Outline di oggi

- Alterazioni stato di coscienza (transitorie e persistenti)
- Encefalopatia

Outline del futuro meeting

- Ipertensione endocranica
- Edema cerebrale
- Perdita acuta della vista (neurite ottica)
- Disturbi acuti della deambulazione e atassia
- Sindrome di Guillain Barré
- Miastenia Gravis
- Disturbi movimenti oculari

La coscienza comprende..

Vigilanza: stato di veglia ad occhi aperti

Formazione reticolare attivatrice ascendente: aggregati neuronali estesi dal bulbo, ponte e mesencefalo al diencefalo, collegati a tutte le afferenze sensoriali, che proietta alla corteccia, talamo e ipotalamo (sistema reticolo talamo corticale)

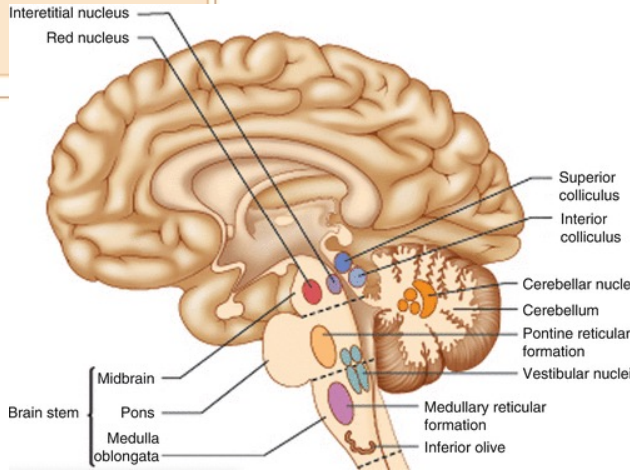
Le alterazioni dello stato di coscienza sono essenzialmente il risultato di due situazioni:

Grave danno di entrambi gli emisferi (una lesione a carico di un solo emisfero in genere non conduce a compromissione dello stato di coscienza)

Alterazioni della sostanza reticolare ascendente (di tipo strutturale o funzionale)

Funzioni cognitive corticali (contenuto della coscienza): consapevolezza

Corteccia e le vie discendenti dalla corteccia e dai nuclei motori del tronco → Funzioni cognitive corticali (contenuto della coscienza)



Alterazione dello stato di coscienza

Transitoria

Sincope

- Breath holding spells
- Cardiogena
- Sindrome da tachicardia posturale ortostatica

Non sincope o Pseudo-sincope

- Metaboliche (ipo-O2 e ipo-glic)
- Intossicazione farmaci
- Neurologiche (epilessia, cefalea, traumi, stroke)
- Psicogene (somatizzazione/conversione)

Persistente

Continuum di stati di veglia ridotta fino al coma

Transitoria

Sincope

perdita di coscienza, transitoria, con o senza prodromi, improvvisa, con incapacità a mantenere il tono posturale e con possibile caduta a terra, breve, con risoluzione spontanea solitamente completa e rapida

Pre-Sincope: sensazione di malessere con restringimento dello stato di coscienza senza perdita di coscienza

Incidenza dei casi di sincope in età pediatrica che richiedono intervento medico: 125.8/100.000

15% dei b.ni può aver avuto esperienza di una sincope < 18 anni

Sincope in PS pediatrico: 0.4-1% degli accessi/anno

Lipotimia [dal gr. λιποθυμία «deliquio», composto di λιπο- «che manca di» e θυμός «animo»]

Situazioni predisponenti e triggers

Luglio-Settembre 2009 • Vol. 39 • N. 155 • Pp. 180-195 LINEE GUIDA

La sincope in età pediatrica

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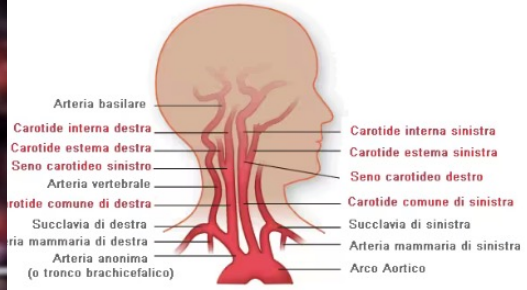
Stimolazione vie aeree	Bagno caldo
Apnea	Minzione
Pressione seni carotidei	Emicrania
Bevande fredde	Oculo-vagale
Tosse	Post-prandiale
Defecazione	Procedure mediche
Diving in apnea	Rasatura barba
Post-esercizio	Starnutire
Riflesso glossofaringeo	Stiramento
Pettinarsi	Deglutizione
Altitudine	Strumenti a fiato
Doccia calda	Manovra di Valsalva
Iperventilazione	Vomito
Vaccinazioni	Calo ponderale

Colpo al mento → onda di pressione nel seno carotideo (interpretato come "pericoloso" dai recettori della pressione arteriosa) –> riflesso del seno carotideo (tenta di contrastare aumento pressione diminuendo rapidamente la frequenza cardiaca e tramite vasodilazione arterie) → riduzione PA → ipoafflusso cerebrale → KO del pugile spesso associata a amnesia, proprio per questa momentanea pdc



Epilepsy & Behavior 20 (2011) 407–409

Contents lists available at ScienceDirect

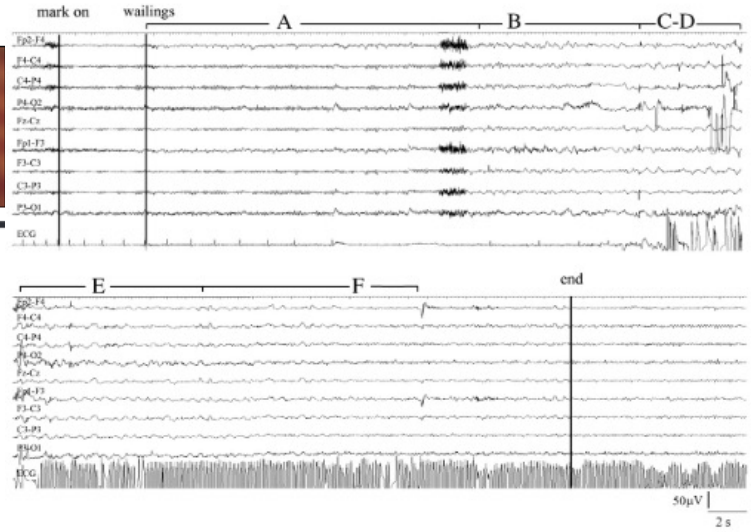
Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

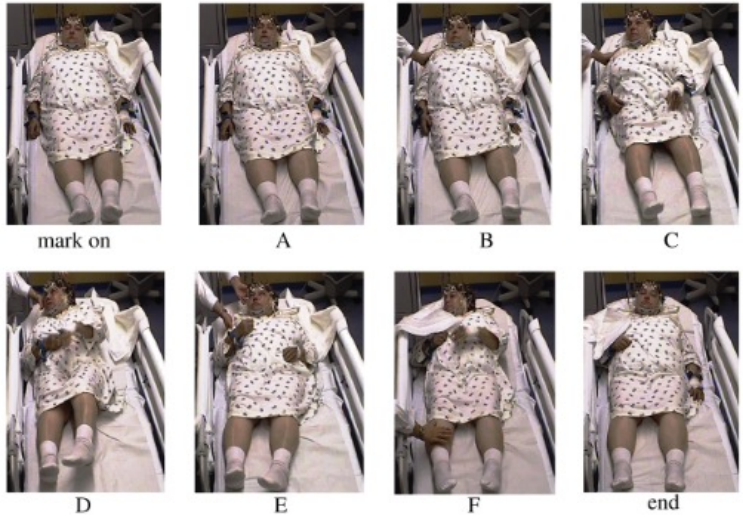
Case Report

Complex pattern of convulsive syncope in glossopharyngeal neuralgia: Video/EEG report and short review

Claudia Varrasi, Gionata Strigaro, Paolo Prandi, Cristoforo Comi, Marco Mula, Francesco Monaco, Roberto M. Cantello *



A 65-year-old woman presented with three "convulsive" events that were preceded by stabbing pain extending from the left submandible zone to the neck and ipsilateral ear. Video-electroencephalography captured a typical attack, where electrocardiography showed bradycardia for 17 seconds and asystole for at least 9 seconds. The patient lost consciousness while her head/gaze turned right. She then manifested tonic extension of her left limbs followed by adduction of her left limb and flexion of her right upper limb. Her gaze deviated upward and her left upper limb manifested swimming-like automatisms. The full episode lasted about 70 seconds, and the EEG showed progressive diffuse high-amplitude slowing. A diagnosis of convulsive syncope resulting from classic glossopharyngeal neuralgia was made. Carbamazepine led to steady remission. Glossopharyngeal neuralgia is a rare condition (incidence of 0.7/100.000/year), whereas the occurrence of syncope is about 20%, and that of convulsive syncope is about 5%.



