Avaliação neuropsiquiátrica de adolescentes com manifestações convulsivas após vacinação contra HPV

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Dra. **Inah Carolina Galatro Faria Proença**

PROJEPSI - IPqHCFMUSP

Conflitos de interesse

- Nenhum membro da equipe técnica possui qualquer vínculo com o Ministério da Saúde ou Indústria Farmacêutica.

PROJEPSI - Programa de Neuropsiquiatria do IPq HC-FMUSP

- Referência nacional para o diagnóstico de crises não epilépticas psicogênicas
- Mais de 25 anos de experiência em neuropsiquiatria de epilepsia
- Vídeo EEG prolongado em todas os casos
- Pioneiro no desenvolvimento de TCC específica para CNEP*

*J Epilepsy Clin Neurophysiol 2007; 13(4, Suppl 1):39-44

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Amicus Plato, sed magis amica veritas

Qual o problema encontrado?

- Entre 30/05/2018 e 31/07/2019, 72 notificações de EAPV por vacina HPV4 em Rio Branco, AC
- 16 notificações consideradas graves em acompanhamento por equipe multiprofissional em Rio Branco
- Pacientes com manifestações convulsivas, além de outras

- MS solicita ao PROJEPSI-Ipq-HCFMUSP a realização do diagnóstico diferencial e esclarecimento do possível nexo causal
- Firmado Termo de Cooperação Técnica entre o MS e o Ipq-HCFMUSP
- 12 pacientes avaliadas entre 03/06/2019 e 07/09/2019

Como definir o problema?

- Crise epiléptica (CE) $\longrightarrow$ descarga epiléptica
- Crise não epiléptica fisiogênica (CNEF) $\longrightarrow$ ausência de descarga epiléptica, mecanismo fisiológico
- Crise não epiléptica psicogênica (CNEP) $\longrightarrow$ ausência de descarga epiléptica, mecanismo psicológico

VEEG padrão-ouro para diagnóstico diferencial (La France et al 2013)

SPECIAL REPORT

Minimum requirements for the diagnosis of psychogenic nonepileptic seizures: A staged approach

A report from the International League Against Epilepsy Nonepileptic Seizures Task Force

*†W. Curt LaFrance Jr., ‡Gus A. Baker, §Rod Duncan, ¶Laura H. Goldstein, and #Markus Reuber

Epilepsia, **(*):1–14, 2013
doi: 10.1111/epi.12356

Table 2. Overview of proposed diagnostic levels of certainty for psychogenic nonepileptic seizures

	History	Witnessed event	EEG
Diagnostic Level			
Possible	+	By witness or self-report/description	No epileptiform activity in routine or sleep-deprived *interictal* EEG
Probable	+	By clinician who reviewed video recording or in person, showing semiology typical of PNES	No epileptiform activity in routine or sleep-deprived *interictal* EEG
Clinically established	+	By clinician experienced in diagnosis of seizure disorders (on video or in person), showing semiology typical of PNES, while not on EEG	No epileptiform activity in routine or ambulatory *ictal* EEG during a typical ictus/event in which the semiology would make ictal epileptiform EEG activity expectable during equivalent epileptic seizures
Documented	+	By clinician experienced in diagnosis of seizure disorders, showing semiology typical of PNES, while on video EEG	No epileptiform activity immediately before, during or after ictus captured on *ictal* video EEG with typical PNES semiology

Key: +, history characteristics consistent with PNES; EEG, electroencephalography (as noted in the text, additional tests may affect the certainty of the diagnosis—for instance, self-protective maneuvers or forced eye closure during unresponsiveness or normal postictal prolactin levels with convulsive seizures).

- Retirada de DAE
- Registro de crises + ausência de descargas epilépticas
- Validação clínica (anamnese + observação)
- Tempo suficiente de registro no VEEG

How Long Does It Take to Make an Accurate Diagnosis in an Epilepsy Monitoring Unit?

Friedman & Hirsch 2009

Abstract: This study reports the existence of patients requiring prolonged monitoring with video-electroencephalography to make an accurate diagnosis and to quantify how often this occurs. The authors performed a retrospective review of 248 consecutive adult patients admitted to the epilepsy monitoring unit during 12 months for event characterization or presurgical evaluation. For the diagnosis of definite epilepsy, at least one epileptic seizure must have been recorded with video-electroencephalography. The median time to first diagnostic event, whether epileptic seizure or nonepileptic event, was 2 days; 35% required 3 or more days and 7% >1 week. Twelve percent of those with definite epilepsy never had interictal epileptiform discharges and 17% of those with nonepileptic events had interictal epileptiform discharges. Six percent of patients with definite epilepsy had neither epileptic seizures nor interictal epileptiform discharges until day 3 or after. Based on our results, it is common to require 3 or more days in an epilepsy monitoring unit to record and diagnose the nature of paroxysmal episodes and not rare to require more than a week. Interictal electroencephalography alone cannot reliably distinguish between those with epileptic seizures and nonepileptic events.

Key Words: Video-EEG monitoring, Epileptic seizures, Nonepileptic seizures, Epileptiform discharges, Length of stay, Cost, Insurance

(*J Clin Neurophysiol* 2009;26: 213–217)

Long-term scalp-recorded digital video-electroencephalography (V-EEG) in an epilepsy monitoring unit (EMU) is one of the cornerstones of comprehensive care for patients with epilepsy, using correlations between behavioral and electrophysiological changes (Binnie et al., 1981; Boon et al., 1994; Cascino, 2002). It is an important tool used for surgical localization in a medically intractable patients (Cascino, 2001; Fish, 1996; Ives, 1987; Quesney and Gloor, 1985). In addition to helping determine localization of seizure onset, the V-EEG is necessary to confirm the epileptic nature of spells, as a significant proportion of patients (up to 32%) referred for refractory epilepsy have nonepileptic events (NEE) (Benbadis et al., 2004; Martin et al., 2003). The diagnostic utility of an EMU was recently demonstrated, resulting in establishing a definitive diagnosis in 76% to 88% of patients and affecting changes in diagnosis or treatment in up to 79% of patients (Lobello et al., 2006; Smolowitz et al., 2007).

Occasionally, patients undergoing V-EEG in the hospital do not display interictal or ictal epileptiform abnormalities for several days (Eisenman et al., 2005). Although this certainly decreases the chances of epilepsy, we observed several patients who proceeded to have epileptic seizures (ES) after several days and even weeks of monitoring without any evidence of epilepsy before recording the seizure. Although the literature suggests most paroxysmal events (88%–96%) are captured within the first 48 hours of recording (Lobello et al., 2006; Parra et al., 1998), extended monitoring is necessary in a subset of patients. Nevertheless, denial of coverage for prolonged inpatient V-EEG by insurance companies is common. We aimed to increase awareness of these patients who require prolonged monitoring to reach an accurate diagnosis, to determine how often this occurs, and to investigate whether such patients have particular clinical characteristics that may allow their identification. To avoid selection bias or anecdotal reporting, we limited the analysis to consecutive patients during 12 months of monitoring.

METHODS

A retrospective review of EMU reports and hospital discha
summaries was conducted for all patients admitted to the adult E
at Columbia University Medical Center from September 20
September 2006. Patient characteristics include
time elapsed from EMU admission until first ap
epileptiform discharges (IEDs; extracted fro
section of the EMU reports), time elapsed until
events, categorization of events as ES or NEE,
and post-EMU diagnosis. Excluded from the st
patients younger than 18 years, patients admi
invasive intracranial recording, and patients ad
part of a clinical trial. The primary reason for
categorized as follows: diagnosis of paroxysm
ization of known seizures, presurgical evalu
subclinical or frequent nonconvulsive seizur
justment or toxicity. Given that we sought t
events in the EMU, only those patients ad
of events or presurgical evaluation we

Patients underwent continuous
throughout their hospitalization. F
to the 10–20 international syste
poral chains (P9/T9/P9 and
were not used. Spike and
screen the EEG in real t
and electrographic se
raw EEG. A train
discharges and
iology fello
samples
Pati

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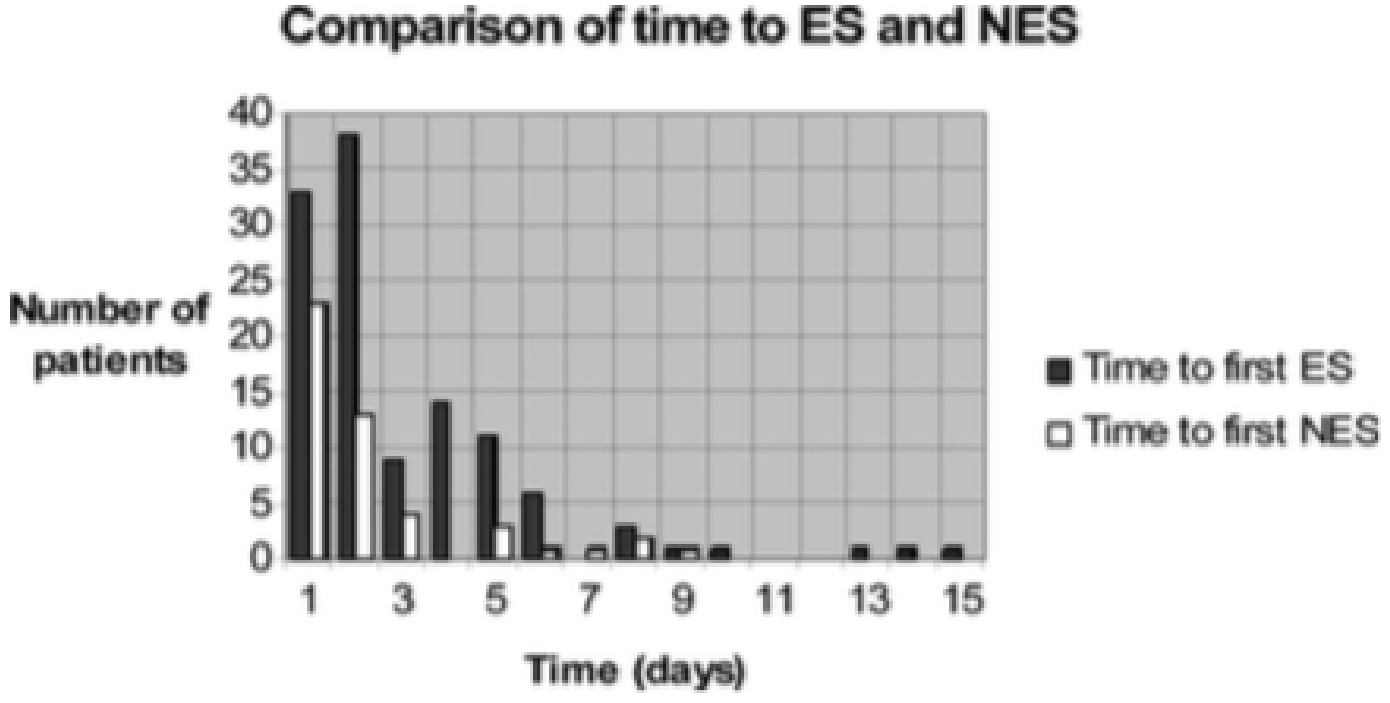
77030, U.S.A.; e-mail: defriedm@bcm.tmc.edu

- Sem VEEG acurácia 67%
- Com 3 dias de VEEG ⟶ acurácia 67% para CE e 83% para CNEP
- Com 7 dias de VEEG ⟶ acurácia 95% para CE e para CNEP
- Com 14 dias de VEEG ⟶ acurácia 100% para CE e para CNEP



Qual foi a metodologia da investigação?

