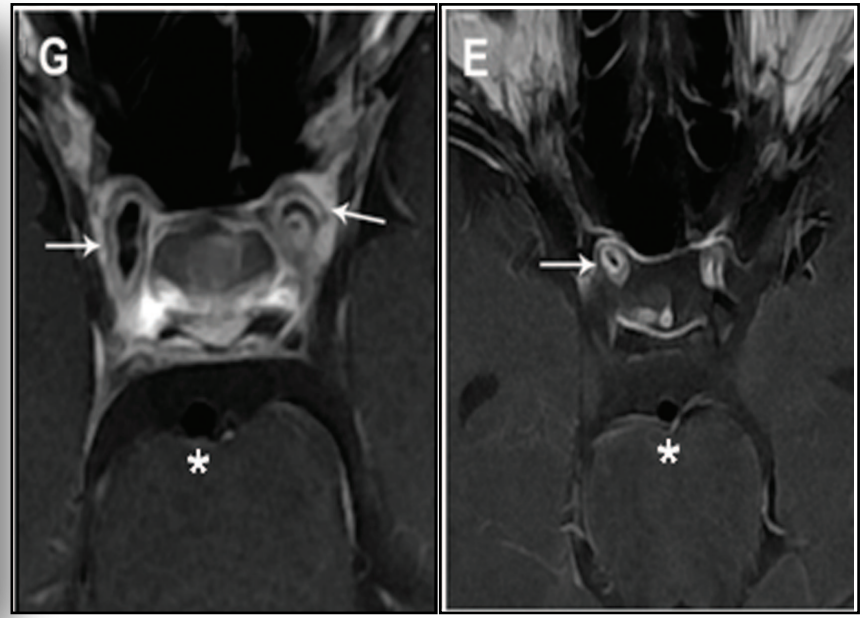
Vasculite do sistema nervoso central:

AngioRM não substitui a arteriografia – estudar vasos pequenos

Arteriografia pode ser normal na vasculite de pequenos vasos.







Rheumatology Advances in Practice, 2023, 7(3), rkad080
Dutra, 2017; European Stroke Journal 2023, Vol. 8(4) 842–879

Neurology® 2009;72:627-634

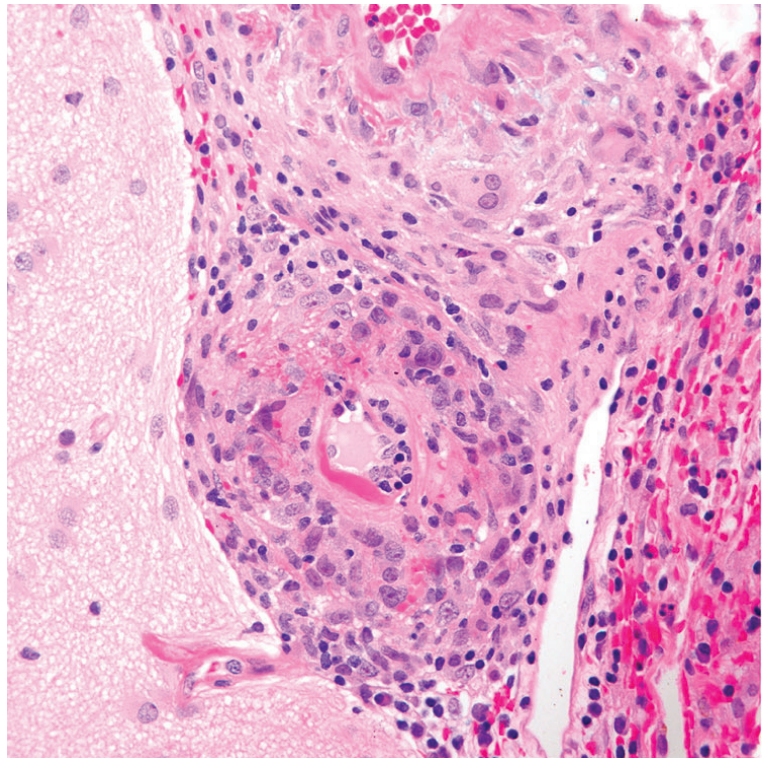
Vasculite primária do SNC

Conceitos gerais

- Processo inflamatório (**granulomatoso, linfocítico, necrotizante, relacionado à deposição de beta-amiloide**) restrito ao SNC
- Diagnóstico de exclusão
- Exames complementares baixa sensibilidade
- Biópsia cerebral é o padrão-ouro.

Vasculite primária do SNC
Biópsia cerebral

- Risco de complicação da Bx 1%
- **MUDA O DIAGNÓSTICO EM 39%**
- Anatomopatológico: Granulomatoso (58%), linfocítico (28%) ou necrotizante (14%), beta-amiloide
- Imunohistoquímica para beta-amiloide e marcadores linfóides



Salvarani, 2008; Birnbaum 2009

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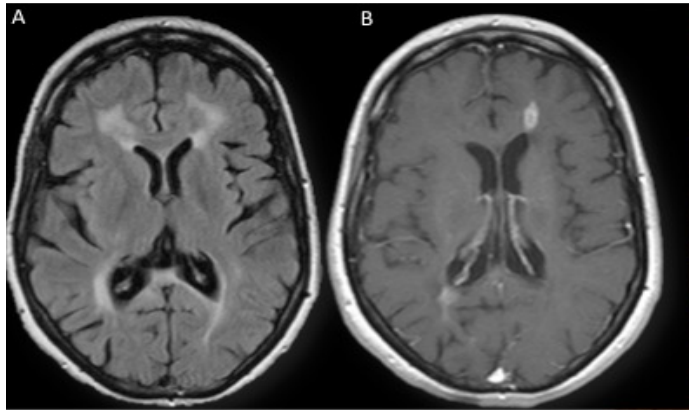
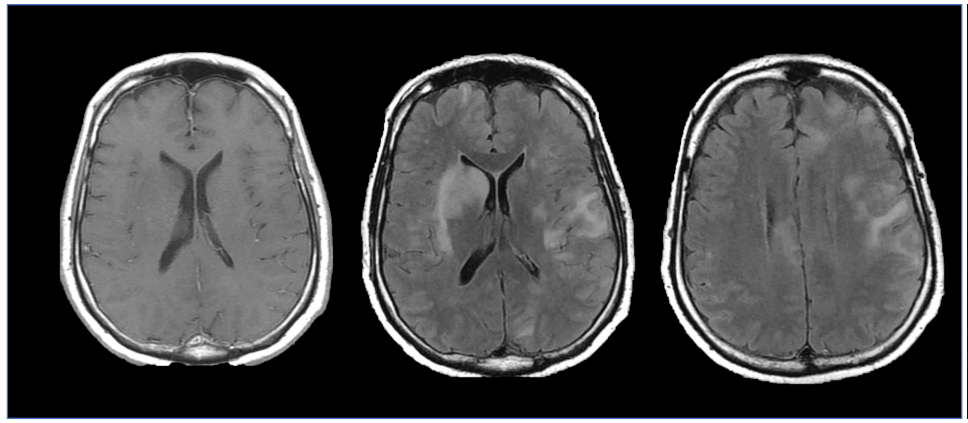
Vasculite do sistema nervoso central