Child's Nervous System (2019) 35:395–402
https://doi.org/10.1007/s00381-018-3995-3

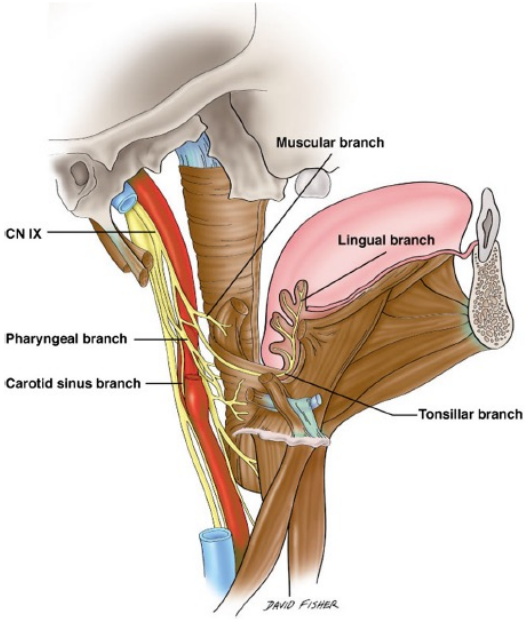
REVIEW ARTICLE

Pediatric glossopharyngeal neuralgia: a comprehensive review

Rafik Shereen[1] · Brady Gardner[2] · Juan Altafulla[2,3] · Emily Simonds[2] · Joe Iwanaga[2] · Zachary Litvack[3] · Marios Loukas[1] · R. Shane Tubbs[1,2]

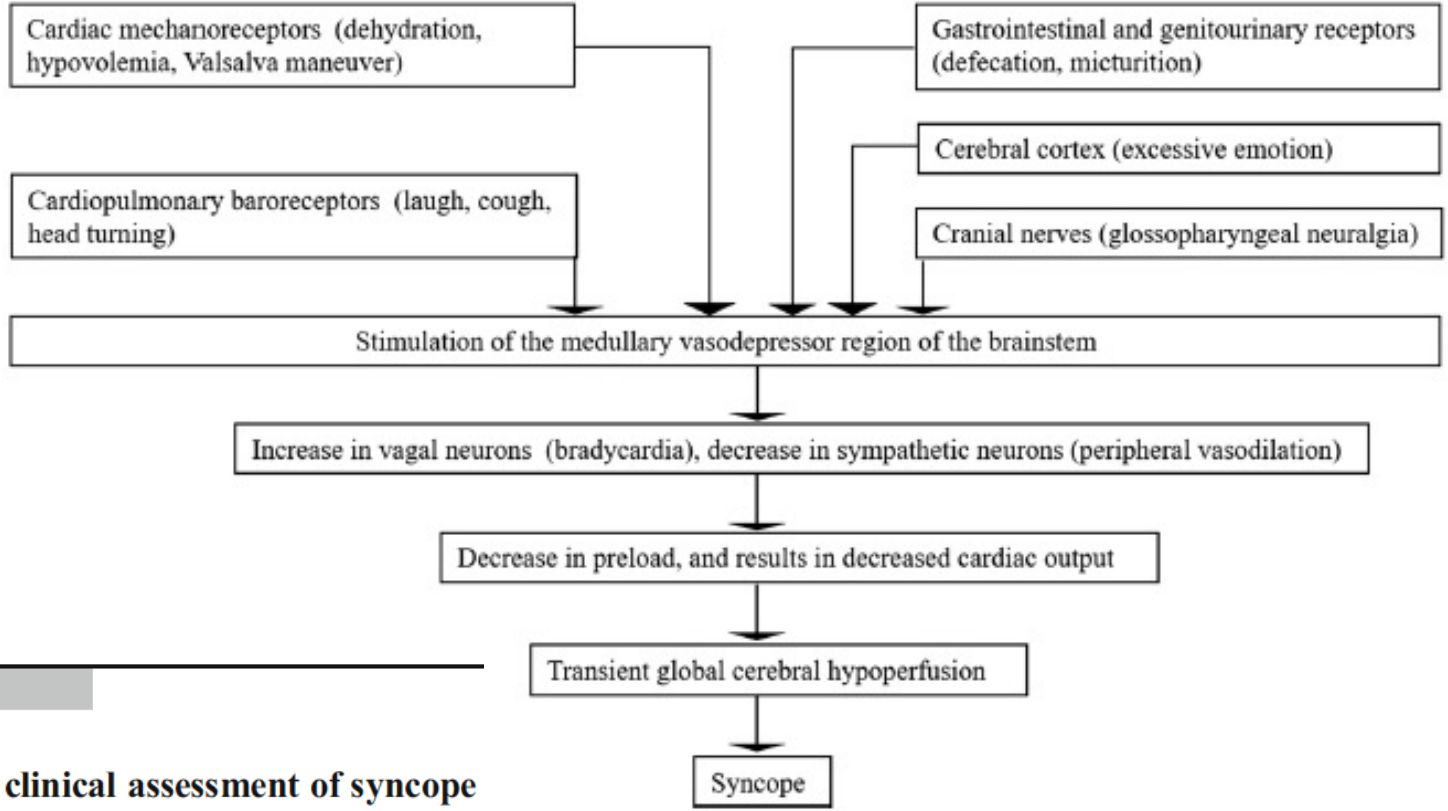
Study type/year	Age/sex	Cause of GN	Treatment	Outcome	Unique finding
Case study/2016	22/M 9 at onset of symptoms*	Neuropathic following radiation and platinum-based chemotherapy treatment for neuroectodermal tumor	Prednisone	Unknown	Bilateral GN
Case study/2015	10/M	C1 malalignment	Chiropractic	Asymptomatic at 1.5 years after treatment	Only chiropractic treated case reported
Literature review and Case study/2015	5/M	Unknown	Multiple pharmacologic agents; treatment still unsuccessful	Still symptomatic at last follow-up	Associated with red ear syndrome*
Comprehensive review/2012—Dubey	Multiple	Multiple	Multiple	Multiple	Covers previous case reports, uses adult neuralgia statistics
Comprehensive review: Headaches and neuralgias/2003—Kondov	Unknown	Multiple	Multiple	Multiple	Covers two of the discussed cases
Case report/2000	13/F	Looping R. PICA	Gabapentin	Unknown	_____
Case report/1996	8/F	Chiari malformation type 1	Surgical decompression	Asymptomatic at 2-year follow-up	Associated with Arnold Chairi type 1

*The case report concerning red ear syndrome in a 5-year-old male did not specifically state a diagnosis of GN, but did describe the patient's symptoms which sounded typical of GN



Branches of the glossopharyngeal nerve

Fisiopatogenesi della sincope neuro-mediate (sincope vaso-vagale)



REVIEW PAPER

Current approaches to the clinical assessment of syncope in pediatric population Childs Nerv Syst (2016) 32:427–436

Sincope riflessa o neuromediata: *3 fasi*

Fase prodromica: secondi → minuti. Vertigini, confusione, nausea, dolore addominale, sensazione di caldo o freddo, diaforesi, modificazioni dell'udito o della vista, cefalea e anticipazione della pdc

Perdita di coscienza: secondi → minuti (in genere 5-20''). Non ricordata dal pz, alcuni sensazione di essere "disconnessi", con capacità di udire le voci, ma incapacità a rispondere. Pallore, cute fredda, sudorazione profusa, dilatazione pupillare (occasionale), incontinenza (rara)

Fase di recupero: 5 → 30 minuti, talvolta ore. Fatica, vertigini, debolezza, cefalea e nausea

Diagnosi Differenziale

Sincopi cardiovascolari extracardiache o da anomalie del tono-controllo-volume vascolare o autonomiche
Sincopi riflesse o neuromediate
• Sincope vasovagale
• Sincope situazionale (Tabella III)
• Breath holding spell o sincope infantile o "spasmi affettivi"
Ipotensione ortostatica (idiopatica, disautonomia familiare)
Sincopi cardiache
Strutturali
• Cardiopatia valvolare
• Cardiomiopatia ipertrofica ostruttiva
• Mixoma striale
• Dissezione aortica acuta
• Malattie del pericardio, tamponamento cardiaco
• Embolia polmonare, ipertensione polmonare
• Anomalie coronariche congenite o acquisite (malattia di Kawasaki)
• A seguito di intervento cardiochirurgico di malattie congenite (in particolare intervento di Mustard, Senning, Fontan)
Aritmiche: tachiaritmiche o bradiaritmiche
• Disfunzione sinusale
• Disturbi della conduzione atrioventricolare
• Tachicardie parossistiche sopraventricolari e ventricolari
• Sindromi ereditarie (S. del QT lungo, S. di Brugada)
• Malfunzionamento di dispositivi impiantabili
• Proaritmia indotta da farmaci

Luglio-Settembre 2009 • Vol. 39 • N. 155 • Pp. 180-195 LINEE GUIDA

La sincope in età pediatrica

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Perdita di coscienza

- **sincope neuromediata 61-80%**
- **non-sincopi neurologiche-NPI 11-19%**
- **pdc cardiaca 6-11,5%**
- **spasmi affettivi 5%**

Giorgia Raponi, Alessandro Ferretti, Jacopo Pagani, Giovanni Di Nardo, Pasquale Parisi
UOC di Pediatria, Cattedra di Pediatria, Azienda Ospedaliero Universitaria Sant'Andrea, Facoltà di Medicina e Chirurgia, Sapienza Università di Roma