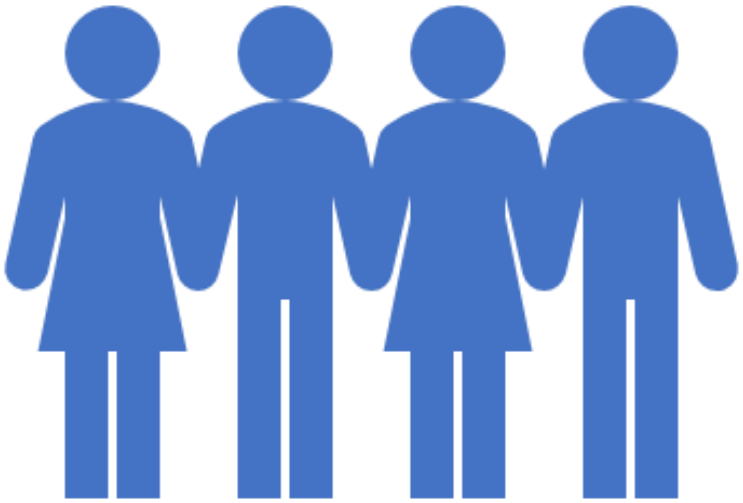
- VEEG 14 dias (± 300 horas)
- Anamnese neuropsiquiátrica
- Registro de eventos espontâneos
- Indução de CNEP por sugestão
- Validação clínica

- Exames neurológico / psiquiátrico
- RM cerebral / LCR
- Outros exames subsidiários
- Avaliação neuropsicológica
- Testes psicológicos
- Elaboração diagnóstica
- Formulação causal
- Compreensão psicológica
- Comunicação terapêutica

E os resultados?

Dados biográficos

- N = 12 pacientes
- Idade: 11-17 anos, média 14 anos
- Sexo: F = 10 / M = 2
- Educação formal: 4-11 anos, média 8,5 anos
- Procedência: todos de Rio Branco
- S. social: todos estudantes, solteiros e morando com familiares, 11 da classe C e 1 da classe D

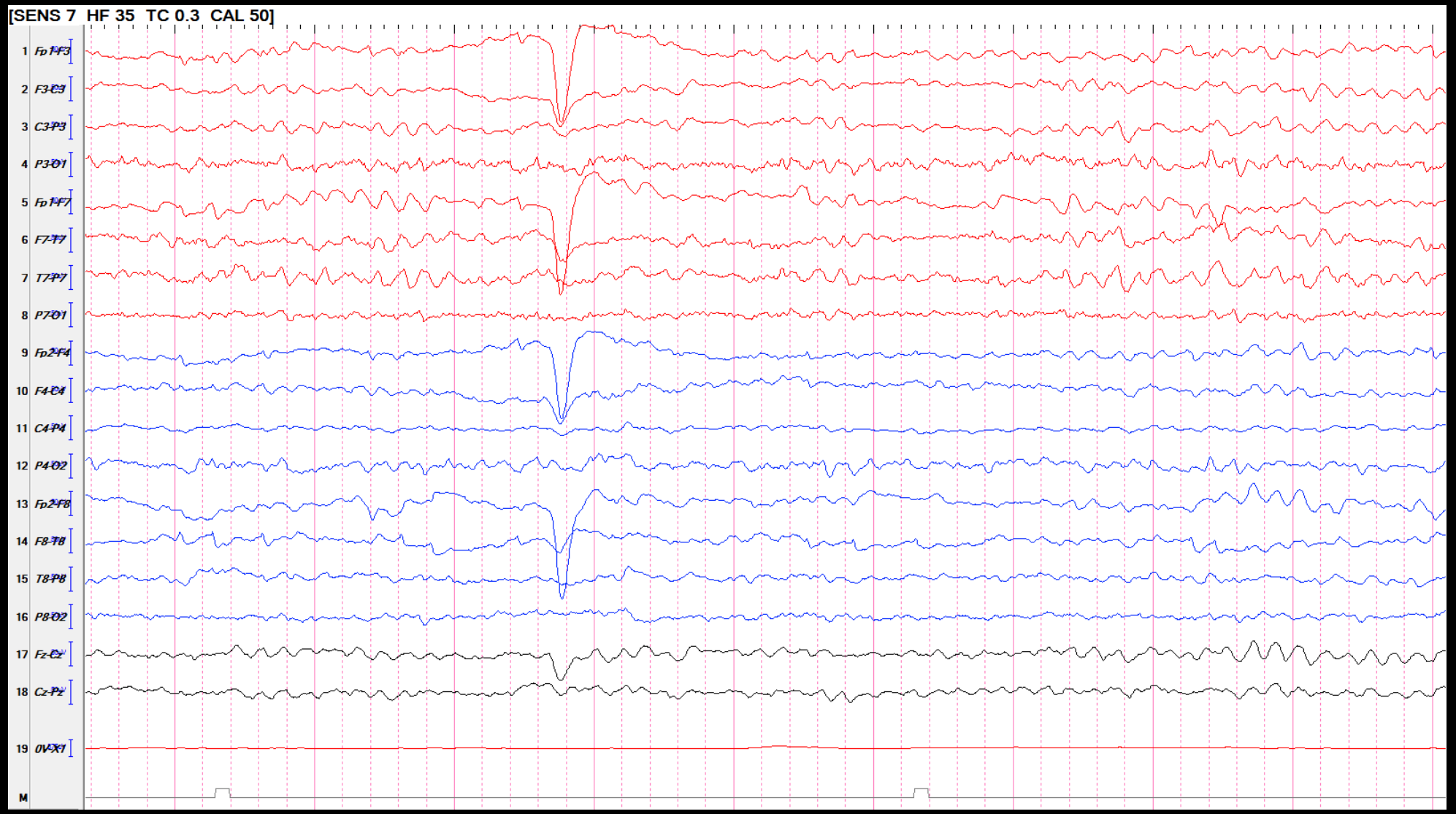


Achados neurológicos

Video EEG

Pac	Atividade de Base	Atividade Epileptiforme	Crises
1	**Alentecimento no hemisfério E**	Ausente	CNEP
2	Normal	Ausente	CNEP
3	Normal	Ausente	CNEP
4	Normal	Ausente	CNEP
5	Normal	Ausente	CNEP
6	Normal	Ausente	CNEP
7	Normal	**Generalizada + Focal**	Sem crises
8	Normal	**Generalizada + Focal**	**Crises mioclônicas**
9	Normal	Ausente	Sem crises
10	Normal	Ausente	CNEP
11	Normal	Ausente	CNEP
12	Normal	Ausente	CNEP

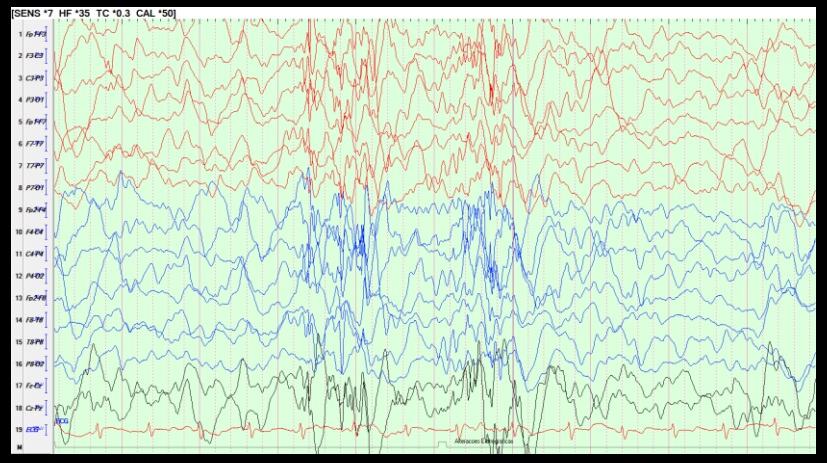
Paciente 1



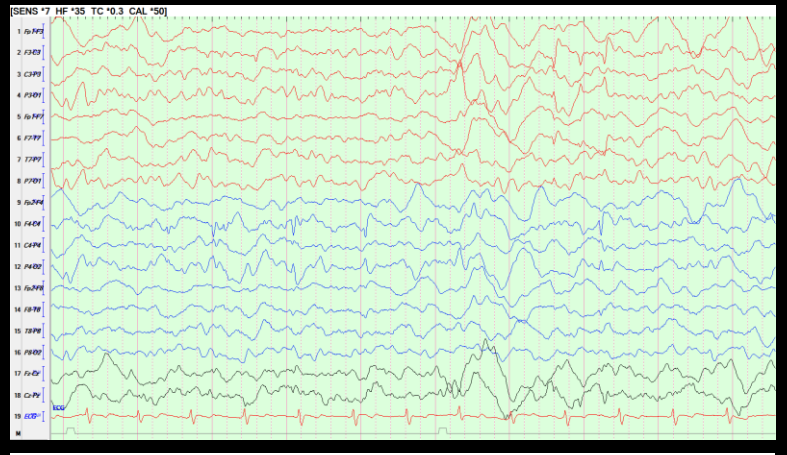
Achado inespecífico, relacionado a alteração imagem que será descrito na sequencia.