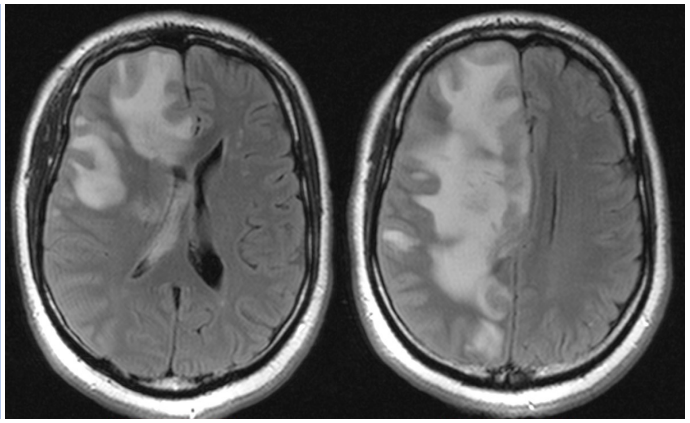
VPSNC

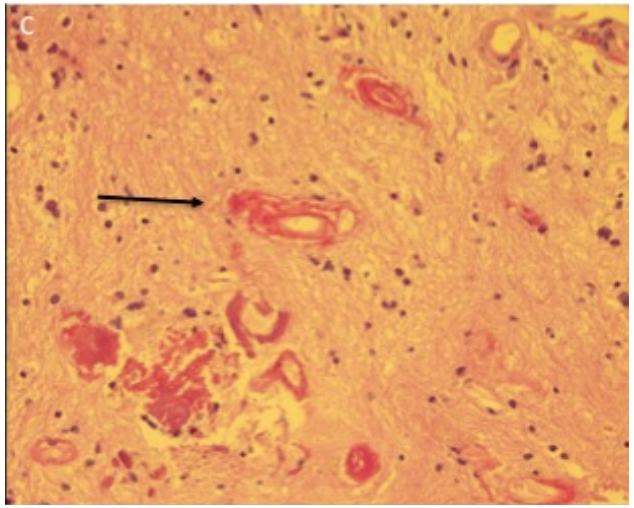


Linfoma B angiocêntrico

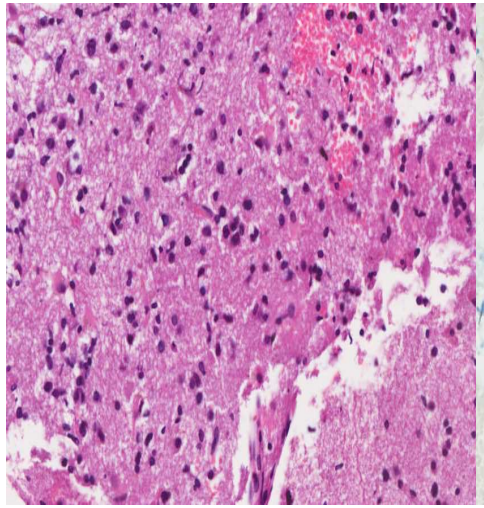


VPSNC

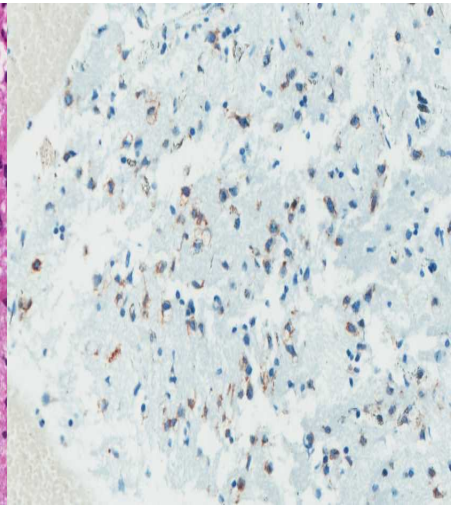


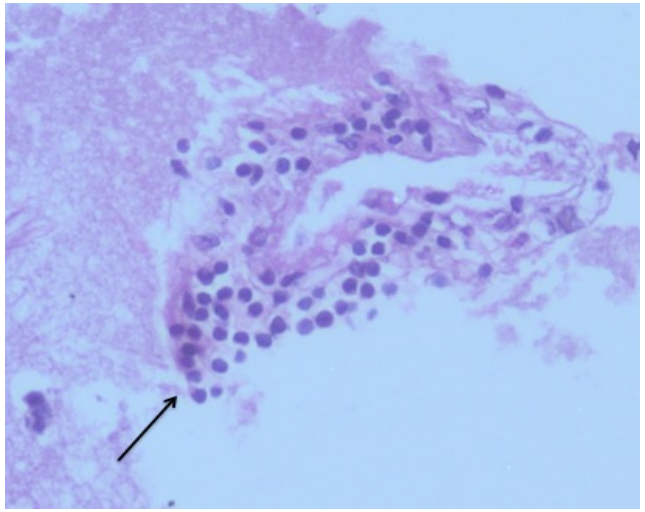


HE



CD20





Dutra, 2017

VASCULITE PRIMÁRIA DO SNC
Diagnóstico diferencial

Vasculites inflamatórias

- Primária
- Sistêmicas (PAN, GPA, LES, linfomatose granulomatoide, sarcoidose)
- Genéticas
- MOG

Vasculites infecciosas

- HIV
- Família Herpes (VZV)
- Meningococo, sífilis, tuberculose, aspergilus

Vasculite primária do SNC

Critérios diagnósticos

Critérios diagnósticos propostos por Calabrese (Alba, 2011)

1 – História e manifestações clínicas de origem indeterminada após investigação inicial;

2 – Arteriografia com achados clássicos de vasculite ou biópsia demonstrando vasculite;

3 – Não há evidência vasculite sistêmica ou de outra doença que possa mimetizar os achados do item 2

Diagnóstico de exclusão

Triar outros sistemas potencialmente envolvidos

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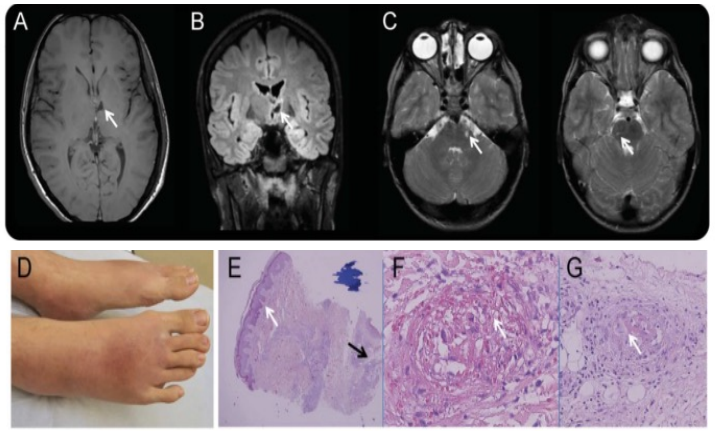
FUTURO DAS VASCULITES:

Exoma, painéis genéticos e metagenômica

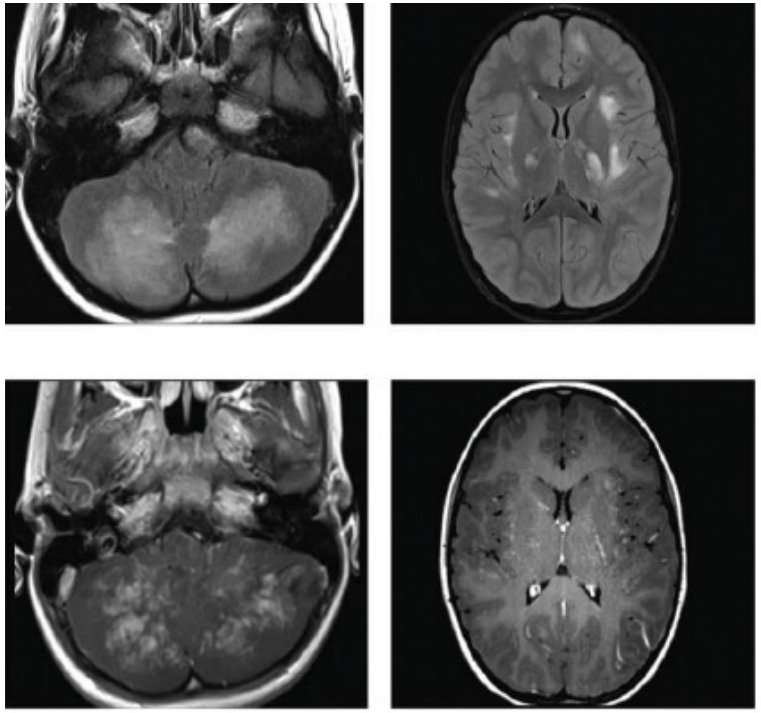
UNEXPLAINED EARLY-ONSET LACUNAR STROKE AND INFLAMMATORY SKIN LESIONS: CONSIDER ADA2 DEFICIENCY



Neurology 2015 May 19;84(20):2092-3.

ARTICLE OPEN ACCESS CLASS OF EVIDENCE

Pediatric CNS-isolated hemophagocytic lymphohistiocytosis



Neurol Neuroimmunol Neuroinflamm 2019;6:e560.

Mimics of Pediatric Small Vessel Primary Angiitis of the Central Nervous System

Coral M. Stredny MD, Melissa M. Blessing DO, Vivian Yi BS, Morgan E. Ryan MS, Bo Zhang PhD, Isaac H. Solomon MD, PhD, Sanjay P. Prabhu MBBS, Sanda Alexandrescu MD, Mark P. Gorman MD

Dos 21 casos, 14 foram readiagnosticados

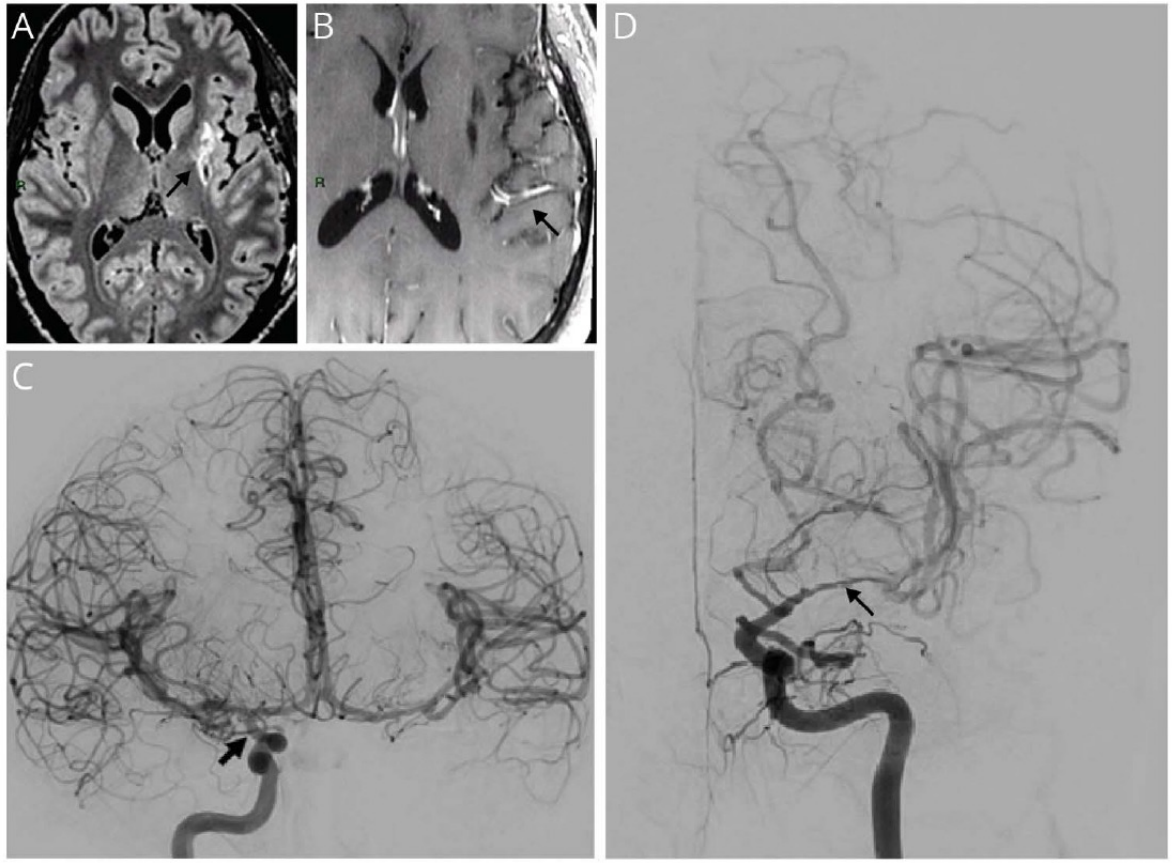
- 9 mog
- 3 LHH
- 1anti-GABA-A
- 1 Aicardi-Goutierres

Ann Neurol 2023 Jan;93(1):109-119.