RIFLESSIONI Universo Pediatria
no XVIII - N. 1, 2023

Il bambino con alterato stato di coscienza

Diagnosi differenziale tra sincope, pseudo-sincope e crisi epilettica

Segni e sintomi	Sincope	Pseudo-sincope	Crisi epilettica
Esordio	Graduale	Variabile	Improvviso
Sintomi prodromici	+++ (malessere, pallore, vertigini, visione offuscata, diaforesi, nausea e/o vomito, dolore addominale)	+	+ (es. dolore addominale)
Colorito cutaneo	Tipicamente pallido	Indifferente	Può esserci cianosi (periorale, cutanea)
Durata	Secondi (fino a 1-2 minuti)	Variabile	Secondi/minuti
Occhi	Chiusi o aperti per perdita tono muscolare	Chiusi	Aperti (fissi o deviati verso un lato/alto)
Manifestazioni motorie	+/-	+/-	++
Traumatismi	+/-	-	++
Morso lingua	+/-	-	++
Incontinenza sfinteri	+/-	-	++
Tempo di recupero	Rapido, con difficoltà a mantenere la posizione eretta prima del completo recupero	Variabile	Confusione/sonnolenza/irritabilità spesso prolungata, ma capacità di tenere la posizione eretta fin da subito
Sintomi dopo il recupero	Generalmente assenti	Variabile	Variabili (es. dolori muscolari, paralisi di Todd)

Cianosi, ipersalivazione, *morsus* e stato confusionale post-critico sono gli elementi che depongono maggiormente per un evento critico di tipo epilettico

LICE
Lega Italiana contro l'Epilessia

PNES

Seizure 18 (2009) 543–553

Contents lists available at ScienceDirect

Seizure

journal homepage: www.elsevier.com/locate/yseiz

Review

Psychogenic non-epileptic seizures—Definition, etiology, treatment and prognostic issues: A critical review

A necessary first step of intervention in patients with PNES seems to be **explaining the diagnosis with care**

Although the evidence for the efficacy of additional treatment strategies is limited, **variants of cognitive (behavioural) therapy showed to be the preferred type of treatment for most patients**

Prognosis is unclear but studies consistently report that **1/3rd to 1/4th of the patients become chronic**

Review > Eur J Neurol. 2019 Feb;26(2):205-e15. doi: 10.1111/ene.13818. Epub 2018 Nov 29.

Management of psychogenic non-epileptic seizures: a multidisciplinary approach

PNES

The **objective was to reach an expert and stakeholder consensus on PNES management**. A board comprising adult and child neurologists, neuropsychologists, psychiatrists, pharmacologists, experts in forensic medicine and bioethics as well as patients' representatives was formed.

After a **systematic review** of the literature, the board met in a consensus conference in Catanzaro (Italy). Further consultations using a **model of Delphi** panel were held

Seizure induction was considered ethical, preferring the least invasive techniques

*The board recommended looking carefully for mood disturbances, personality disorders and psychic trauma in persons with PNES and considering **cognitive-behavioural therapy as a first-line psychological approach** and pharmacological treatment to manage comorbid conditions, namely anxiety and depression*

Psychogenic non-epileptic seizure management should be multidisciplinary

Paroxysmal non-epileptic events - Benign neonatal/infantile sleep myoclonus

Benign neonatal/infantile sleep myoclonus occurs only during sleep and ceases after awakening.

The incidence of the only neonatal form is about 0.8-3/1,000 newborns (Maurer et al., 2010).

The typical age ranges from a few days to six months; it mostly disappears at the age of three months (Orivoli et al., 2015).

Myocloni can be symmetric or asymmetric and can involve one or more limbs.

The EEG shows normal brain activity

Nagy E, Hollody K. Epileptic Disord. 2019

Paroxysmal non-epileptic events - Shuddering attack

Shuddering attacks usually occur
in the first year of life.

These may recur several times a day.

The movements resemble the reaction a child would
have if an ice cube slid down his/her back, leading to shaking and grimacing.

During this event, the patient's reactions remain intact, and the EEG is normal.
Shuddering attacks disappear spontaneously within the first decade of life.

The pathophysiology of these events is still unknown (Jan, 2010).

Nagy E, Hollody K. Epileptic Disord. 2019

Paroxysmal non-epileptic events - Paroxysmal tonic upgaze

Spontaneous paroxysmal tonic upgaze can be similar to absence seizures, where the eye balls slide upwards and the gaze of the child becomes vacant.

Paroxysmal tonic upgaze is a completely benign phenomenon in the majority of cases, and it remits spontaneously in an otherwise healthy child.

However, patients should be examined thoroughly and followed, as learning difficulties occur in 40% of cases and moderate or severe cognitive deficit in 10% cases, later on.

In about a quarter of children, residual ataxia and ocular motility anomalies may be present (Ouvrier and Billson, 2005).

To date, the pathophysiology has not been identified.

Ouvrier and Billson (2005) suspected involvement of structural lesions of the upper dorsal brainstem, but the intermittent nature refers to a functional problem. Kartal (2019) reported a case caused by vitamin B12 deficiency.

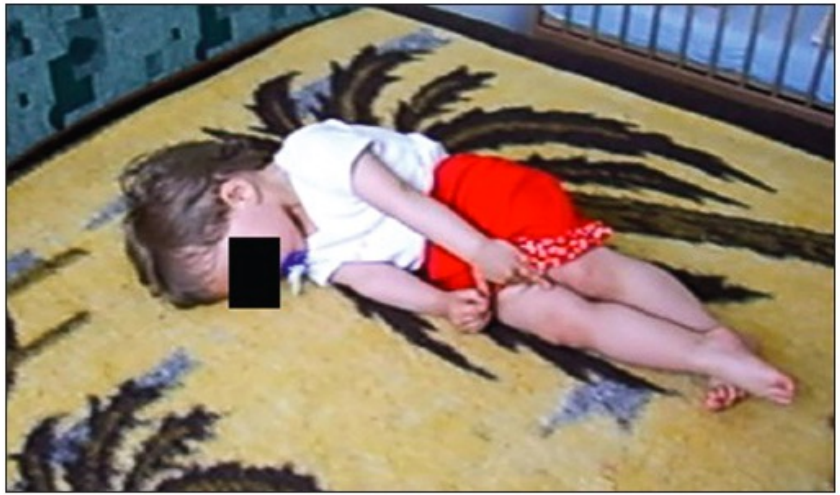
Nagy E, Hollody K. Epileptic Disord. 2019

Paroxysmal non-epileptic events - Infantile gratification or masturbation

Infantile masturbation or gratification is a stereotypic movement that may last even hours.

Manual stimulation is usually not involved.

The typical age ranges from three months to three years and occurs mainly in girls.



It may be accompanied by sounds, wheezing, flushing, and sweating.

Consciousness is not altered (Mallants and Casteels, 2008).

The parents should be reassured that this is normal behaviour and part of the child's psychomotor development. It causes a pleasing sensation for the child similar to thumb sucking.

No further investigation is needed.

Nagy E, Hollody K. Epileptic Disord. 2019

Breath-holding spells - Spasmi affettivi

The onset of a breath-holding spell may be from some mysterious terror or a fright from somebody shouting, or in the midst of crying the child is not able quickly to recover his breath, as often happens to children; but when any of these things happen to him, at once the body is chilled, he becomes speechless, does not draw his breath, the breathing fails, the brain stiffens, the blood is at a standstill

Il tessalo Ippocrate, originario di Cos, nato dalla razza immortale di Febo, riposa qui. Ha innalzato molti trofei, vincendo le malattie con le armi di Igea; ha acquisito grande gloria, non per fato ma per scienza

Insorgenza: 6-18 mesi, raramente nella prima settimana di vita o dopo i 2 anni, completa remissione dopo i 5 anni

Interessa lo 0.1-4.6% dei bambini sani

Diagnosi grazie al riconoscimento di una **specifica e stereotipata sequenza di eventi clinici**:

evento scatenante (rabbia, frustrazione, dolore) → pianto o stato emozionale → silenziosa e prolungata espirazione forzata + variazione del colorito cutaneo → pdc e del tono posturale, possibile presenza di spasmi clonici generalizzati, opistotono e bradicardia

Current Pediatric Reviews, 2019, *15*, 22-29

REVIEW ARTICLE

BENTHAM SCIENCE

Breath-Holding Spells in Pediatrics: A Narrative Review of the Current Evidence

Etiopathogenesis is multifactorial

autonomic nervous system dysregulation:

- significant **hypersensitive reactivity of pupils** was observed on instillation of 0.125% **pilocarpine** into the conjunctival sac of children with known breath-holding spells when compared to healthy children without breath-holding spells;
- frequent occurrence of **respiratory sinus arrhythmia** in children with breath-holding spell;
- children with breath-holding spells had significantly **higher runs of respiratory sinus arrhythmia** compared with the control group;
- there was also a **significant relationship between the frequency of respiratory sinus arrhythmia and frequency of breath-holding spells**

vagally-mediated cardiac inhibition (parasympathetic hyperactivity):