Paciente 7

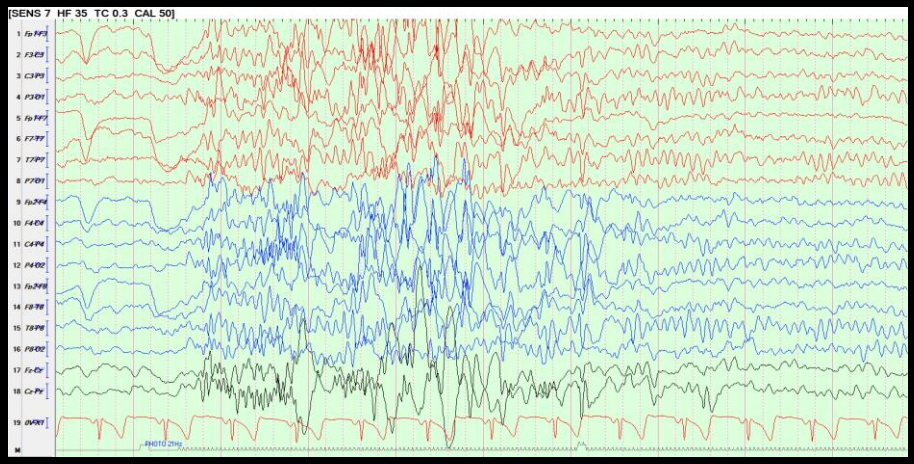
- 11 anos, sexo F, irmã de pac. 08
- 1ª DV aos 10 anos. Após 2 dias: crise convulsiva
- Desde então CTC, mioclonias e ausências
- EEG interictal atividade epiléptica generalizada + focal + resposta fotoparoxística
- VEEG: ausência de CE + ausência de CNEP
- Diagnóstico: epilepsia generalizada idiopática (causa genética)



Atividade epileptiforme generalizada



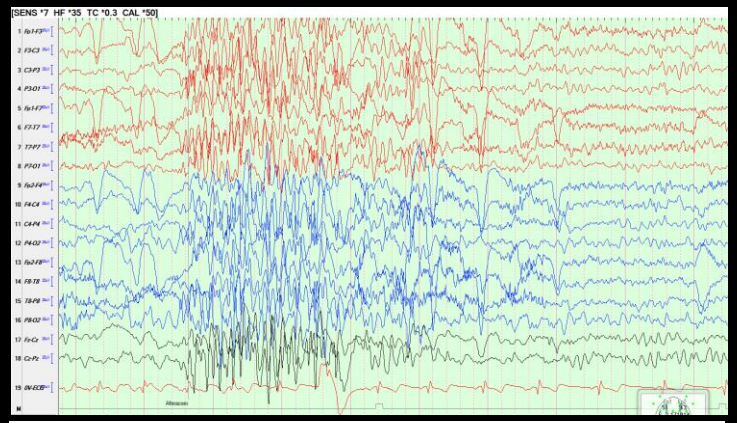
Atividade epileptiforme focal



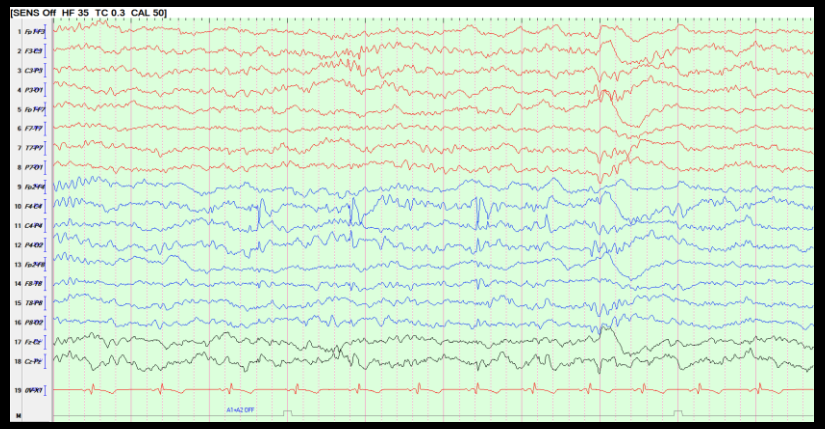
Resposta fotoparoxística

Paciente 8

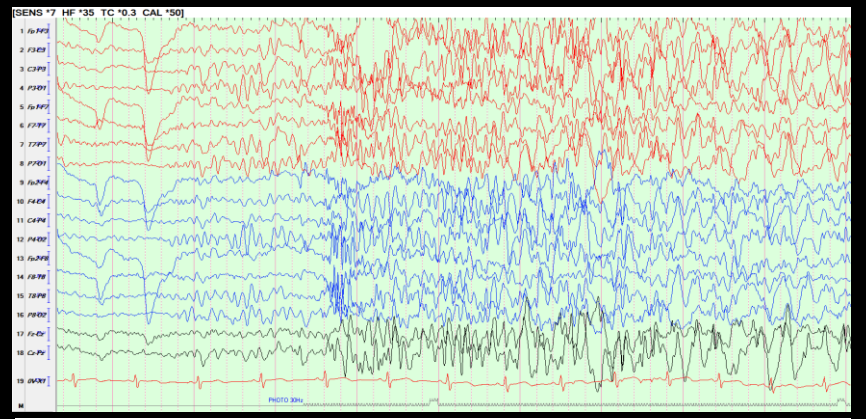
- 13 anos, sexo M, irmão de pac. 07
- 1ª DV aos 11 anos. Após 2 semanas: crise convulsiva
- Desde então CTC e mioclonias
- EEG interictal atividade epiléptica generalizada + focal + resposta fotoparoxística
- VEEG: CE (mioclonias) + ausência de CNEP
- Diagnóstico: epilepsia generalizada idiopática (causa genética)



Atividade epileptiforme generalizada



Atividade epileptiforme focal



Resposta fotoparoxística

PEDIATRICS
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Etiologies for Seizures Around the Time of Vaccination

Nienke E. Verbeek, Floor E. Jansen, Patricia E. Vermeer-de Bondt, Carolien G. de Kovel, Marjan J.A. van Kempen, Dick Lindhout, Nine V.A.M. Knoers, Nicoline A.T. van der Maas and Eva H. Brilstra

Pediatrics 2014;134;658; originally published online September 15, 2014;
DOI: 10.1542/peds.2014-0690

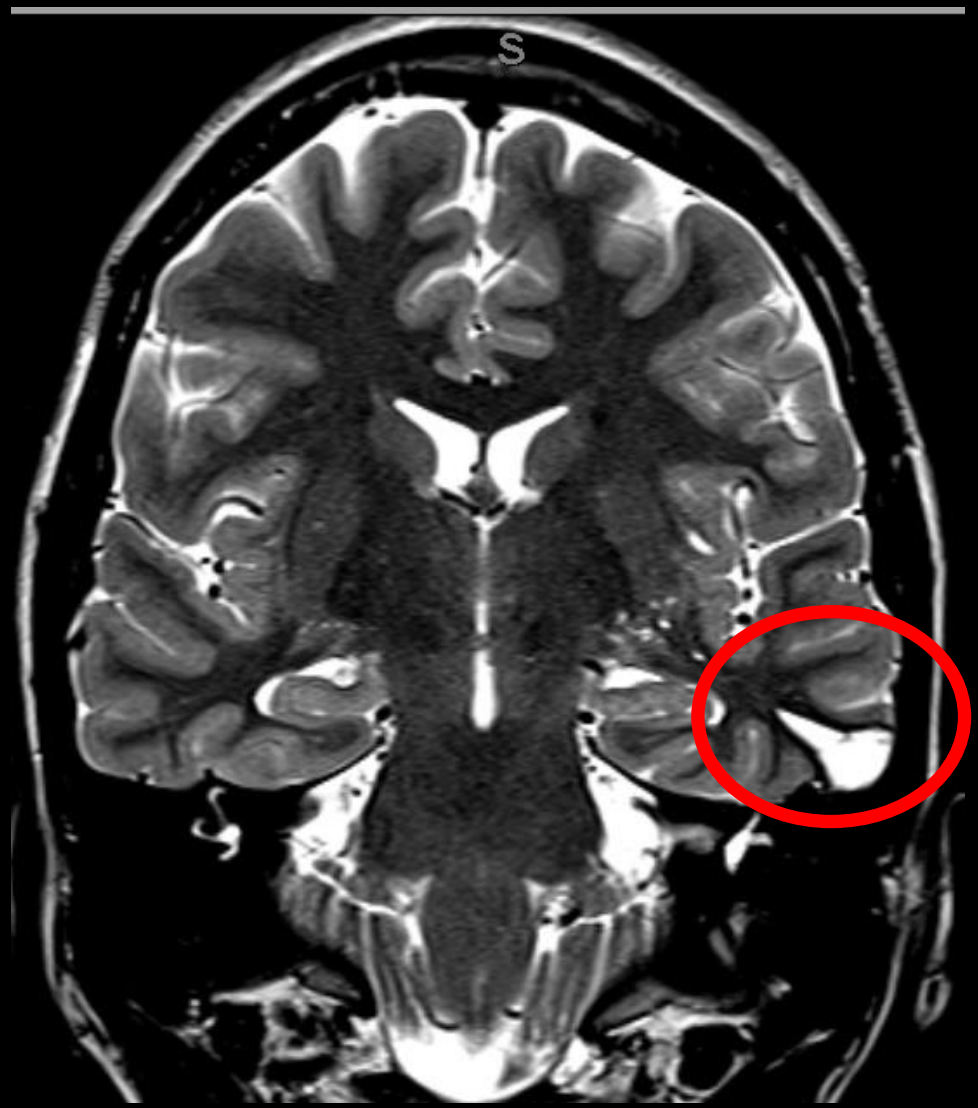
WHAT'S KNOWN ON THIS SUBJECT: Childhood vaccinations mildly increase the risk of febrile seizures in the general pediatric population, during specific risk periods. However, vaccinations are common precipitants for (first) seizures in the genetically determined, fever-sensitive Dravet syndrome (formerly severe myoclonic epilepsy of infancy).