Westendrop, 2015

FUTURO DAS VASCULITES:

Exoma, painéis genéticos e metagenômica



CLINICAL/SCIENTIFIC NOTE

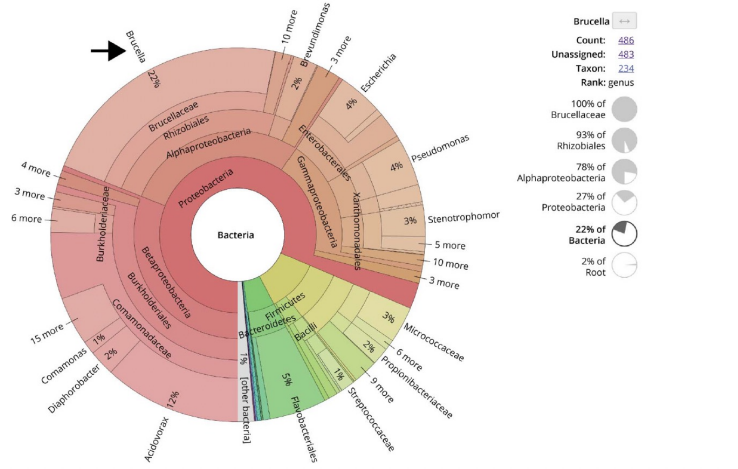
Neurobrucellosis Mimicking Primary CNS Vasculitis—Should We Perform CSF Metagenomics Before Brain Biopsy?

A Case Report

Marina Barrionuevo Mathias, Fernando Gatti Menezes, MD, PhD, Gustavo Bruniera Peres Fernandes, MD, MSc, Vitor Ribeiro Paes, MD, Gisele Sampaio Silva, Pedro Braga-Neto, MD, PhD, Alcino Alves Barbosa, MD, Augusto César Penalva De Oliveira, MD, PhD, Carlos Eduardo Baccin, MD, and Lívia Almeida Dutra, MD, PhD

Correspondence
Dr. Dutra
liviaadutra@hotmail.com

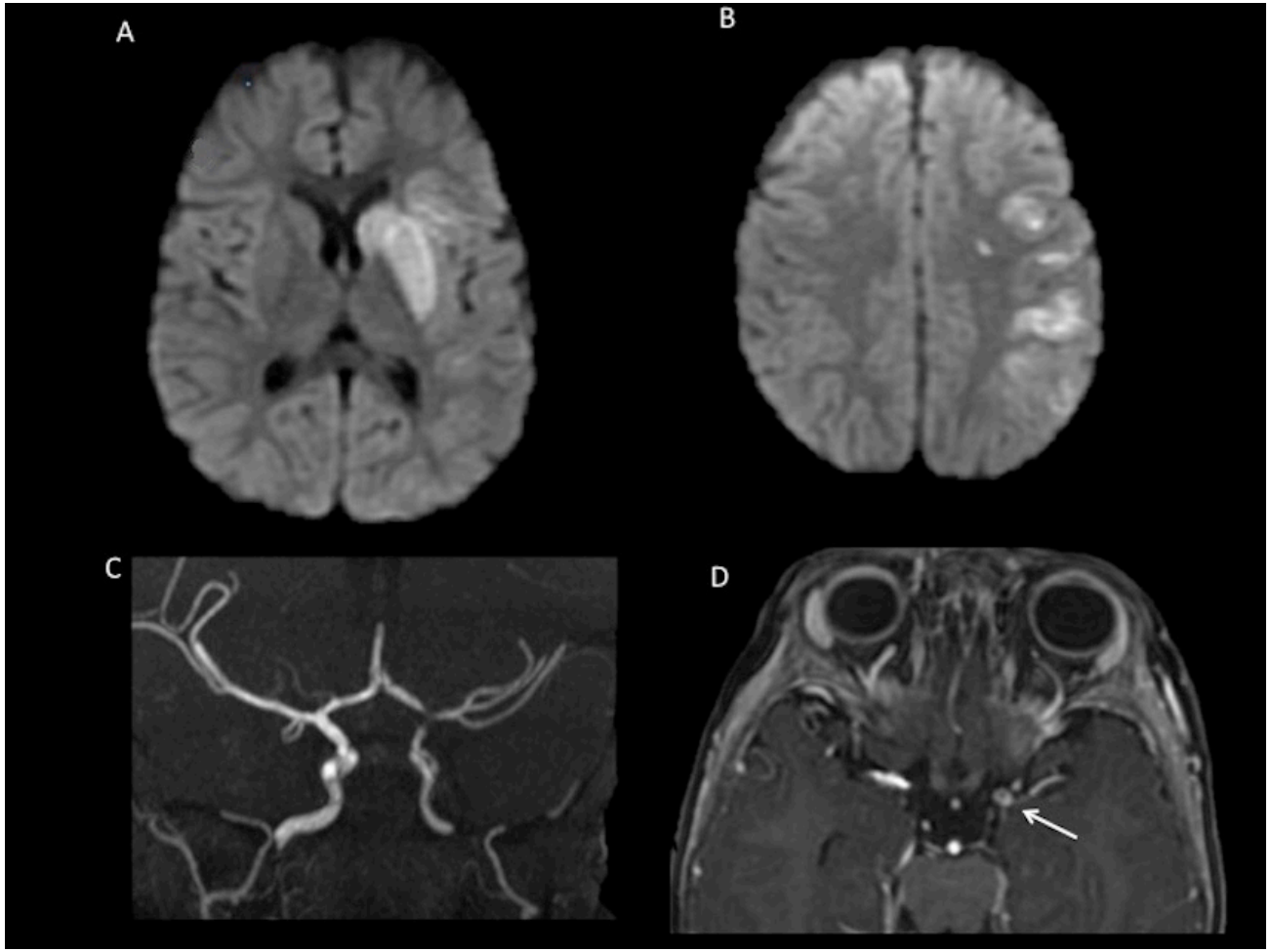
Figure 3 Metagenomic Results



Neurology: Clinical Practice 2023;13:e200167.

Westendrop, 2015

Vasculites infecciosas:
Vasculopatia associada ao VZV



Vasculopatia associada ao VZV

- Principal causa de AVC em crianças abaixo de 2 anos (primoinfecção).
- Adultos após zoster podem evoluir com AVC/ IAM pela reativação viral nas arterias
- **Manifestações neurológicas até 12 meses após manifestações cutâneas.**
- LCR normal, PCR negativo, Elisa **positivo**
- Curso crônico e recorrente. **REQUER TRATAMENTO**

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Vasculopatia associada ao VZV

Table 3 Hazard ratios (95% CI) for stroke, TIA, and MI after herpes zoster occurrence