- **ocular compression** in this group shows a hypersensitive cardiac inhibitory reflex that is not present in an age-matched control group

delayed myelination of the brain stem:

- the interpeak latencies of **brainstem auditory evoked potential** test were significantly prolonged in those children with breath-holding spells in comparison to the control group

Current Pediatric Reviews, 2019, *15*, 22-29

REVIEW ARTICLE

BENTHAM SCIENCE

Breath-Holding Spells in Pediatrics: A Narrative Review of the Current Evidence

Etiopathogenesis is multifactorial

Iron deficiency anemia:

- iron is essential for **catecholamine metabolism and functions as a cofactor for various enzymes and neurotransmitters** present in the central nervous system → may have an impact on autonomic nervous system dysregulation;
- children with iron deficiency anemia are **more irritable and more easily provoked**, leading to breath-holding;
- children with anemia have **lower oxygen-carrying capacity** and lower cerebral oxygen tension which may precipitate a breath-holding spell;
- breath-holding spells **in association with other types of anemia**, including transient erythroblastopenia of childhood and sideroblastic anemia, have also been described;
- **7.5 to 69% of children with breath-holding spells have anemia**; This is not surprising as *the peak age of onset for both breath-holding spells and iron deficiency anemia is between 6 and 24 months old*

Breath-holding spells cianotici o pallidi

	Cianotici	Pallidi
Frequenza	70-80%	20-30%
Fattori precipitanti	Rabbia e frustrazione, anche dal riso	Dolore o paura
Semeiologia	grido breve e forte → improvvisa e involontaria trattenuta del respiro nell'espirazione forzata → cianosi, ipertono o ipotono diffuso → transitoria perdita di coscienza → crisi epilettica generalizzata se apnea prolungata → Prolungata inspirazione e ripresa della coscienza	pianto può essere minimo o "silenzioso" → rapida apnea di breve durata → pallore → possibile crisi epilettica se durata > 45 sec
Fisio-patogenesi	Ipossia cerebrale	La bradicardia è comune, probabile asistolia, causati dalla cardio-inibizione vagale (rischio cardiaco)
Durata	In entrambi i tipi, da 10 a 60 sec (episodi più lunghi di 1 min vanno indagati per altre cause)	

In caso di spasmi pallidi atipici e frequenti, gli episodi possono essere stimolati dalla compressione oculare per 10 sec, durante monitoraggio EEG/ECG, con positività della prova in caso ci comparsa di asistolia maggiore di 2 sec → diagnosi differenziale tra spasmi affettivi e crisi epilettiche

Diagnosi differenziale

Epilepsy
Sudden breath-holding during sleep
Sepsis
Hyperkplexia (stiff baby syndrome or startle disease)
Shuddering
Congenital laryngeal stridor
Laryngospasm
Whooping cough

LABORATORY EVALUATION

In the setting of a typical history and a normal physical examination, laboratory evaluation **is usually not necessary in patients with cyanotic breath-holding spells**.

There is no specific test to confirm the diagnosis.

A **complete blood count and serum ferritin should be performed if anemia is suspected**.
ECG may be considered in children with frequent and severe breath-holding spells, especially those with **pallid breath-holding spells** whose ocular compression test is positive.
The ECG helps to rule out a prolonged QT syndrome

Current Pediatric Reviews, 2019, *15*, 22-29

REVIEW ARTICLE

BENTHAM SCIENCE

Breath-Holding Spells in Pediatrics: A Narrative Review of the Current Evidence

Dei bambini con spasmi affettivi…

Descritti casi in epoca neonatale

Bhat MA, Ali W. Cyanotic breath holding spell in a neonate. A rare entity. Neurosciences (Riyadh) 2008
Breukels MA, et al. Breath holding spells in a 3-day-old neonate.. Neuropediatrics 2002

Entrambe i sessi affetti (lmaschi>femmine lieve)

Yilmaz U, et al. The value of neurologic and cardiologic assessment in breath holding spells. Pak J Med Sci 2014

10-15% presenta spasmi clonici generalizzati (convulsioni anossiche)

Horrocks IA, et al. Anoxic-epileptic seizures: observational study of epileptic seizures induced by syncopes. Arch Dis Child 2005

Incidenza di epilessia, sovrapponibile alla popolazione generale

Leung AK. Breath-holding spells. In: Leung AK, Ed. Common problems in ambulatory pediatrics: New York: Nova Science Publishers, Inc., 2011

15-20% sincopi vasovagali

Di Mario F Jr. Prospective study of children with cyanotic and pallid breathholding spells. Pediatrics 2001

25-30% presenta familiarità, ereditarietà dominante con ridotta penetranza

Lombroso CT, et a. Breath-holding spells (cyanotic and pallide infantile syncope). Pediatrics 1967
Leung AK. Breath-holding spells. In: Leung AK, Ed. Common problems in ambulatory pediatrics: New York: Nova Science Publishers, Inc., 2011

Alcune sindromi genetiche (microdelazione 16p11.2 e snd Riley-Day) associate a precoce esordio e maggiore severità

Bhat J, et al. Atypical cyanotic breath-holding spells in an infant with 16p11.2 microdeletion syndrome. Clin Pediatr (Phila) 2018
Maayan C, et al. Laughter is not always funny: Breath-holding spells in familial dysautonomia. Clin Pediatr (Phila) 2015

Trattamento

Arch Dis Child 1999;81:261–262

Breath holding spells in 91 children and response to treatment with iron

Table 2 Mean values of blood indexes in the patients with and withour iron deficiency anaemia (IDA)

	IDA (n = 63)	*Non-IDA (n = 28)*	*p Value*
Haemoglobin (g/l)	99 (10.5)	11.1 (1.69)	< 0.01
MCV (fl)	68 (7.32)	73.2 (8.28)	< 0.01
SI (mg/dl)	34.7 (17.41)	66.4 (34.16)	< 0.01
TIBC (mg/dl)	414.4 (67.9)	373.4 (41.6)	< 0.05
TS (%)	9.1 (3.71)	20.1 (6.03)	< 0.05
Remission (n (%))			
Complete	32 (50.7)	2 (7.1)	< 0.02
Partial	21 (33.3)	4 (14.3)	< 0.02
None or minimal	10 (16)	22 (78.6)	

Values are mean (SD) except where stated.

MCV, mean corpuscular volume; SI, serum iron; TIBC, total iron binding capacity; TS, transferrin saturation.

Trattamento

2015

Medicine®

OBSERVATIONAL STUDY

Novel Findings in Breath-Holding Spells

A Cross-Sectional Study

	Group I (n = 32)		Group II (n = 14)		Group III (n = 30)			
	n	%	n	%	n	%	X^2	*P*
Anemia	19	59.4	7	50	15	50	0.66	0.72
Low serum iron	11	34.4	5	35.7	9	30	0.2	0.9
Low serum ferritin	17	53.1	8	57.1	7	23.3	7.23	0.02
Low serum zinc	8	25	6	42.9	6	20	2.62	0.26

32 childrenwith cyanotic BHS; 14 childrenwith pallid BHS; 30 healthy children

pagepress

2011

Iron supplementation reduces the frequency and severity of breath-holding attacks in non-anaemic children

Anthony Zehetner

Department of Paediatrics, Teaching and Research Unit, The University of Newcastle Gosford Hospital, Gosford, Australia

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Cochrane Database of Systematic Reviews

[Intervention Review]

Iron supplementation for breath-holding attacks in children

2010

Main results

Two trials (87 children) fulfilled the inclusion criteria. In these trials, iron supplementation significantly reduced the frequency of breath-holding attacks in children (OR 76.48; 95% CI 15.65 to 373.72; P < 0.00001). A meta-analysis that solely examined iron supplementation causing complete resolution of breath-holding attacks maintained this significance (OR 53.43; 95% CI 6.57 to 434.57; P = 0.0002).

Authors' conclusions

Iron supplementation (at 5 mg/kg/day of elemental iron for 16 weeks) appears to be useful in reducing the frequency and severity of breath-holding attacks. Supplementation is of particular benefit in children with iron deficiency anaemia, responses correlating with the improvements in haemoglobin values. Iron may still be of assistance in children who are not anaemic or who have low, normal haemoglobin levels. Further high-quality randomised control trials of iron supplementation to treat breath-holding attacks in children are required.

Bambina di 2 anni e 6 mesi, non problematiche alla nascita e norm

Episodi di pianto inconsolabile con cianosi, apnea e apparente rap
(freq: anche 10 ep/die).

A maggio 2022 ricovero in Neurologia OPBG:
- EN
- H
- CR
- mo
- PL
- sie
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TSH
- av
-ves

Acetazolamide e topiramato: inibitori dell'anidrasi carbonica → riduzione della ricaptazione del bicarbonato nei reni → acidosi metabolica.
Studi sull'acetazolamide nel trattamento dell'apnea notturna: questa acidosi induce una lieve iperventilazione → riduzione pressione parziale del sangue diossido → stabilizza la ventilazione in modo che i cambiamenti nel pattern respiratorio abbiano meno probabilità di portare ad apnea o respirazione periodica.
Miglioramenti della aritmia respiratoria nella sindrome di Rett e nella Pitt Hopkins snd

Bone M, et al. Child Neurol Open. 2022

Diag
sincopi nel pianto, vescica neurogena in cateterismo intermittente
corso).