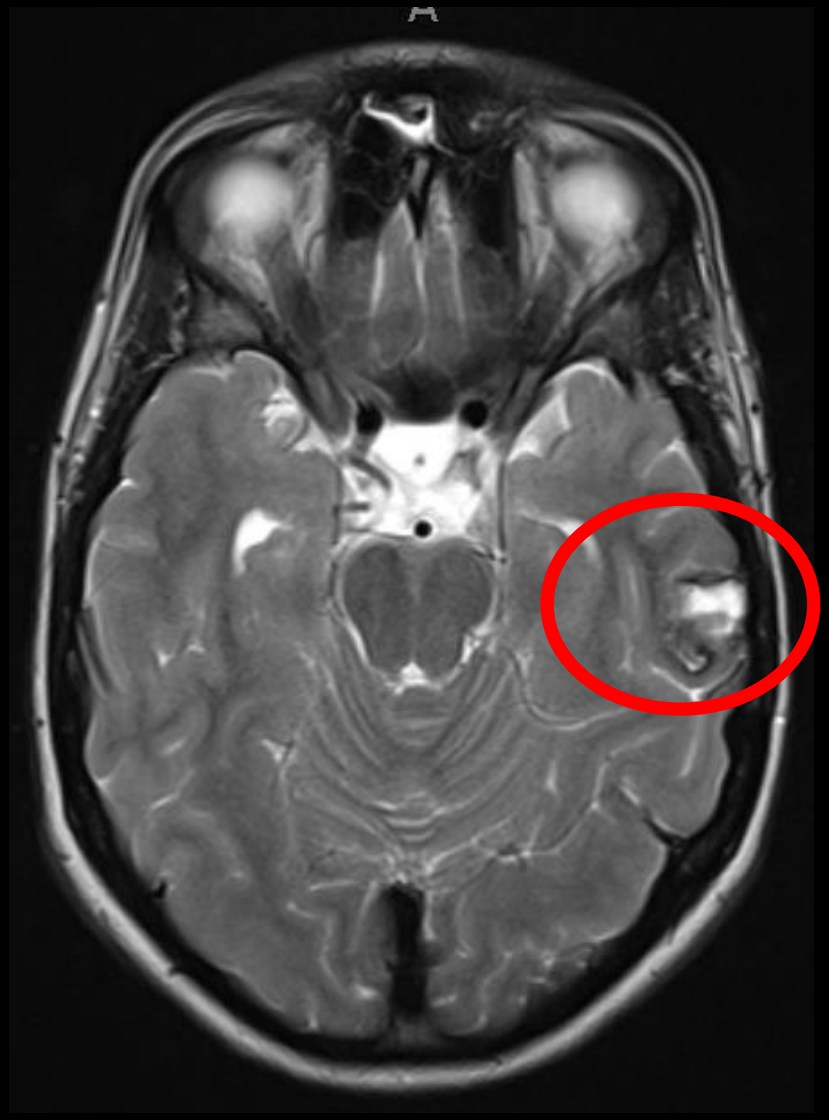
WHAT THIS STUDY ADDS: This study shows that in most children with epilepsy onset after vaccination, genetic or structural causes of epilepsy can be identified. This claim includes children with Dravet syndrome (~55%) but also children with benign epilepsy or preexistent encephalopathy.

Ressonância crânio e AngioRM

Paciente	Ressonância Crânio	AngioRM
1	Gliose Temporal E – sequela TCE	NR
2	Aumento hipófise	NR
3	Normal	Normal
4	Hipocampos assimétricos, menor a D	NR
5	Heterotopia + malformação (congênito)	Hipoplasia seios venosos E
6	Normal	Assimetria seios venosos
7	Normal	NR
8	Normal	NR
9	Aumento hipófise	Normal
10	Normal	NR
11	Normal	Normal
12	Focos alteração sinal subst. branca	NR

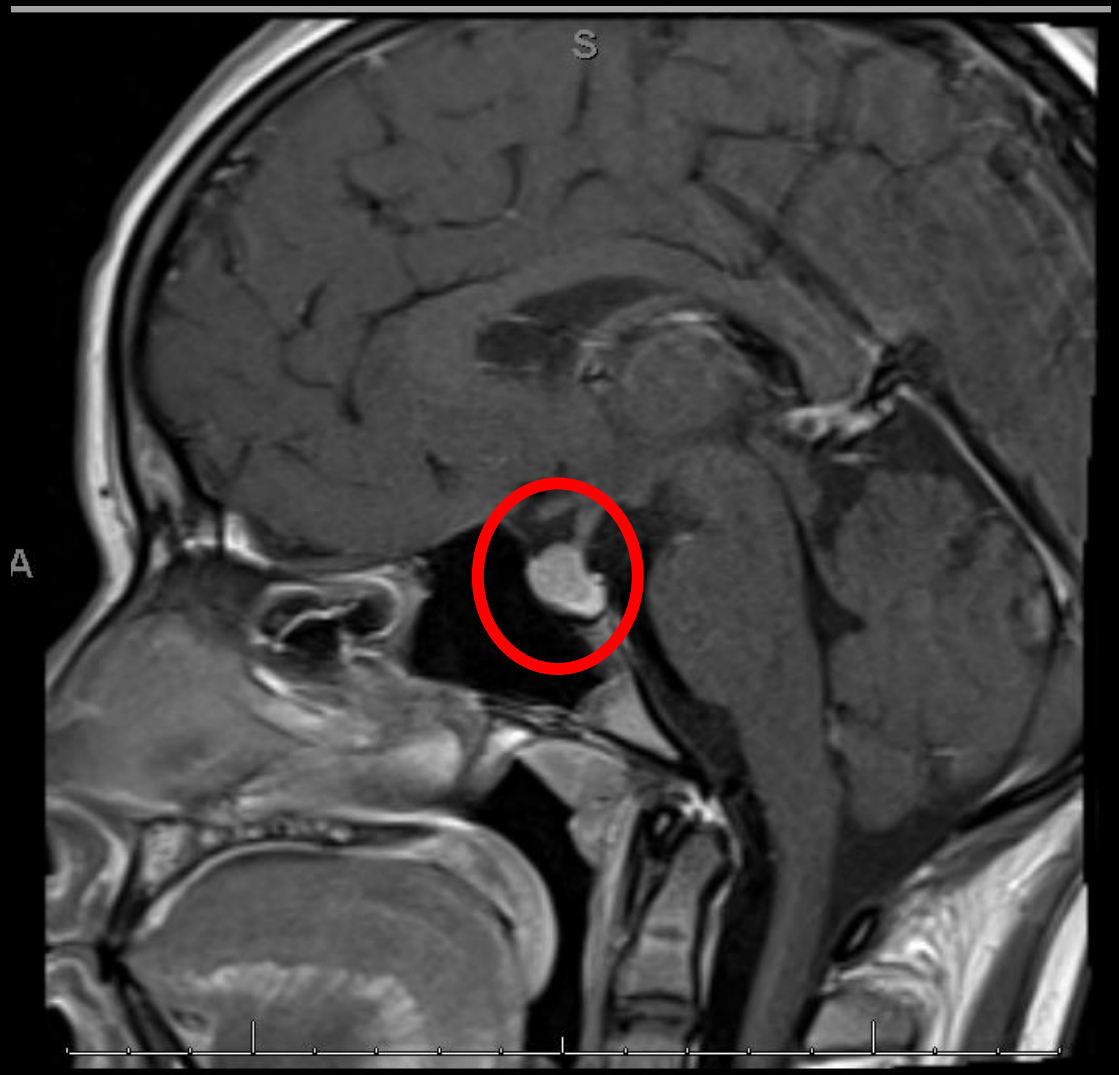
Paciente 1





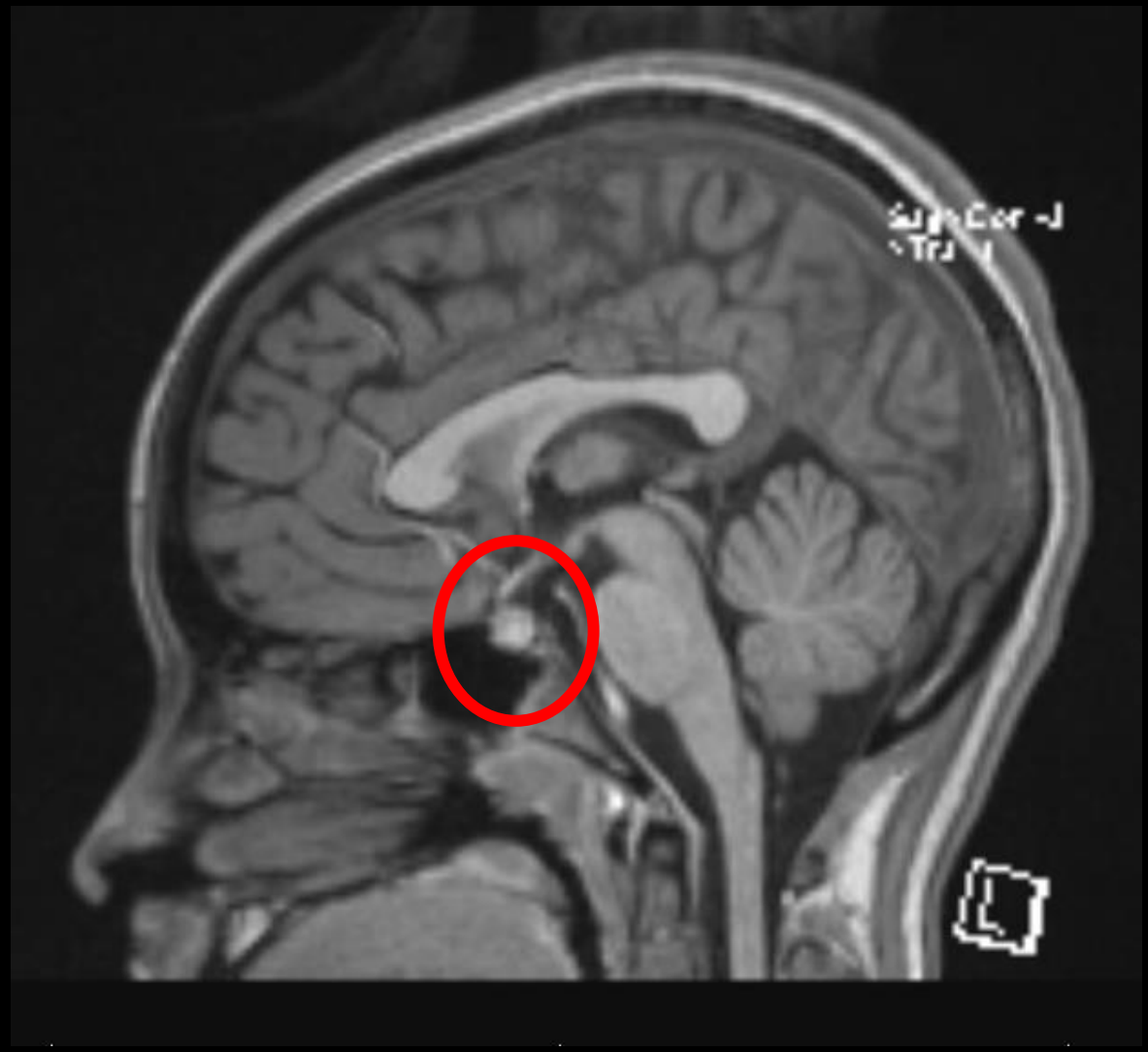
Área gliose temporal esquerdo – TCE queda moto dezembro/2018