Vascular event[a]	Cases (n = 106,601), n (%)	Controls (n = 213,202), n (%)	Hazard ratio (95% CI)	
			Unadjusted	Adjusted[b]
Stroke	2,727 (2.56)	5,252 (2.46)	1.04 (0.99-1.09)	1.02 (0.98-1.07)
MI	2,762 (2.59)	4,835 (2.27)	1.15 (1.09-1.20)	1.10 (1.05-1.16)[c]
TIA	2,275 (2.13)	3,904 (1.83)	1.17 (1.11-1.23)	1.15 (1.09-1.21)[c]
Stroke in patients with HZO (cases = 1,710; controls = 3,240)	68 (3.98)	130 (3.80)	1.06 (0.79-1.42)	1.03 (0.77-1.39)
Stroke in subjects 18-40 y (cases = 19,301; controls = 38,602)	40 (0.21)	45 (0.12)	1.79 (1.17-2.73)	1.74 (1.13-2.66)[c]
MI in subjects 18-40 y (cases = 19,301; controls = 38,602)	51 (0.26)	67 (0.17)	1.53 (1.06-2.20)	1.49 (1.04-2.15)[c]
TIA in subjects 18-40 y (cases = 19,301; controls = 38,602)	25 (0.13)	20 (0.05)	2.51 (1.39-4.52)	2.42 (1.34-4.36)[c]

Abbreviations: CI = confidence interval; HZO = herpes zoster ophthalmicus; MI = myocardial infarction.
[a] Period of follow-up 1 to 23.7 years.
[b] Hazard ratios were adjusted for sex, age, obesity (body mass index >30 kg/m^2), smoking status, history of cholesterol >6.2 mmol/L, hypertension, diabetes, ischemic heart disease, atrial fibrillation, intermittent arterial claudication, carotid stenosis, and valvular heart disease.
[c] $p < 0.05$.

Breuer, 2014

Review

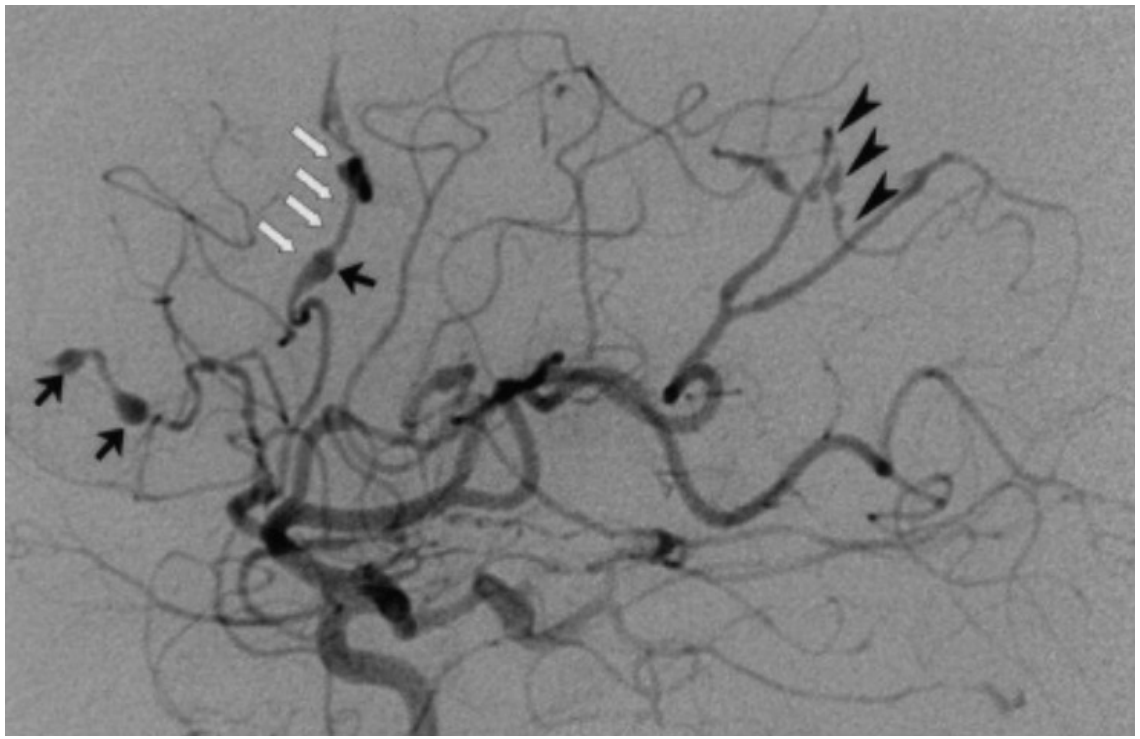
HIV-associated Intracranial Aneurysmal Vasculopathy in Adults

DEBORAH A. GOLDSTEIN, JOSEPH TIMPONE, and THOMAS R. CUPPS

J Rheumatol 2010;37;226-233

Human immunodeficiency virus-associated vasculopathy with CNS compartmentalization of HIV-1

Bruno Fukelmann Guedes · Helio Rodrigues Gomes · Leadro Tavares Lucato · Paulo Puglia Jr · Ricardo Nitrini · Luiz Henrique Martins Castro



- Pacientes CD4< 200, CV alta
- Aneurismas fusiformes com hemorragia e isquemia
- Adultos sintomáticos,
- 1,6% das crianças HIV+ assintomáticas
- Compartimentalização do HIV

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Histiocitose

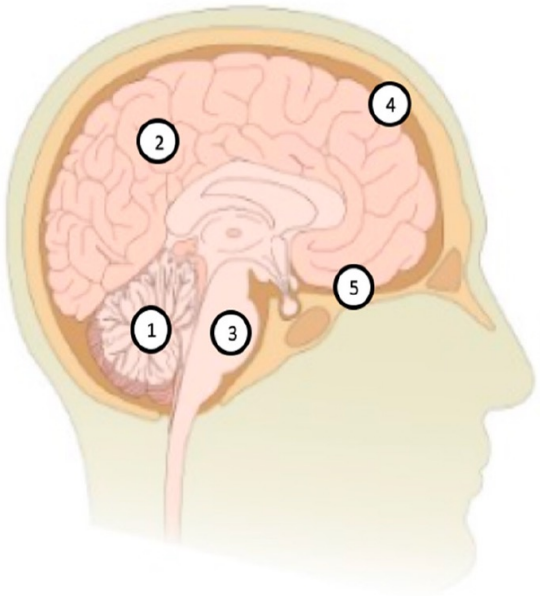
- Doença clonal, infiltração de histiócitos (linhagem mieloide)

- Erdheim-Chester disease (ECD), Langerhans cell histiocytosis (LCH), Rosai-Dorfman disease (RDD)

- 90% apresentam mutações na via MAPK/ERK, 50% anti-BRAF LCH
- 33% dos RDD mutação MAPK/ERK

- Vemurafenib anti-BRAF (melanoma) – usado também no histiocitose

Histiocitose



1. Intraparenchymal cerebellar 25%
2. Intraparenchymal 50%
3. Intraparenchymal Brainstem 35%
4. Dural 17.5%
5. Intraparenchymal and Dural 10%