Terapia:
In considerazione dell'alta frequenza degli episodi era stato propos
aver poi deciso di non somministrare

Received: 9 September 2021 | Revised: 14 September 2021 | Accepted: 18 September 2021
DOI: 10.14814/phy2.15071

ORIGINAL ARTICLE

Physiological Reports

Effects of acetazolamide on control of breathing in sleep apnea patients: Mechanistic insights using meta-analyses and physiological model simulations

Christopher N. Schmickl[1] | **Shane Landry**[2,3] | **Jeremy E. Orr**[1] | **Brandon Nokes**[1] | **Bradley A. Edwards**[2,3] | **Atul Malhotra**[1] | **Robert L. Owens**[1]

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Funding information
No funding information provided.

Abstract
Obstructive and central sleep apnea affects ~1 billion people globally and may lead to serious cardiovascular and neurocognitive consequences, but treatment options are limited. High loop gain (ventilatory instability) is a major pathophysiological mechanism underlying both types of sleep apnea and can be lowered pharmacologically with acetazolamide, thereby improving sleep apnea severity. However, individual responses vary and are strongly correlated with the loop gain reduction achieved by acetazolamide. To aid with patient selection for long-term trials and clinical care, our goal was to understand better the factors that determine the change in loop gain following acetazolamide in human subjects with sleep apnea. Thus, we (i) performed several meta-analyses to clarify how acetazolamide affects ventilatory control and loop gain (including its primary components controller/plant gain), and based on these results, we (ii) performed physiological model simulations to assess how different baseline conditions affect the change in loop gain. Our results suggest that (i) acetazolamide primarily causes a left shift of the chemosensitivity line thus lowering plant gain without substantially affecting controller gain; and (ii) higher controller gain, higher $paCO_2$ at eupneic ventilation, and lower CO_2 production at baseline result in a more pronounced loop gain reduction with acetazolamide. In summary, the combination of mechanistic meta-analyses with model simulations provides a unified framework of acetazolamide's effects on ventilatory control and revealed physiological predictors of response, which are consistent with empirical observations of acetazolamide's effects in different sleep apnea subgroups. Prospective studies are needed to validate these predictors and assess their value for patient selection.

Sindrome da tachicardia posturale ortostatica - POTS

Insufficienza vegetativa → inabilità del sistema vascolare periferico a vasocostringersi adeguatamente in risposta all'ortostatismo. ++ adulti

Caratteristiche: tachicardia e sintomi di ipoperfusione cerebrale durante la stazione eretta, palpitazioni e sensazione di testa leggera, intolleranza all'esercizio fisico, visione offuscata, tremori, talvolta segni di edema e acrocianosi

POTS

REVIEW

Postgrad Med J 2007;83:478–480.

Postural orthostatic tachycardia syndrome

Box 1 Classification of postural tachycardia syndrome

Primary forms
- Partial dysautonomic
- Immune mediated pathogenesis
- Adolescence
- Hyperadrenergic state

Secondary forms
- Diabetes mellitus
- Amyloidosis
- Heavy metal poisoning
- Sjogren syndrome
- Hypermobility syndrome
- Paraneoplastic syndrome

Box 2 Symptoms of orthostatic intolerance

- Headache
- Fatigue
- Sleep disorder
- Weakness
- Hyperventilation/dyspnoea
- Tremulousness
- Sweating
- Anxiety/palpitation
- Dizziness/vertigo
- Pre-syncope/syncope

Criteri diagnostici POTS

Criteri diagnostici
Ritmo cardiaco basale sinusale in assenza di evidenze di aritmia o di patologia cardiaca
Incremento della frequenza cardiaca persistente > 30 battiti al minuto rispetto alla frequenza basale, nei primi 10 minuti dall'assunzione della posizione eretta o dall'inizio del tilt test
Frequenza cardiaca > 120 battiti al minuto nei primi 10 minuti dall'assunzione della posizione eretta o dall'inizio del tilt test e che si risolve con l'assunzione del clinostatismo
Sintomi presenti da più di 3 mesi: sensazione di testa leggera, debolezza, palpitazioni, visione offuscata, difficoltà respiratorie, nausea, cefalea
Criteri di esclusione
Ipotensione ortostatica definita come diminuzione della pressione arteriosa sistolica di 30 mmHg o più nei primi 3 minuti del tilt test
Gravidanza o allattamento
Presenza di altre cause di insufficienza vegetativa
Presenza di patologie sistemiche che possono interessare il Sistema Nervoso Autonomo
Terapie concomitanti con anticolinergici, α-adrenergici e antagonisti β-adrenergici o altre farmaci che possono interferire nella valutazione delle funzioni vegetative

Pattern specifico al tilt test che inizia al passaggio dal clinostatismo all'ortostatismo

Sincope cardiaca

Familiarità
Inspiegabile morte improvvisa in soggetti di età inferiore ai 40 anni
Aritmia o malattia cardiaca familiare nota (S. QT lungo, cardiomiopatia)
Infarto miocardico precoce
Anamnesi personale remota
Malattia cardiaca strutturale nota
Aritmia nota
Sospetta patologia cardiaca (intolleranza all'esercizio fisico, astenia recente)
Anamnesi patologica prossima
Sincope preceduta da palpitazioni o dolore toracico
Sincope che avviene durante l'esercizio fisico o stress
Sincope in piscina
Sincope che avviene in posiziona supina
Sincope senza prodromi
Sincope dopo rumore forte/fastidioso
Eventi che necessitano di rianimazione cardiopolmonare
Eventi con sequele neurologiche
Esame obiettivo alterato: ritmo irregolare, toni e soffi cardiaci patologici, sfregamento pericardico
ECG alterato

Diagnosi:
triade anamnesi + EO + ECG

Nei bambini e adolescenti, la sincope
può rappresentare il sintomo di esordio di
condizioni life threatening
Sd del QT lungo, Sd di Kearn-Sayre
(oftalmoplegia associata a progressivo blocco
cardiaco),
Sd di Brugada, FA in pazienti con Sd di WPWe,
TV polimorfa catecolaminergica,
aritmie in pazienti con cardiopatie congenite,
ecc

da Massin, 2007

Non sincopi o Pseudo-sincopi

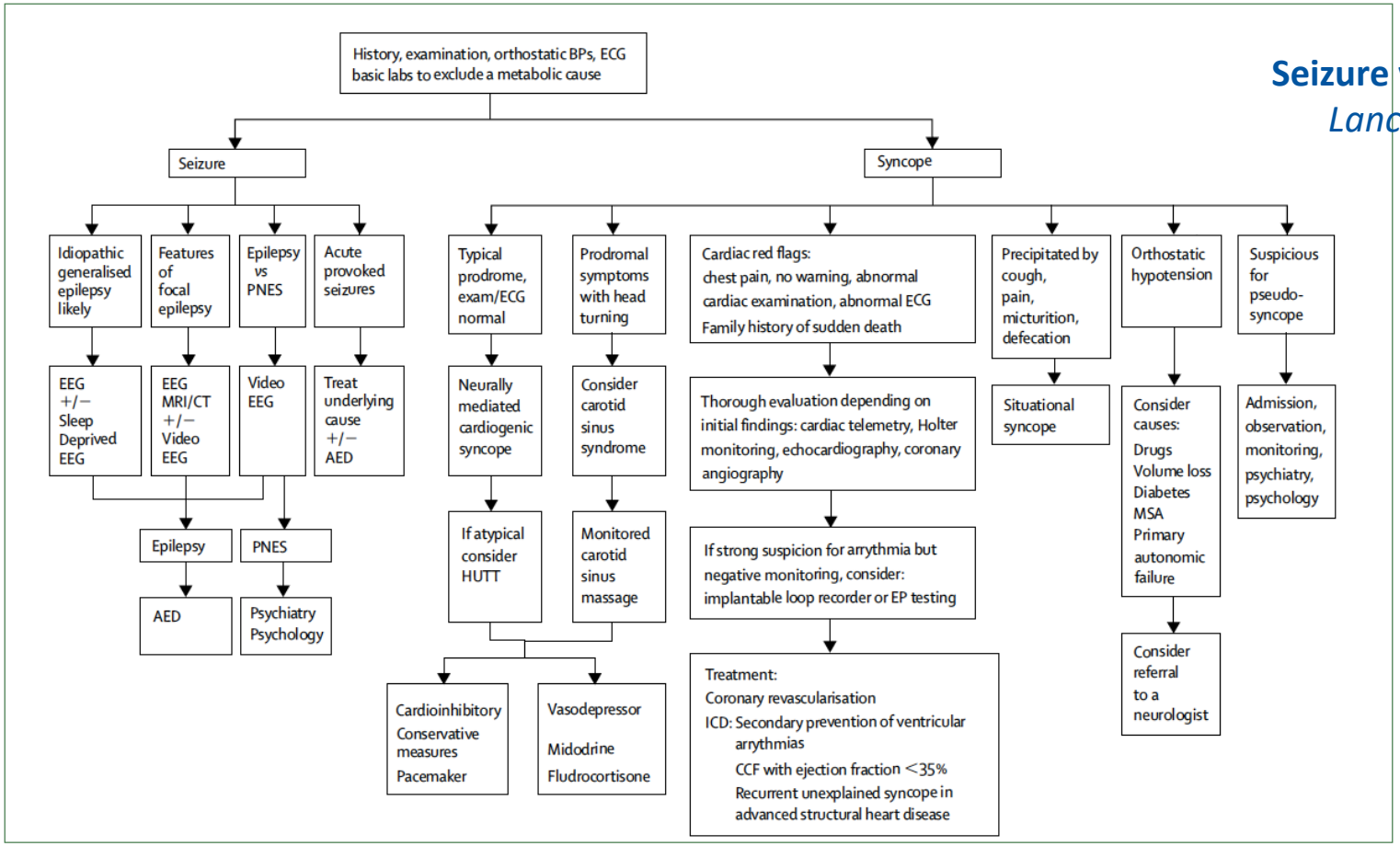
Origine metabolica (ad esempio ipossiemia, ipoglicemia)
Intossicazione da farmaci-sostanze da abuso
Origine neurologica (epilessia, cefalea, accidenti cerebrovascolari, traumi)
Origine psicogena (disturbi di somatizzazione e/o conversione, depressione, iperventilazione psicogena, attacchi di panico, sindrome di Munchausen per procura)