Paciente 2



Aumento hipófise – achado sem correlação com quadro

Paciente 9



Aumento hipófise – achado sem correlação com quadro

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Volume 86, Issue 7
1 July 2001

Normal Pituitary Hypertrophy as a Frequent Cause of Pituitary Incidentaloma: A Follow-Up Study FREE

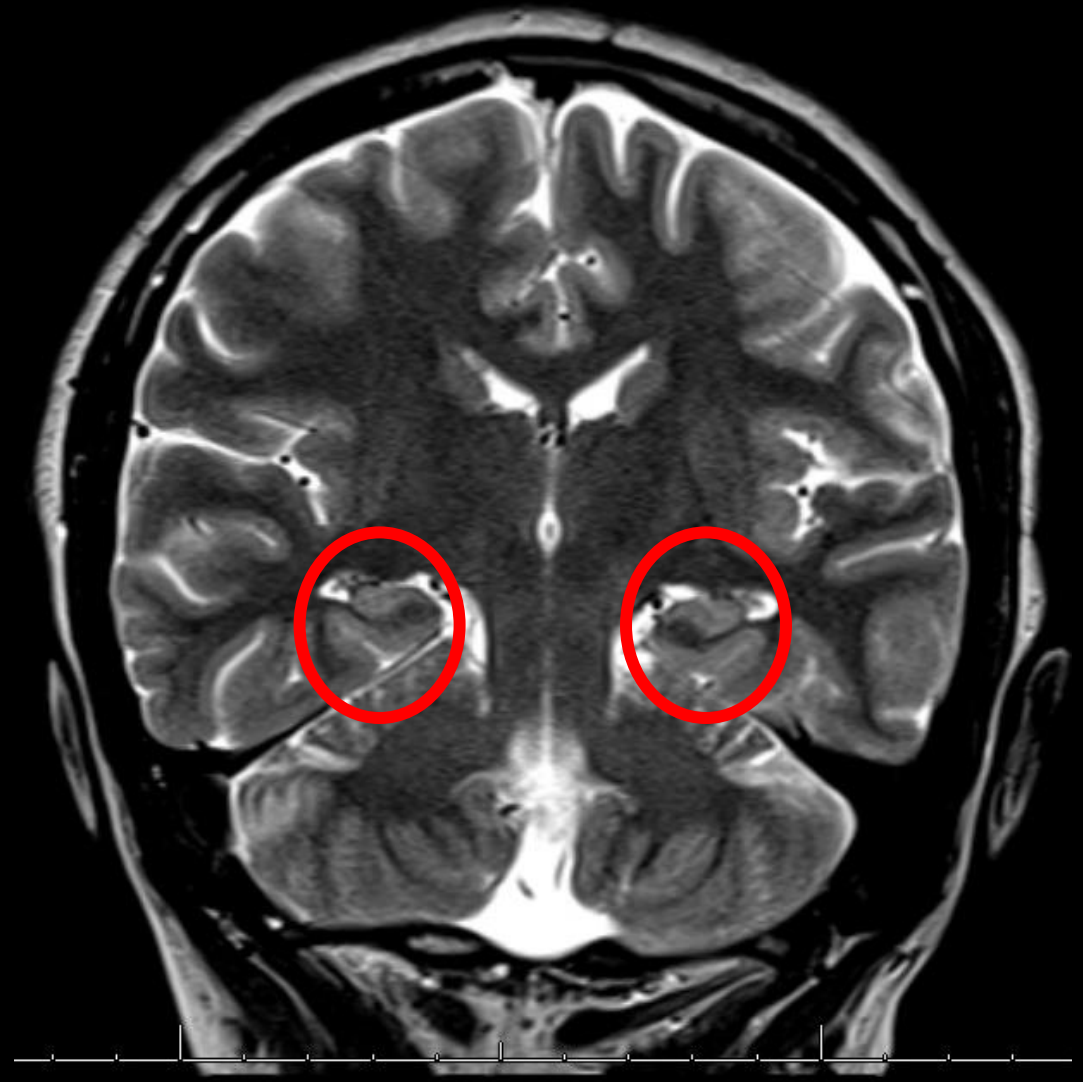
Philippe Chanson ✉, France Daujat, Jacques Young, Angela Bellucci, Michèle Kujas, Dominique Doyon, Gilbert Schaison

The Journal of Clinical Endocrinology & Metabolism, Volume 86, Issue 7, 1 July 2001, Pages 3009–3015, https://doi.org/10.1210/jcem.86.7.7649

Published: 01 July 2001 **Article history** ▼

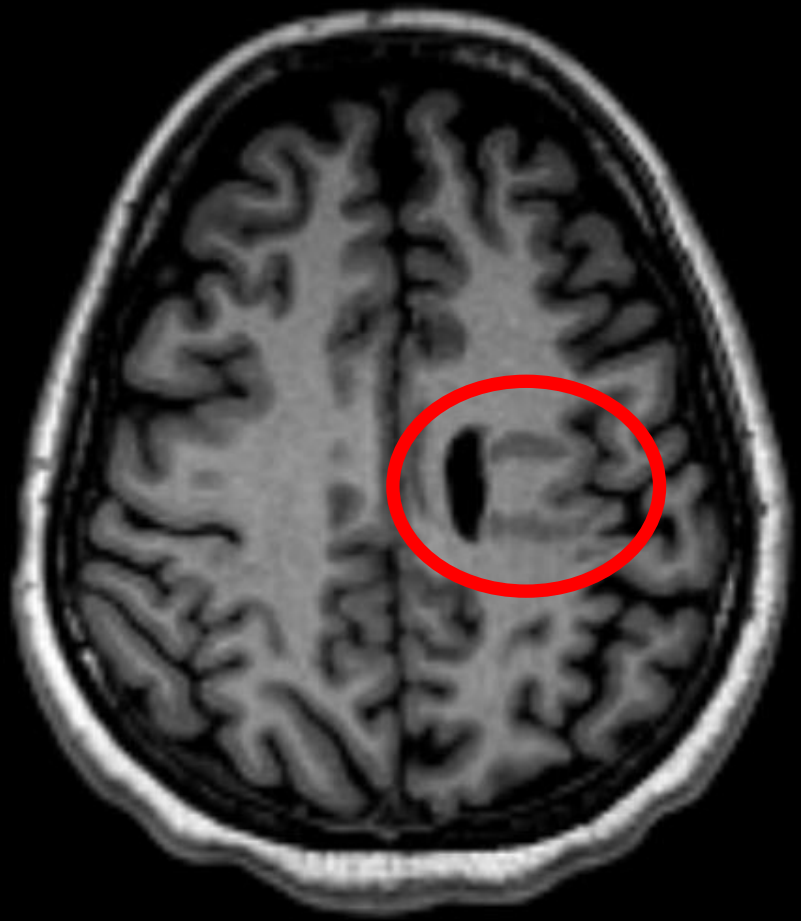
Enlargement of the pituitary gland is a frequent cause of incidentaloma and of referrals to endocrinologists for hormonal evaluation and therapeutic advice. In neuroradiological series, 25–50% of healthy women who are 18–35 year old have a convex superior pituitary contour, but pituitary height exceeds 9 mm in less than 0.5% of cases.