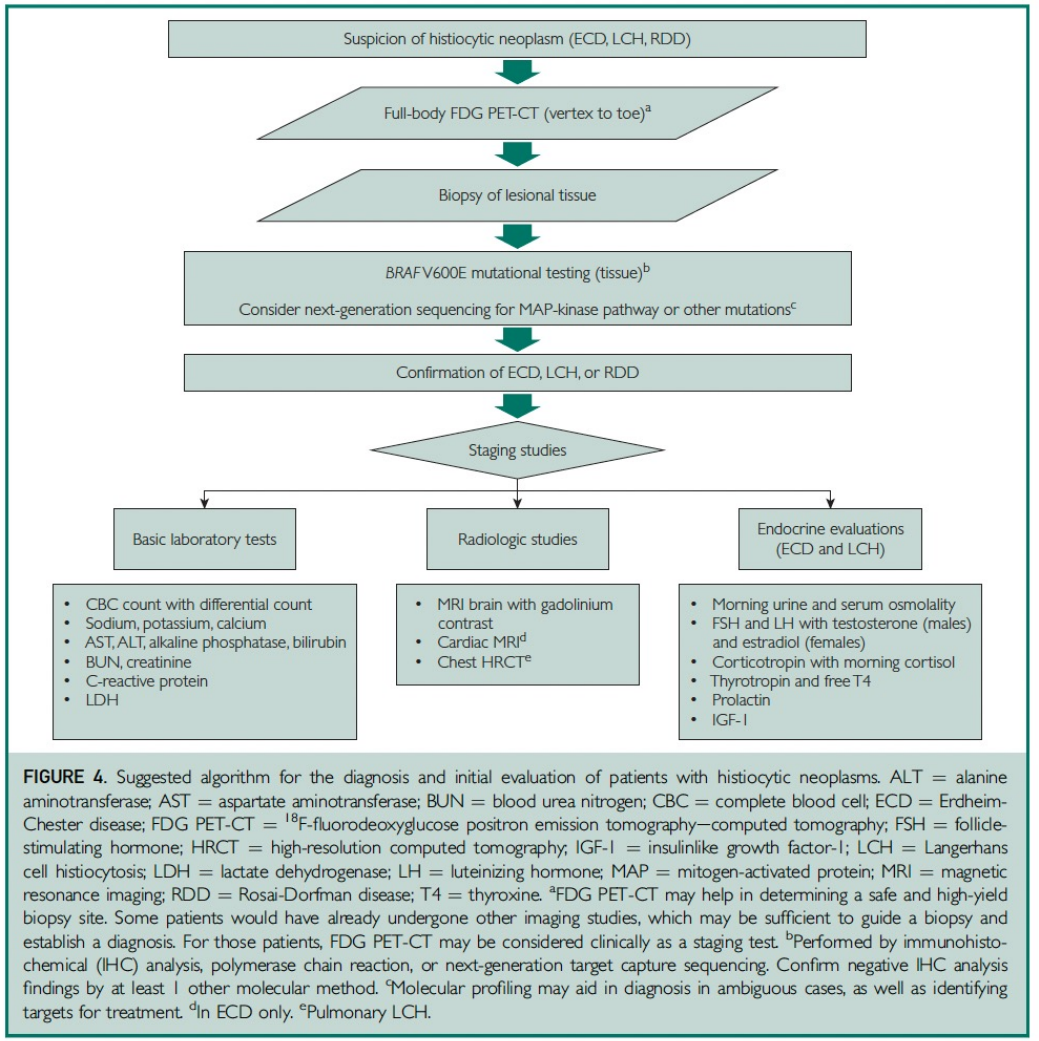


FIGURE 4. Suggested algorithm for the diagnosis and initial evaluation of patients with histiocytic neoplasms. ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CBC = complete blood cell; ECD = Erdheim-Chester disease; FDG PET-CT = ^{18}F-fluorodeoxyglucose positron emission tomography–computed tomography; FSH = follicle-stimulating hormone; HRCT = high-resolution computed tomography; IGF-1 = insulinlike growth factor-1; LCH = Langerhans cell histiocytosis; LDH = lactate dehydrogenase; LH = luteinizing hormone; MAP = mitogen-activated protein; MRI = magnetic resonance imaging; RDD = Rosai-Dorfman disease; T4 = thyroxine. [a]FDG PET-CT may help in determining a safe and high-yield biopsy site. Some patients would have already undergone other imaging studies, which may be sufficient to guide a biopsy and establish a diagnosis. For those patients, FDG PET-CT may be considered clinically as a staging test. [b]Performed by immunohistochemical (IHC) analysis, polymerase chain reaction, or next-generation target capture sequencing. Confirm negative IHC analysis findings by at least 1 other molecular method. [c]Molecular profiling may aid in diagnosis in ambiguous cases, as well as identifying targets for treatment. [d]In ECD only. [e]Pulmonary LCH.

Mayo Clin Proc. 2019;nn(n):1-18
Front Immunol. 2023 Sep 22;14:1260193
Neurol. Int. 2022, 14, 716–726.