Luglio-Settembre 2009 • Vol. 39 • N. 155 • Pp. 180-195 LINEE GUIDA

La sincope in età pediatrica

U. Raucci[1] *(coordinatore)*, P. Di Pietro[2], R. Longhi[3], A. Palmieri[2], M. Osti[1], S. Scateni[1], A. Tozzi[1] (SIP); A. Reale[1] (SIMEUP);

Algorithm in paroxysmal loss of consciousness



Seizure vs Syncope

Lancet 2006

Iter diagnostico

ECG a 12 derivazioni è l'unico esame strumentale da effettuare nella valutazione iniziale della sincope. Refertazione: cardiologo con competenza pediatrica

Consulenza cardiologica quando la valutazione iniziale evidenzia il dubbio di una cardiopatia strutturale e/o aritmica quale causa di sincope

Esami ematochimici: se si sospetta che la sincope sia dovuta a emorragia o disidratazione o nei quadri clinici simil sincopali, quando si sospetta una causa metabolica

Iter diagnostico

Consulenza neurologica: nei pz in cui la pdc non è attribuibile a sincope o a disturbi metabolici, specialmente nei primi anni di vita

EEG: solo nel sospetto di epilessia e nei pz con disturbo dello stato di coscienza non definito, quindi non attribuibile a sincope o a disturbi metabolici, soprattutto nei primi anni di vita

Indagini neuroradiologiche: se segni focali o altri segni o sintomi suggestivi di interessamento del SNC e possibilmente concordate dopo visita neurologica

Documento congiunto LICE - SIMG

Guida pratica per la gestione del paziente affetto da epilessia

***LICE**: Roberto Michelucci, Angela La Neve, Oriano Mecarelli, Ettore Beghi*

***SIMG**: Claudio Cricelli, Francesco Mazzoleni, Ernesto Fumagalli*

*«Esistono situazioni in cui l'EEG non è raccomandato perché disinformativo.
Nelle sincopi, soprattutto in soggetti giovani con sincopi neuro-mediate, è frequente il rilievo all'S/EEG di alterazioni aspecifiche basali che possono favorire l'errore diagnostico.»*

ORIGINAL ARTICLE

EEG in Suspected Syncope: Do EEGs Ordered by Neurologists Give a Higher Yield?

Laurence Poliquin-Lasnier, Fraser G.A. Moore

ABSTRACT: ***Background:*** Prior studies have shown that the electroencephalogram (EEG) is of low diagnostic yield in the evaluation of syncope but have not looked at the yield according to referring physician specialty. The goals of this study were to determine if the yield of the EEG is higher when ordered by neurologists and whether EEGs with abnormal findings resulted in any significant change in patient management. ***Methods:*** We retrospectively reviewed the records of the EEGs requested for a clinical diagnosis of syncope, convulsive syncope, loss of consciousness, or falls from 2003 to 2007 at our institution. We obtained further information from the medical record of patients with an abnormal EEG. ***Results:*** Of 517 EEGs meeting our inclusion criteria, only 57 (11.0%) were read as abnormal. No EEG was positive for epileptiform activity and only 9 (1.6%) showed potentially epileptic activity. EEGs ordered by neurologists did not have a higher yield compared to non-neurologists. Five abnormal EEGs resulted in further investigations being ordered. One patient was ultimately started on phenytoin. ***Conclusions:*** EEGs requested for the evaluation of patients with suspected syncope have an extremely low diagnostic yield and do not significantly alter the management of the patients, regardless of the specialty of the referring physician.

Can. J. Neurol. Sci. 2009; 36: 769-773

517 EEG, 57 refertati con anomalie, un pz ha iniziato PHT

EEG nelle sincopi: basso potere diagnostico e non modifica management pz

Spunto per un prossimo studio retrospettivo in età ped.. → prospettico

ELSEVIER CrossMark

Canadian Journal of Cardiology 33 (2017) 1604–1610

Systematic Review/Meta-analysis

Diagnostic Value of Neurological Studies in Diagnosing Syncope: A Systematic Review

Payam Pournazari, MD, Zardasht Oqab, MD, and Robert Sheldon, MD, PhD

Libin Cardiovascular Institute of Alberta, University of Calgary, Calgary, Alberta, Canada

Systematic review 1970-2015, 15 studies, 6944 pts

EEG, CT, MR, carotid doppler ultrasound: low diagnostic yield and they should be obtained only with a very high degree of clinical suspicion

Background: Syncope is common and approaches to establishing etiology remain a matter of clinical and financial importance. Patients often undergo comprehensive neurologic investigations despite a lack of compelling indications. The aim was to determine the prevalence of use and diagnostic yield of electroencephalography (EEG), head computed tomography (CT), head magnetic resonance imaging (MRI), and carotid Doppler ultrasound (CUS) examinations.

Methods: We conducted a systematic search in EMBASE, PubMed, and Cochrane from 1970 to 2015 for studies reporting on the use of EEG, CT, MRI, and CUS in diagnosing the cause of syncope. The inclusion criteria were: (1) observational and randomized trials; (2) frequency of use of investigations; and (3) diagnostic yield. Diagnostic studies of the more general transient loss of consciousness were excluded.

Results: Of 149 screened studies, 15 studies having 6944 patients met the criteria. No studies met all 6 prespecified quality descriptors. The mean prevalence of test use were: EEG, 17.0%; CT, 57.3%; MRI, 10.5%; and CUS, 17.8%. The articles reported the likelihoods of a test providing diagnostic information for syncope etiology were: EEG, 1.35%; CT, 1.18%; MRI, 3.74%; and CUS, 2.4%. Only 2 new and informative results were noted in 6334 tests.

Conclusions: Neurologic investigations for assessment of patients deemed to have syncope are used widely and are widely ineffective. Neurologic investigations should be obtained only with a very high degree of clinical suspicion.

doi:10.1093/brain/awt332 Brain 2014: 137; 576–585
BRAIN
A JOURNAL OF NEUROLOGY

The semiology of tilt-induced reflex syncope in relation to electroencephalographic changes

Vasovagal reflex syncope is by far the most common cause of non-traumatic transient loss of consciousness, with an estimated 30–40% of people experiencing one or more episodes in their lifetime (Moya et al., 2009)

The first EEG pattern of syncope to be described was the 'slow-flat-slow' pattern:

- in the first slow phase the alpha rhythm and other normal activity is lost and supplanted by slow activity, decreasing in frequency from theta to delta waves while wave amplitude increases.
- The second phase is marked by a fairly sudden flattening of the EEG.
- The third phase consists of slow activity, in which frequency and amplitude change in the reverse order as in the first slow phase.

The second EEG pattern consists of increasing and decreasing slowing only.

The slow-flat- slow pattern is generally believed to denote more severe hypoperfusion; *it was first described in asystolic syncope induced by eyeball pressure, and cardio-inhibitory reflex syncope has been associated with a slow-flat-slow pattern.*

However, the slow-flat-slow pattern can occur without asystole.