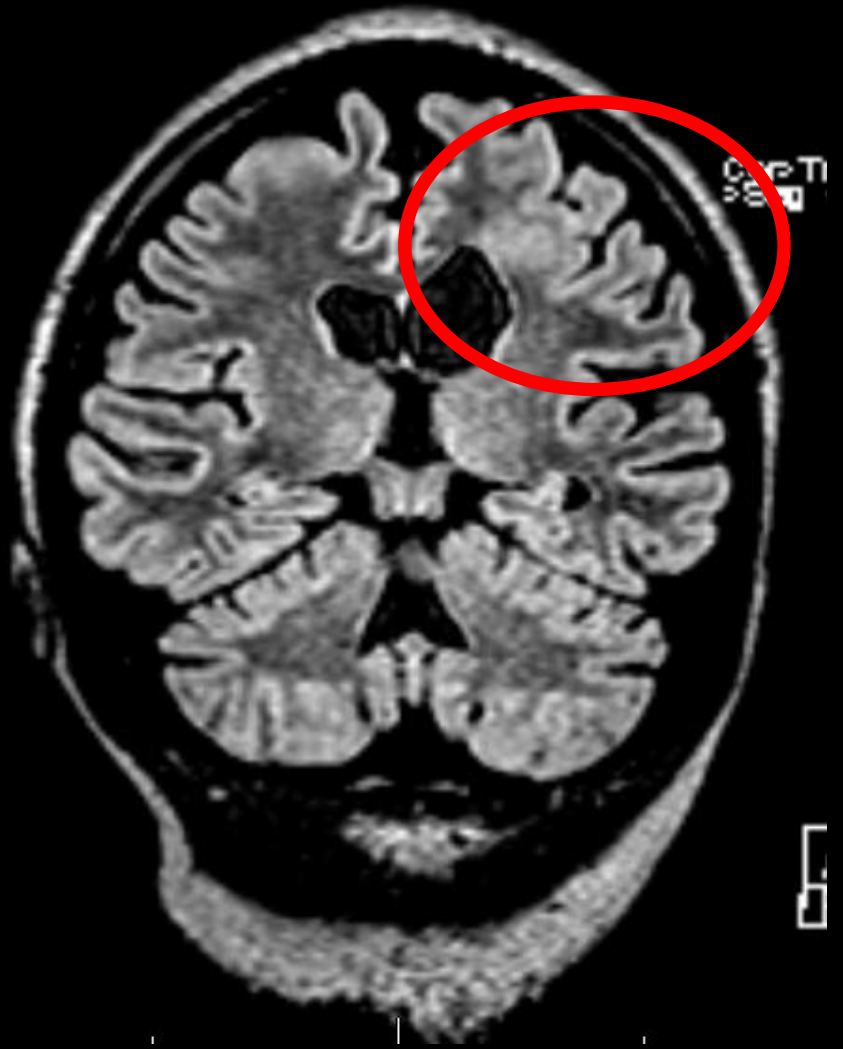
Paciente 4



Hipocampos assimétricos, menor a direita – variação da normalidade

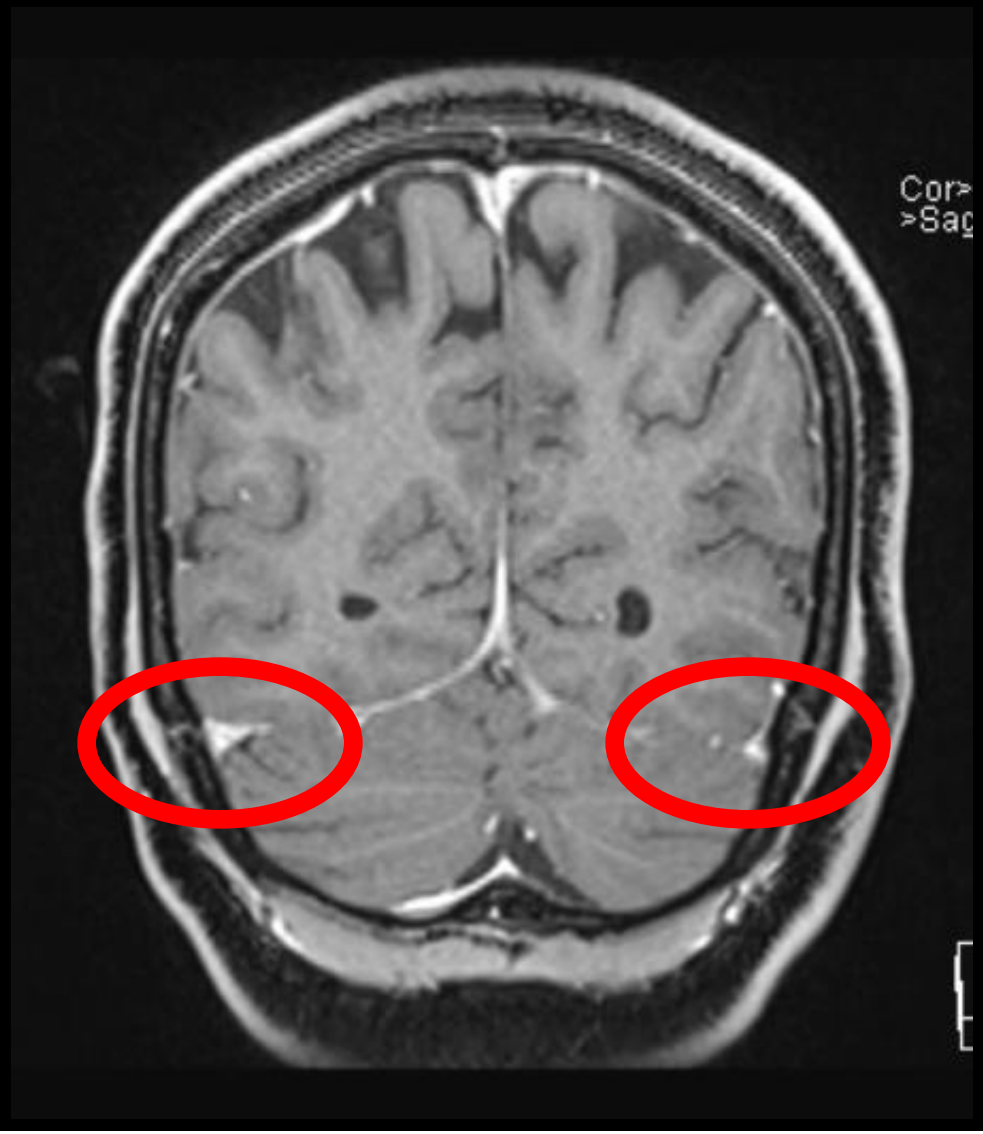
Paciente 5





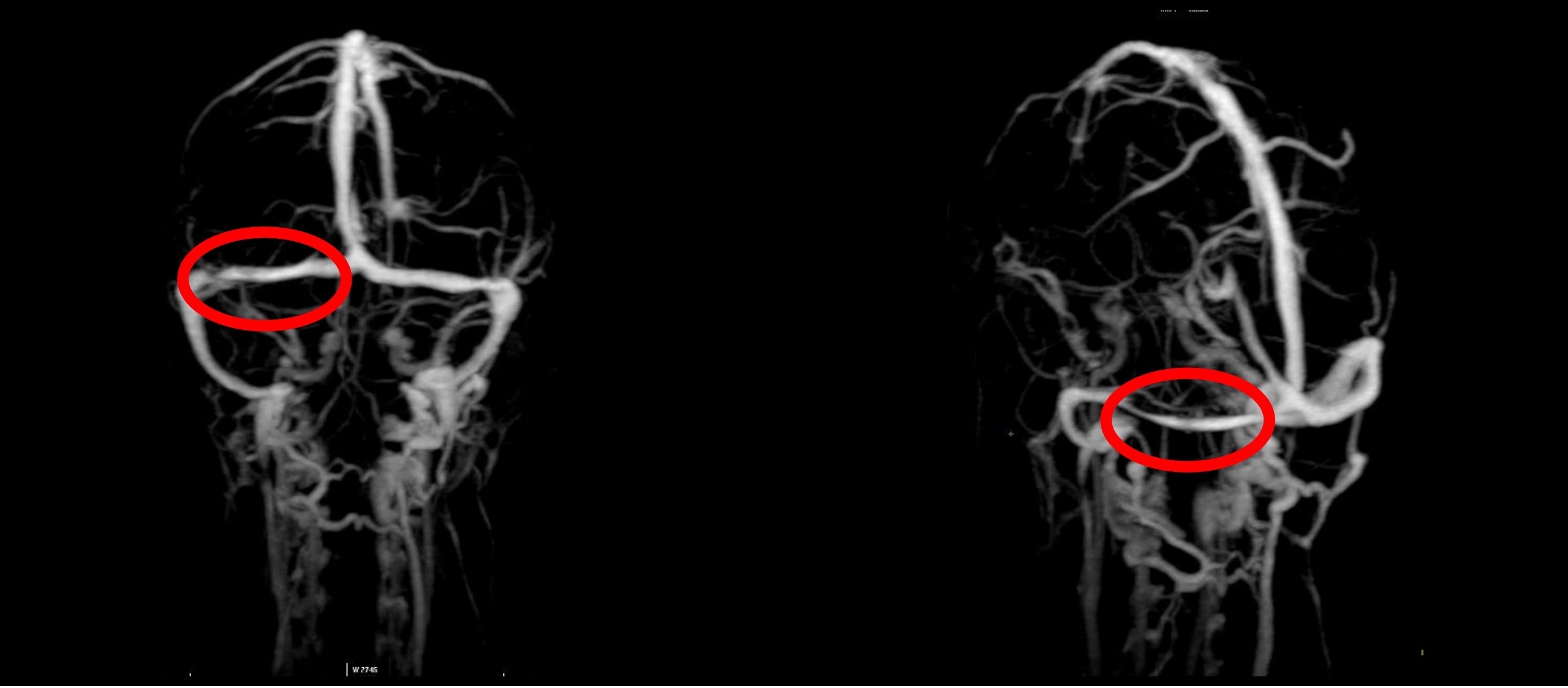
Substância cinzenta heterotópica (duas bandas) com alteração do córtex – malformação congênita