Histiocitose

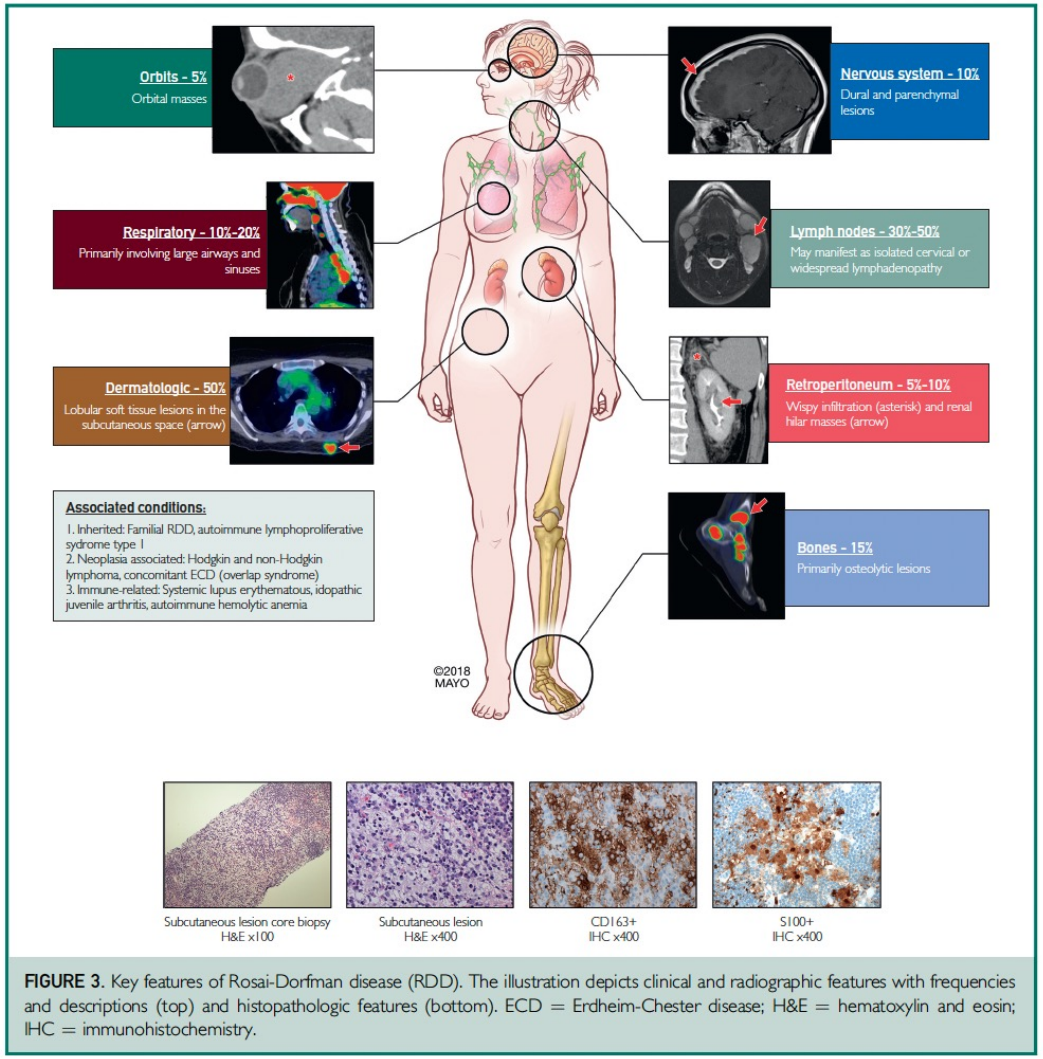


FIGURE 3. Key features of Rosai-Dorfman disease (RDD). The illustration depicts clinical and radiographic features with frequencies and descriptions (top) and histopathologic features (bottom). ECD = Erdheim-Chester disease; H&E = hematoxylin and eosin; IHC = immunohistochemistry.

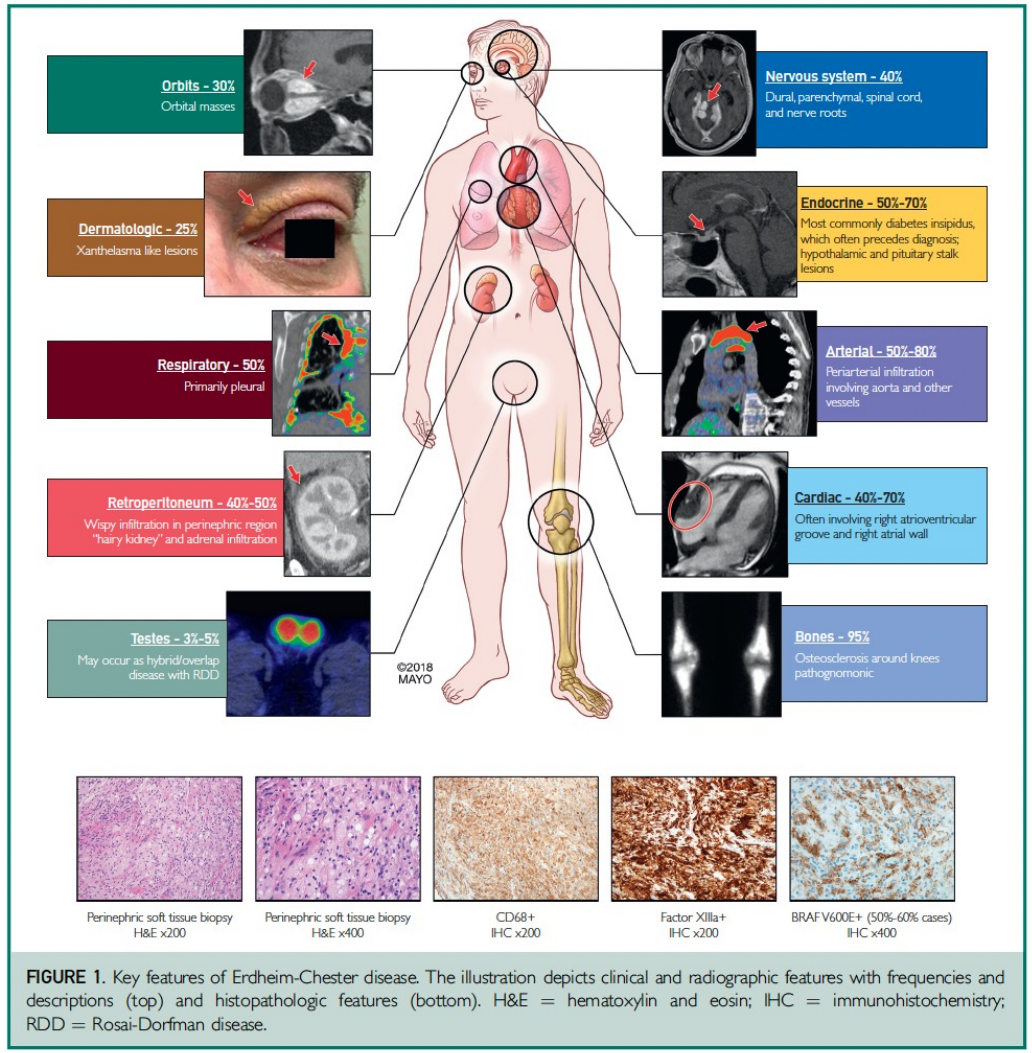


FIGURE 1. Key features of Erdheim-Chester disease. The illustration depicts clinical and radiographic features with frequencies and descriptions (top) and histopathologic features (bottom). H&E = hematoxylin and eosin; IHC = immunohistochemistry; RDD = Rosai-Dorfman disease.

Mayo Clin Proc. 2019;nn(n):1-18
Front Immunol. 2023 Sep 22;14:1260193
Neurol. Int. 2022, 14, 716–726.

Vasculite primária do SNC

Tratamento e prognóstico

- O prognóstico e evolução depende do tamanho do vaso acometido.
- Evolução de **anos e curso recorrente** descrito na literatura, principalmente **pacientes jovens**
- Relapse 26% e vários pacientes da última série estão estáveis.
- Subtipo pequenos vasos pode responder a corticoide e arteriografia negativa podem responder apenas a corticoide.