Pediatric Neurology 62 (2016) 27–33

Contents lists available at ScienceDirect

Pediatric Neurology

journal homepage: www.elsevier.com/locate/pnu

Original Article

The Clinical and Electroencephalographic Spectrum of Tilt-Induced Syncope and "Near Syncope" in Youth

Geoffrey L. Heyer MD [a,b,c,*], Caitlin Schmittauer RN [d], Monica P. Islam MD [a,b,c]

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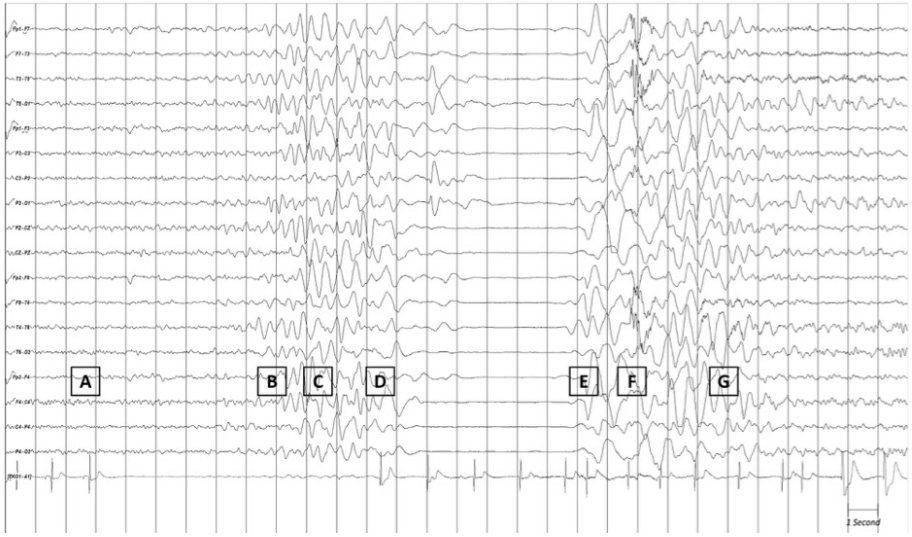
[b] Department of Pediatrics, The Ohio State University, Columbus, Ohio
[c] Department of Neurology, The Ohio State University, Columbus, Ohio
[d] Department of Pediatrics, Nationwide Children's Hospital, Columbus, Ohio

ABSTRACT

BACKGROUND: The aim of the study was to characterize the clinical and electroencephalographic (EEG) patterns associated with tilt-induced reflex syncope and delayed orthostatic hypotension without syncope in youth. **METHODS:** We conducted a prospective observational study of 95 patients referred to a pediatric neurology clinic for head-upright tilt testing. Clinical signs, symptoms, video EEG, and continuous blood pressure and heart rate were monitored. **RESULTS:** Eighty patients had reflex syncope, and 15 had delayed-onset hypotension without syncope. The mean age was 15.3 (standard deviation ±2.3) years; 75 (78.9%) were female. All patients with hypotension only had corresponding signs and symptoms; 13 (86.7%) had corresponding EEG slowing. The duration of EEG slowing with hypotension far exceeded the presyncope interval from onset of slowing to loss of consciousness among patients with syncope ($P < 0.001$). Although prior near-syncope and presyncope episodes were reported commonly in both groups, patients with delayed hypotension without syncope were less likely to have experienced loss of consciousness during episodes of orthostatic intolerance ($P < 0.001$). Patients with syncope had either slow-flat-slow (n = 23) or slow-only (n = 57) EEG patterns. Compared to those with slow-only EEG patterns, patients with the slow-flat-slow pattern had greater rates of asystole ($P < 0.001$), myoclonic movements ($P < 0.001$), facial grimace ($P = 0.003$), vocalizations ($P = 0.002$), and arm flexion ($P < 0.001$) or extension ($P = 0.006$) during tilt-induced syncope. **CONCLUSIONS:** Among otherwise healthy youth, orthostatic signs and symptoms vary across the spectrum of tilt-induced reflex syncope and delayed hypotension without syncope. Delayed hypotension without syncope may represent the poorly defined phenomenon of "near syncope" in some patients.



The slow-flat-slow syncope pattern on EEG. Hypotension is the first clinical sign. (A) Asystole begins. (B) The first phase of EEG slowing begins. (C) Slumping of the shoulders and gaze shifted upward (without substantial head drop) indicate loss of consciousness. This is followed by a single myoclonic jerk. (D) EEG slowing transitions to flattening. There is head and conjugate eye turning to the left, followed rapidly by flexor posturing. The first QRS wave following asystole is seen. (E) EEG flattening transitions to the second slow phase. (F) A series of myoclonic jerks, groaning vocalizations, and lip smacking occurs. These movements are marked, in part, by muscle artifact on EEG. (G) EEG slowing begins to normalize as the patient recovers.

Iter diagnostico

Valutazione psichiatrica: quando i sintomi suggeriscono un episodio di "non sincope" di origine psicogena o se il pz ha una malattia psichiatrica già diagnosticata

Ecocardiogramma: non va considerato come esame di routine, ma quando è sospettata una malattia cardiaca

Test da sforzo: solo se sincope durante lo sforzo fisico; è diagnostico quando induce sincope durante o immediatamente dopo sforzo, in presenza di alterazioni ECG e/o emodinamiche oppure se induce BAV di II grado tipo Mobitz 2 o di III grado, anche senza sincope

Iter diagnostico

Indicazioni
Sincopi ricorrenti con > 2 episodi ogni 6 mesi
Sincopi da causa ignota senza evidenza di cardiopatia significativa
Anche singolo episodio sincopale se è stato causa di trauma o di incidente (soprattutto se avvenuto in situazioni potenzialmente pericolose)
Presenza di una cardiopatia che potrebbe non essere la causa dell'episodio sincopale, dopo che sono state comunque escluse cause cardiache
Sincope indotta o associata ad attività fisica
Ricorrenti episodi convulsivi da causa ignota, con EEG ripetutamente negativi e che non rispondono a terapia standard
Controindicazioni
Cardiopatia ostruttiva ventricolare sinistra severa (per esempio stenosi aortica e/o mitralica)
Cardiopatia ostruttiva ventricolare destra
Ipertensione polmonare
Coronaropatia ostruttiva prossimale
Malattia cerebrovascolare ostruttiva critica

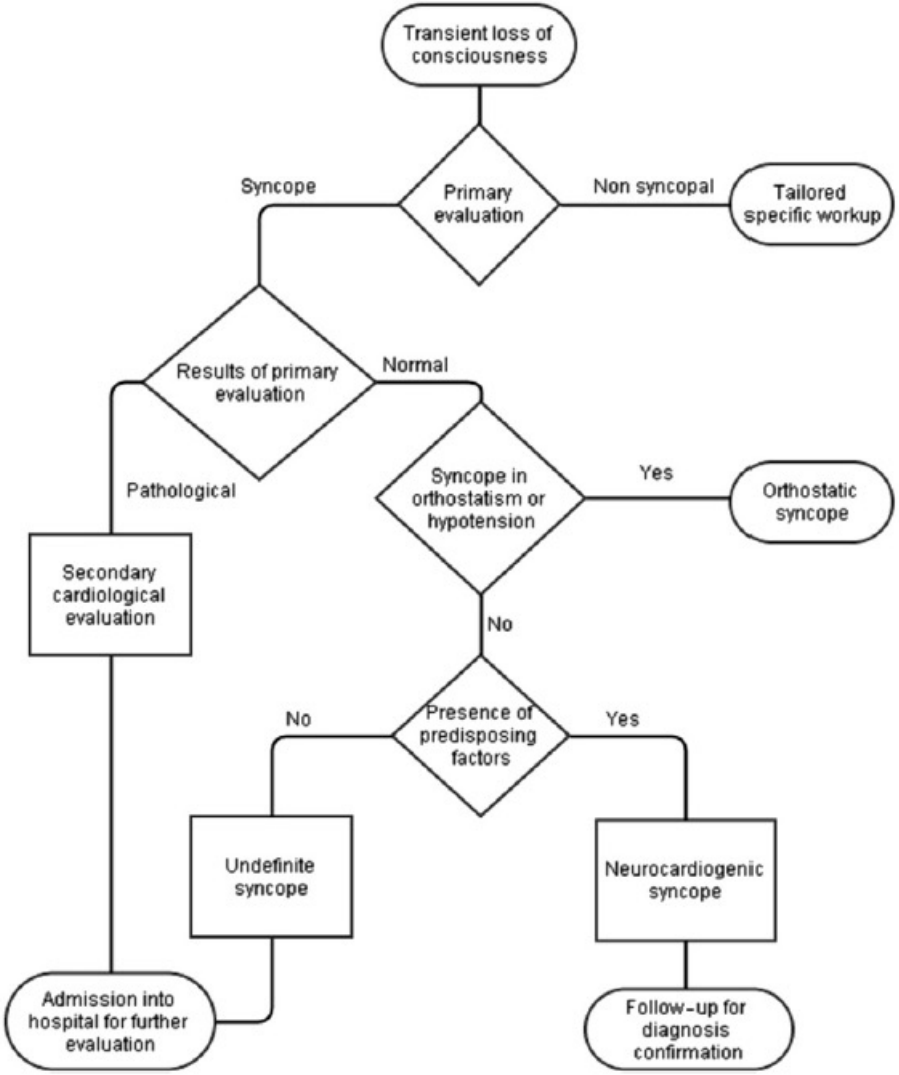
Tilt test in condizioni basali e/o con stimolo farmacologico (isoproterenolo o nitroglicerina sublinguale): in casi selezionati, in soggetti con sincope atipica o ricorrente non definita o nella diagnosi differenziale tra sincope
e forme non sincopali di origine psicogena e/o epilettica