Paciente 5



AngioRM – assimetria seios venosos, menor a esquerda – variação da normalidade

Paciente 6



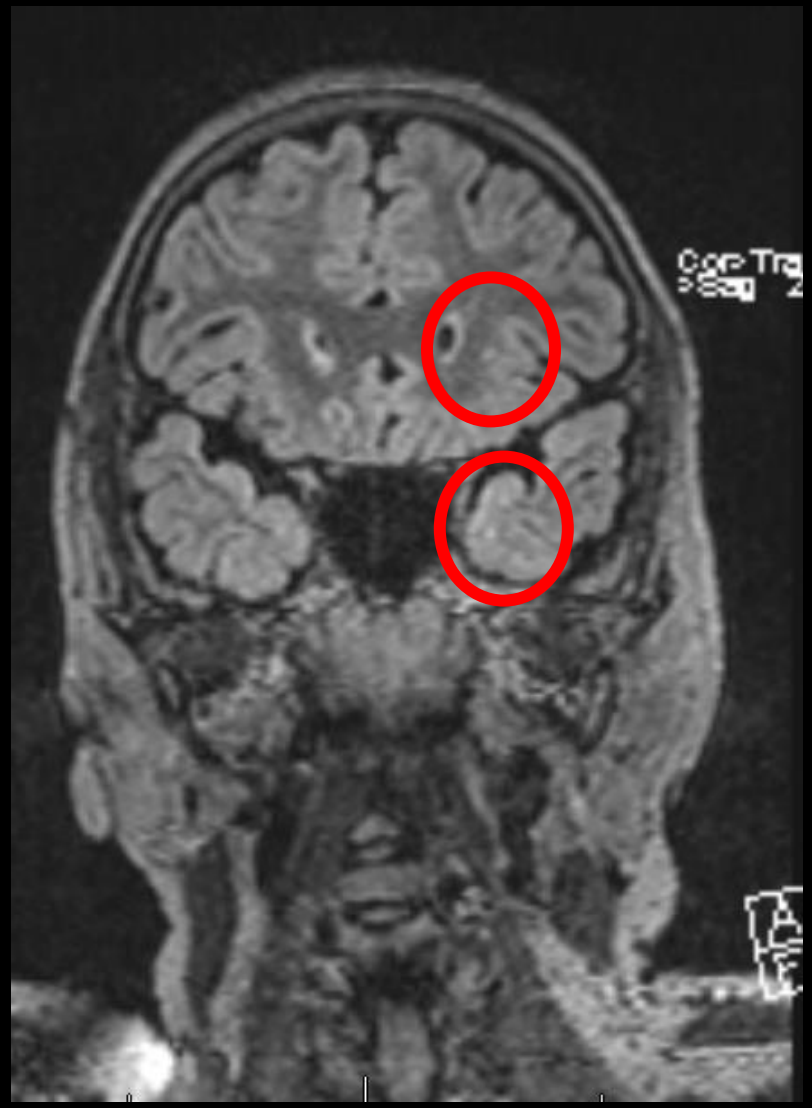
AngioRM – assimetria seios venosos, mais afilado a direita – sem correlação com quadro

Achados AngioRM

- ✓ Assimetria do seio transverso é um achado comum, considerado variação do normal – visto em até 49% casos
- ✓ Aplasia ou hipoplasia unilateral ocorre em 20% a 39% das pessoas

Zouaoui A & Hidden G. Acta Anat (Basel) 1988;133:318 –324.
Han K, Chao AC, Chang FC, et al. *Medicine (Baltimore)*. 2016;95(10):e2862.

Paciente 12



Focos de alteração sinal substância branca – inespecíficos, sem valor nesse contexto

Líquor

Pac	Celularidade	Proteina	Glicose	BOG	EFP	PCRs
1	3	29	67	Negativo	10,1%	Negativo
2	9	22	59	Negativo	8,1%	Negativo
3	1	25	51	Negativo	9,3%	Negativo
4	1	26	56	Negativo	8,5%	Negativo
5	12 (acidente)	38	54	Negativo	13,2%	NR
6	3	24	56	Negativo	8,2%	NR
7	2	29	55	Negativo	6,7%	NR
8	1	17	65	Negativo	7,9%	NR
9	1	25	62	Negativo	8,2%	NR
10	3	28	64	Negativo	9,3%	NR
11	1	12	65	Negativo	10,5%	NR
12	3 eosinofilos 54%	32	56	Negativo	13,8%	Negativo

Paciente 2

- ✓ 1ª Vacina em abril/2014
- ✓ 2ª Vacina inicio 2015 – inicia com sintomas
- ✓ Maio/2018 – paralisia ascendente, dor, sonda para alimentação, não deambulava, recuperação em 6 meses
- ✓ Após melhora desse quadro inicia com eventos sugestivos de CNEP

➔ Síndrome Guillain Barre? Parte do quadro funcional?

VAERS Table of Reportable Events Following Vaccination*	
Vaccine/Toxoid	**Event and interval** from vaccination**
influenza-IIV, IIV3, IIV4, RIV3, ccIIV3, LAIV4	D. Guillain-Barré Syndrome (42 days) E. Any acute complication or sequelae (including death) of above events (interval - not applicable) F. Events described in manufacturer's package insert as contraindications to additional doses of vaccine (interval - see package insert)
Human Papillomavirus (Quadrivalent, Bivalent, or 9 valent) - 9vHPV, 4vHPV, 2vHPV	A. Anaphylaxis or anaphylactic shock (7days) B. Shoulder Injury Related to Vaccine Administration (7 days) C. Vasovagal syncope (7 days) D. Any acute complication or sequelae (including death) of above events (interval - not applicable) E. Events described in manufacturer's package insert as contraindications to additional doses of vaccine (interval - see package insert)

Resumo dos achados neurológicos:

- ✓ Dois pacientes (irmãos) com Epilepsia Generalizada Genética / Idiopática
- ✓ Uma paciente com malformação cerebral ➔ sem epilepsia ativa, apesar de potencial risco de desenvolver no futuro
- ✓ Uma paciente com sequela TCE ➔ sem evidência de epilepsia no momento, risco baixo
- ✓ Vários achados exames sem correlação com quadro, incluindo alterações seios venosos

Achados psiquiátricos

10 pacientes com diagnóstico final de CNEP

No	Interictal	No CE	No CNEP	Diag	Nível C Diag
1	AHE	0	2	CNEP	Def
2	N	0	3	CNEP	Def
3	N	0	2	CNEP	Def
4	N	0	1	CNEP	Def
5	N	0	2	CNEP	Def
6	N	0	2	CNEP	Def
9	N	0	0	CNEP	Clin
10	N	0	1	CNEP	Def
11	N	0	1	CNEP	Def
12	N	0	1	CNEP	Def

Quais foram os fatores de risco encontrados para as CNEP?

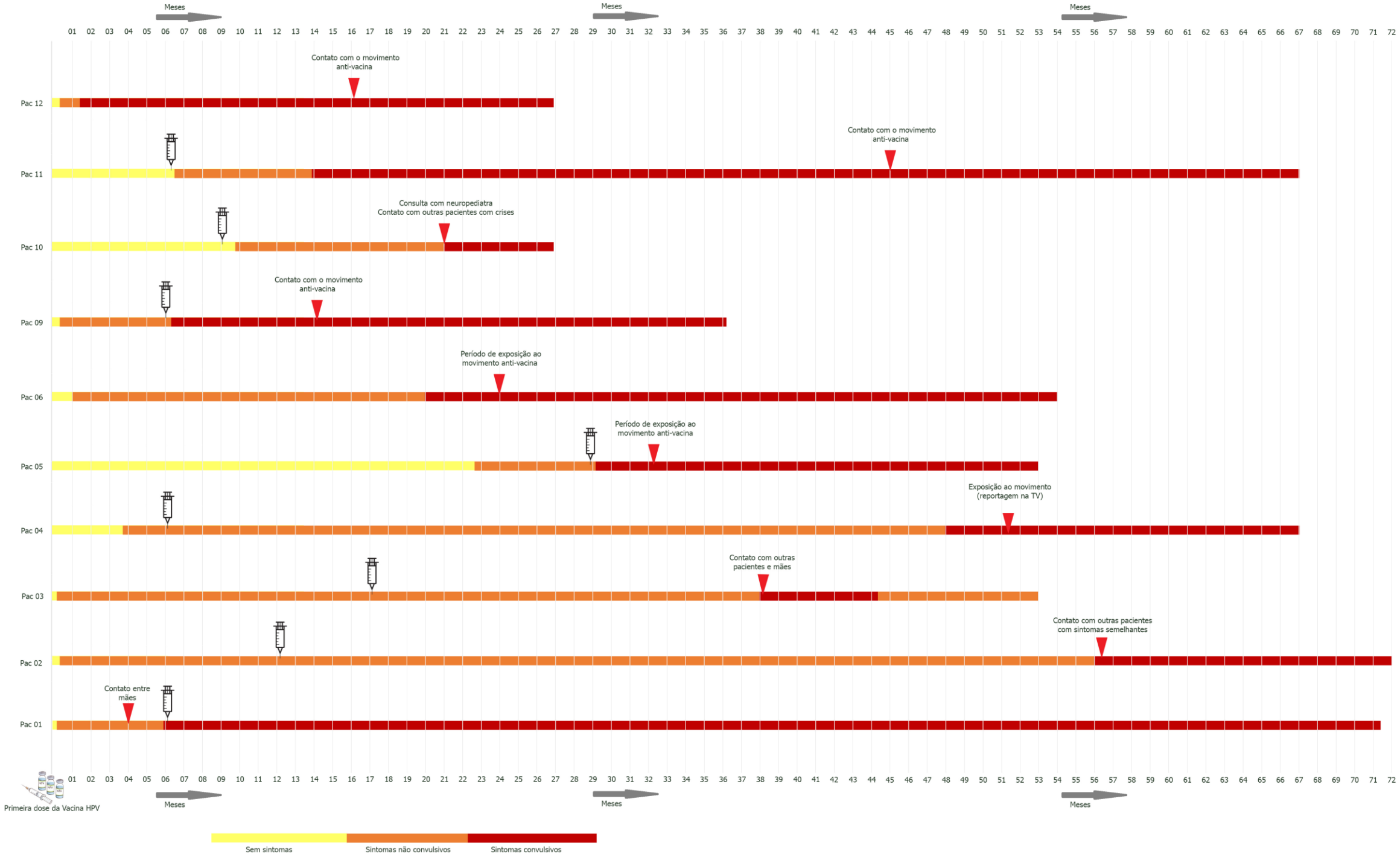
No	R pós-Vac	Exp	C Exc	G Soc	A F Psiq	Modelo	A D Crônica	A T mental	F Disf	Trauma	Negl
1	X	X	X	X					X		
2		X	X		X		X		X		X
3	X	X	X						X		X
4	X	X	X		X				X		X
5	X	X	X		X			X	X	X	
6		X	X	X					X		X
9	X	X	X				X		X		
10		X	X			X					
11	X	X	X			X			X	X	X
12	X	X	X		X	X			X		

Quais foram os fatores de risco também aventados para as CNEP?