Calabrese, 2016; Dutra 2017; Hajj Ali, 2019

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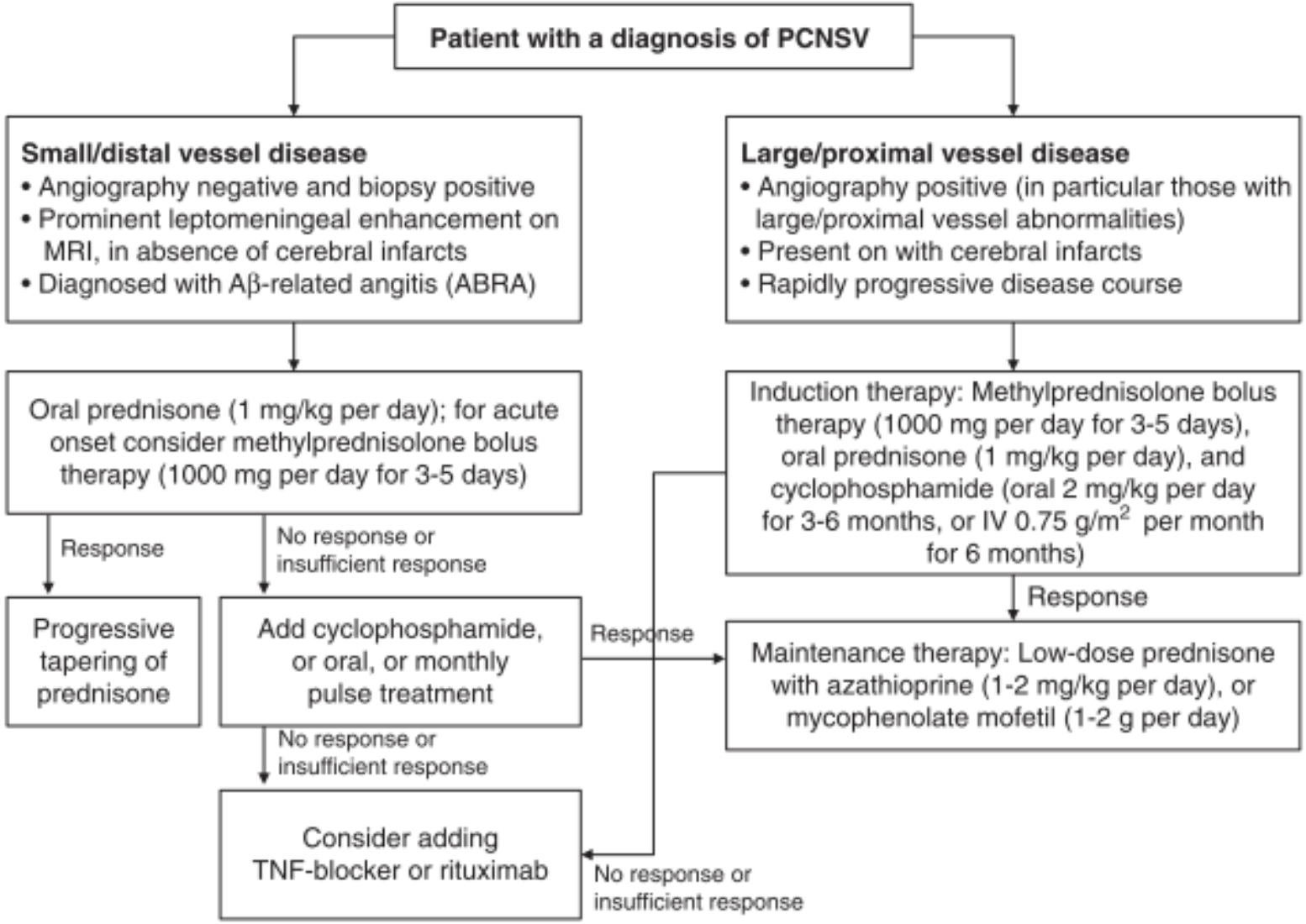
Vasculite primária do SNC

Tratamento e prognóstico

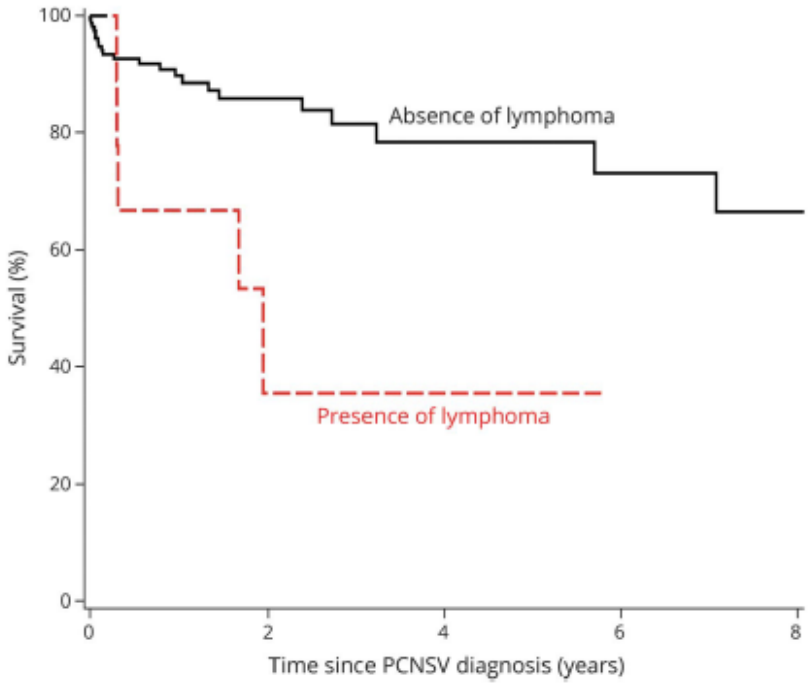


Calabrese, 2016

Primary central nervous system vasculitis associated with lymphoma

Carlo Salvarani, MD, Robert D. Brown Jr, MD, MPH, Teresa J.H. Christianson, BS, John Huston III, MD, Stephen M. Ansell, MD, Caterina Giannini, MD, and Gene G. Hunder, MD

Neurology® 2018;90:e847-e855. doi:10.1212/WNL.0000000000005062



Survival of patients with lymphoma was significantly reduced compared to that of patients without lymphoma ($p = 0.008$).Significance remained after adjustment for age at diagnosis. PCNSV = primary CNS vasculitis.

- Dos 168 pacientes com PACNS , 10 (5.9%) apresentaram linfoma, 6 Hodgkin.
- Pacientes com linfoma eram mais frequentemente homens,
- com maior realce meníngeo

Vasculites do SNC em doenças sistêmicas

- Variável preditora de pior prognóstico
- Manifestação neurológica pode ser 1a. manifestação da doença
- Afastar infecção do SNC e SAAF
- Tratamento direcionado pela doença de base

Take home messages

- Se houver hipótese de vasculite primária do SNC:

- Vasculite x vasculopatia
- Defina se há comprometimento sistêmico
- Lembre do vessel wall
- Lembre da metagenomica e exoma
- Se possível biopsiar sempre (muda conduta em 39%)
- Lembre vasculopatia da varicela
- Escolher adequadamente terapia de indução.

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- UFMG (Prof. Francisco Cardoso)
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- UFC (Prof. Pedro Braga-Neto)
- UFPE (Prof. Eduardo Mello)
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- UFPR (Prof. Helio Teive)
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- Hospital Pequeno Príncipe, Curitiba
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Brazilian Autoimmune encephalitis Network

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