- Privação material
- Estrutura social patriarcal em choque com desemprego masculino
- Crenças antivacinacionistas
- Condições adversas de vacinação
- Demora para o diagnóstico
- Hostilização por agentes de saúde
- Reforço e contágio pela rede social

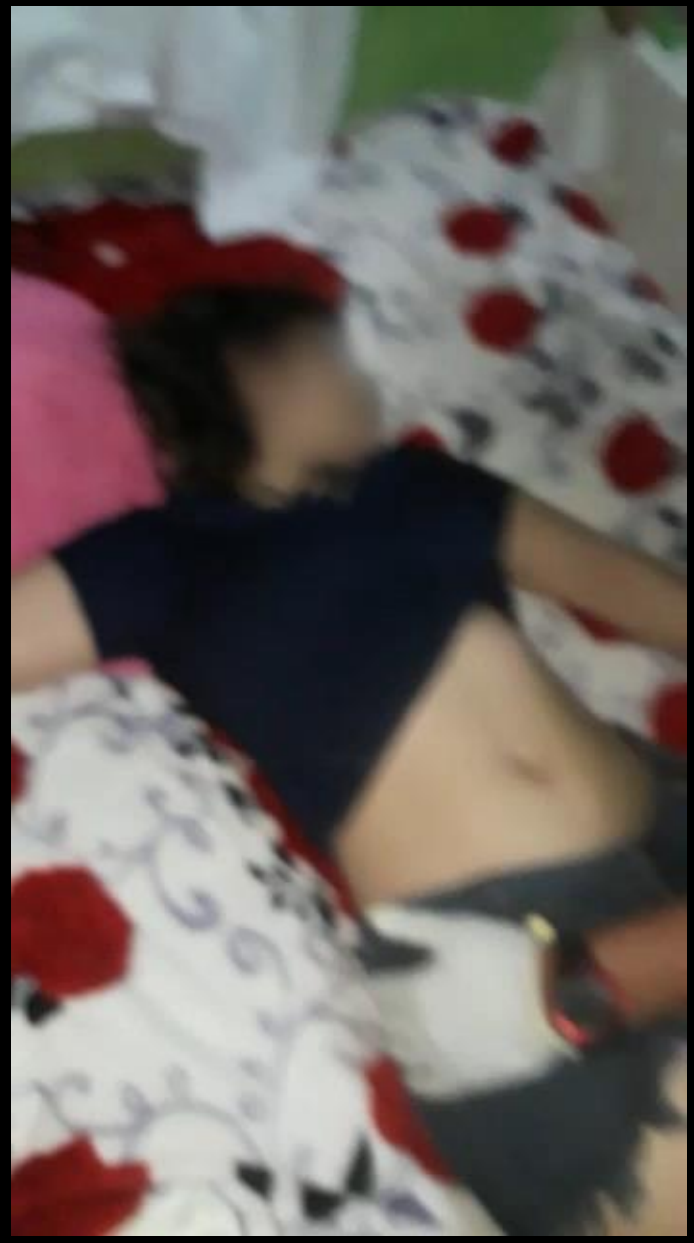
Qual a característica clínica dos pacientes com CNEP?

- Sintomas inicias não convulsivos dias a semanas após vacinação
- CNEP semanas a meses após vacinação
- Curso crônico e incapacitante
- Ausência de relação causal biológica com a vacina
- Desencadeamento pelo estresse relacionado à vacinação
- Fatores causais psicossociais
- Doença psicogênica pós-vacinal de curso crônico


Meses
Meses
Meses
01 02 03 04 05 06 07 08 09 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72
Contato com o movimento anti-vacina
Pac 12
Contato com o movimento anti-vacina
Pac 11
Consulta com neuropediatra
Contato com outras pacientes com crises
Pac 10
Contato com o movimento anti-vacina
Pac 09
Período de exposição ao movimento anti-vacina
Pac 06
Período de exposição ao movimento anti-vacina
Pac 05
Exposição ao movimento (reportagem na TV)
Pac 04
Contato com outras pacientes e mães
Pac 03
Contato com outras pacientes com sintomas semelhantes
Pac 02
Contato entre mães
Pac 01
01 02 03 04 05 06 07 08 09 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72
Meses
Meses
Meses
Primeira dose da Vacina HPV
Sem sintomas
Sintomas não convulsivos
Sintomas convulsivos

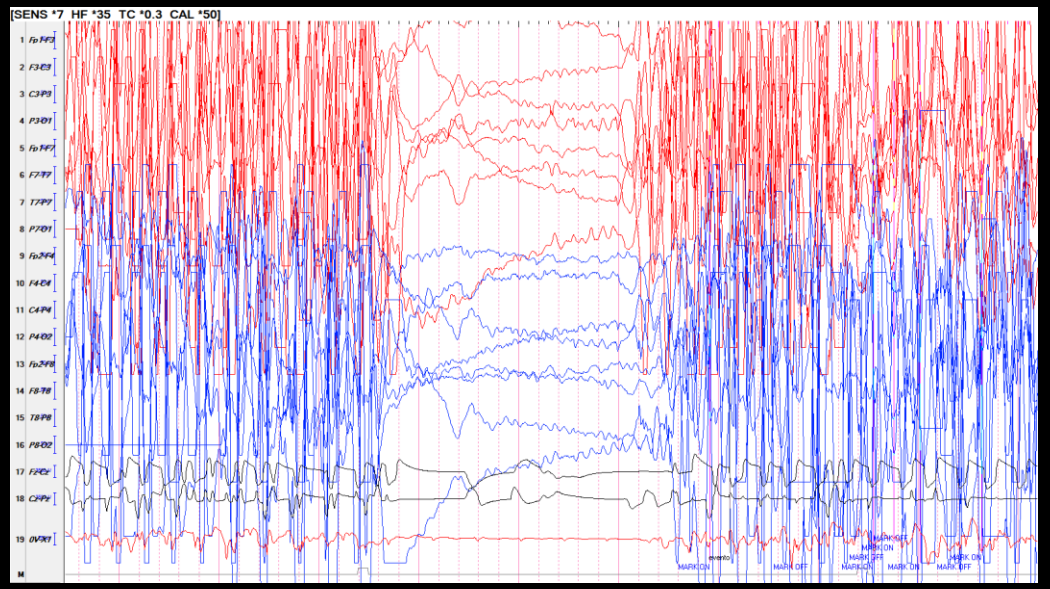
Caso 06

- Pac. 06, 15 anos, sexo F
- 1ª DV aos 11 anos. Após 1 mês: crises de sufocamento, angústia, falta de ar e batedeira no coração e desmaios. Após 20 meses: crises convulsivas
- Impacto: Internações frequentes em PS/UPA, afastamento da escola
- Sem contato com pai desde nascimento. Brigas frequentes com mãe. Cuidada pela avó após os 10 anos. Criação permissiva e superprotetora. Contato social intenso com meninas com quadro pós-vacinal. Avó engajada na luta contra a vacina do HPV



Caso 06

- EEG interictal, RM, Angio-RM, LCR, exames laboratoriais, avaliação neurológica, avaliação oftalmológica sem alterações.
- VEEG: ausência de CE + presença de crises espontânea e induzida sem descargas epilépticas (CNEP)
- Avaliação psiquiátrica: Convulsões dissociativas (CID10: F44.5)



Considerações importantes sobre as CNEP e outras manifestações psicogênicas

- Problema médico
- Os sintomas são involuntários
- Não é simulação ou síndrome factícia
- Causa sofrimento, incapacitação e risco para a saúde devido a iatrogenias
- É tratável
- Múltiplas causas psicológicos e sociais
- Pode ser desencadeada por procedimentos médicos

(Marchetti et al 2007, Marchetti 2019, Baslet 2012, LaFrance 2013)

- Pode ser desencadeada por vacinação de qualquer tipo
- Mecanismo não está ligado às propriedades biológicas da vacina, mas sim ao estresse do ato de vacinar

(Loharikar et al 2018)

Eight published reports of anxiety-related AEFI clusters.

Year	Country	Setting	Number vaccinated	Number of case-patients (%)	Age group or grade in school	Number of females (%)	Vaccine involved	Symptoms	Clinical management characteristics
1992	Iran	School	26	10 (38)	Age 14 years	10 (100)[a]	Tetanus	Pseudoseizure, tremors, blurred vision, headache, fainting	Hospitalized; multiple labs done (including lumbar puncture)
1995	Italy	School	24	7 (29)	7th grade	4 (57)	Hepatitis B	Dizziness, headache, fainting, paraesthesia	Hospitalized
1998	Jordan	Multiple schools	25,667	806 (3)	10th grade	379 (47)	Tetanus-diphtheria	Headache, dizziness, chest tightness, pyrexia, hypotension, feeling faint	Hospitalized; blood testing done; treated with steroid and antihistamine
2001	India	School	200	58 (29)	10th grade	58 (100)[a]	Tetanus	Headache, fainting, giddiness, falling, nausea, vomiting	Hospitalized; treated with steroid and antihistamine
2001	Vietnam	School	234	97 (41)	12 years	49 (51)	Oral cholera	Cold extremities, headache, nausea, abdominal pain, pruritis	Emergency room visit; treated with intravenous fluid, oral rehydration solution, and/or antihistamine
2007	Australia	School	720	26 (4)	Age 12–17 years	26 (100)[a]	HPV	Dizziness, fainting, weakness, palpitations, aphasia	Emergency room visit; testing included neuroimaging
2009	Taiwan	Multiple schools	9115	350 (4)	Age 12–15 years	237 (68)	H1N1 influenza	Dizziness, nausea, headache, hyperventilation	Not reported
2010	United States	Military reserve	201	14 (7)	Age 20+	6 (43)	H1N1 influenza	Weakness, headache, dizziness	Hospitalized; index patient completed nerve conduction studies

[a] Only girls were vaccinated, either because vac ed for girls (eg. HPV, tetanus).

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Anxiety-related adverse events following immunization (AEFI): A systematic review of published clusters of illness

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Conclusões

- 10 pacientes receberam diagnóstico final de CNEP (CID10 F44.5) = doença psicogênica pós-vacinal crônica
- 02 pacientes receberam diagnóstico final de epilepsia generalizada idiopática
- Não houve relação causal biológica com a vacina HPV4