Iter diagnostico

Monitoraggio elettrocardiografico (invasivo o non invasivo) nelle seguenti condizioni:

1. ospedaliero (a letto/telemetria), in caso di significative cardiopatie, ad alto rischio di aritmia, potenzialmente letali
2. Holter 24-48 ore, in pz che presentano caratteristiche cliniche o ECG che suggeriscono una sincope aritmica ed episodi sincopali frequenti (>= 1 per settimana) e nei pazienti con cardiopatia strutturale
3. loop recorder esterno o impiantabile in pz con episodi sincopali ricorrenti, soprattutto se con traumi e caratteristiche cliniche e/o ECG suggestive di una sincope potenzialmente aritmica o di eziologia indeterminata dopo valutazione completa

Monitoraggio della PA 24 ore: nei pz con storia suggestiva di ipotensione familiare o costituzionale, di età > ai 3 anni



THE JOURNAL OF PEDIATRICS • www.jpeds.com ORIGINAL ARTICLES

The Availability and the Adherence to Pediatric Guidelines for the Management of Syncope in the Emergency Department

Umberto Raucci, MD, PhD[1], Simona Scateni, MD[1], Alberto Eugenio Tozzi, MD[2], Fabrizio Drago, MD[3], Ugo Giordano, MD[4], Michela Marcias, MD[1], Francesca Faa, MD[1], and Antonino Reale, MD[1]

Diagnostic workup of children with transient loss of consciousness

Alterazione dello stato di coscienza

Transitoria

Sincope

- Breath holding spells
- Cardiogena
- Sindrome da tachicardia posturale ortostatica

Non sincope o Pseudo-sincope

- Metaboliche (ipo-O2 e ipo-glic)
- Intossicazione farmaci
- Neurologiche (epilessia, cefalea, traumi, stroke)
- Psicogene (somatizzazione/conversione)

Persistente

Continuum di stati di veglia ridotta fino al coma

Alterazione dello stato di coscienza

Persistente

Continuum di stati di veglia ridotta..

Stato confusionale: rallentamento del pensiero, alterato rapporto con l'ambiente e riduzione della attenzione e del "re-call", risposta agli stimoli alterata ad intermittenza, +/- associato ad agitazione psico-motoria

Delirium: disorientamento, paura, irritabilità, grave irrequietezza motoria, allucinazioni visive e dispercezione stimoli sensoriali. Possono esserci momenti lucidi

Stato soporoso: tendenza ad assopirsi in assenza di **stimoli verbali**

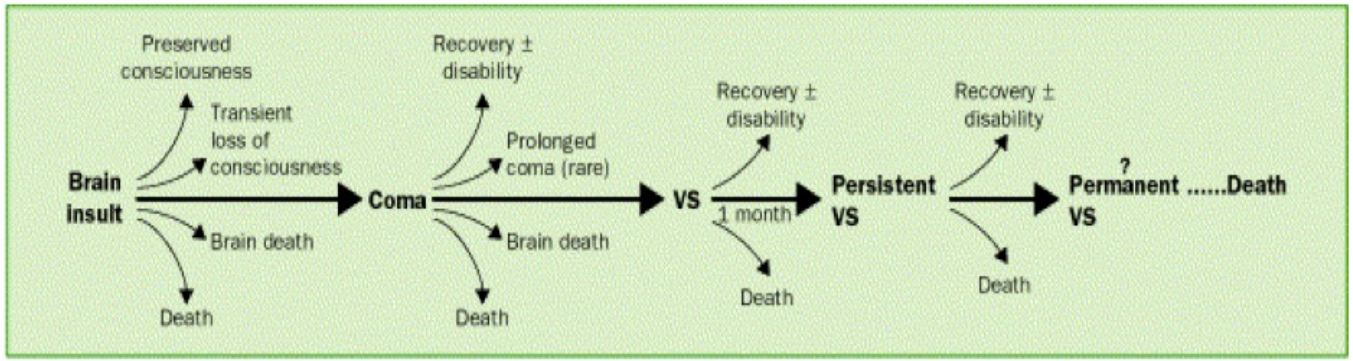
Obnubilazione: stato di ottundimento mentale con apatia e inattività; sonnolenza, è possibile ottenere risposte verbali rare e imprecise

Stupor: stato dal quale il pz può essere risvegliato solo con **stimoli vigorosi (dolore!),** risposta motoria per evitare stimoli irritanti, comunicazione quando suscitata con monosillabi e comportamenti semplici, rapido ritorno alle condizioni prima della stimolazione

Fino al..

Coma: stato di alterazione della vigilanza prolungato, **non risposta a stimoli esterni (neanche al dolore!)**, **occhi chiusi**, **alterazioni delle funzioni vegetative** (attività cardiaca, respiratoria, PA)

*Il coma è uno **stato transitorio** → recupero, disabilità, stato vegetativo, exitus*



Disturbi dello stato di coscienza: eziologia

Crisi epilettica/SME convulsivo e non convulsivo

Infettiva

Infiammatoria

Carenziale

Metabolica/Tossica

Ipossico-ischemica

Cerebrovascolare

Disturbi psichiatrici

Coma/Stupor emicranico
Emicrania confusionale

Disturbi del sonno

Traumatica

Malformazioni cerebrali

Ipertensiva

Cause di coma

Coma con funzione del tronco encefalico intatta, in assenza di meningismo e assenza di segni neurologici focali

Handbook of Clinical Neurology, Vol. 90 (3rd series)
Disorders of consciousness
G.B. Young, E.F.M. Wijdicks, Editors

Chapter 4

Coma and stupor

ROBIN S. HOWARD*

The Batten/Harris Neurological Intensive Care Unit, National Hospital for Neurology and Neurosurgery, London, UK

Causes of coma

1. Coma with intact brainstem function, no meningism, and no lateralizing motor signs	
Toxins	Carbon monoxide
	Methanol
	Lead
	Cyanide
	Thallium
Alcohol	
Drug toxicity	Sedatives
	Barbiturates
	Tranquilizers
	Opioids
	Psychotropics
	Amphetamines
	Others
Extrapyramidal	Status dystonicus
	Neuroleptic malignant syndrome
Seizures	Status epilepticus
	Postictal
	Postictal drug induced
	Functional
Psychiatric	Catatonia
	Conversion reaction
Infections	Transmissible spongiform encephalopathy
Anoxic–ischemic encephalopathy	
Respiratory	Hypoxia, hypercapnia
Electrolytes	Hyponatremia, hypernatremia, hypercalcemia, hypocalcemia, hypermagnesemia
Diabetic	Hypoglycemia
	Ketoacidosis
	Lactic acidosis
	Hyperosmolar nonketotic diabetic coma
Renal	Uremia
Hepatic	Hepatic encephalopathy
Endocrine	Hypopituitarism, hypothyroidism, hyperthyroidism
	Addison's disease
	Hashimoto's encephalopathy
Temperature	Hypothermia
	Hyperpyrexia
Nutritional	Wernicke's encephalopathy
Inborn errors of metabolism	Hyperammoniacal
	Aminoaciduria
	Organic aciduria
Others	Porphyria
	Reye's syndrome
	Idiopathic recurrent stupor

Coma con funzione del tronco encefalico intatta e segni neurologici focali

3. Coma with intact brainstem function and lateralizing signs

i) Asymmetrical lateralizing signs

Vascular	Infarction	Ischemia	
		Embolic	Cardiac
			Large vessel
			Fat
		Hypoperfusion/hypotension	
	Hemorrhage	Extradural	
		Subdural	
		Subarachnoid	
		Intracerebral (primary or secondary)	
		Congophilic amyloid angiopathy	
		Angioimmunoblastic lymphoma	
	Vasculitis		
	Venous thrombosis		
	Mitochondrial disease		
	Hypertensive encephalopathy		
	Eclamptic toxemia		
	Endocarditis	Bacterial	
		Libman–Sacks	
		Marantic	
Infection	Abscess		
	Subdural empyema		
	Creutzfeldt–Jakob disease		
Tumor			
White matter	Multifocal leukoencephalopathy		
	Adrenoleukodystrophy		
	Multiple sclerosis		
	Leukoencephalopathy associated with chemotherapy/radiotherapy		
	Acute disseminated encephalomyelitis		
	Acute hemorrhagic leukoencephalitis		

ii) Symmetrical lateralizing signs

Diffuse axonal brain injury		
Bilateral subdural hematoma/ empyema		
Vascular	Multiple infarcts due to	Fat emboli
		Cholesterol emboli
		Disseminated intravascular coagulation
		Thrombotic thrombocytopenic purpura
		Vasculitis

Coma con meningismo (+/- funzione del tronco encefalico intatta e segni neurologici focali)

2. Coma with meningism (± intact brainstem function and lateralizing signs)

Infection	Meningitis
	Encephalitis
Vascular	Subarachnoid hemorrhage

Coma con segni focali di alterazione del tronco encefalico

4. Coma with signs of focal brainstem dysfunction

Herniation syndrome	
Intrinsic brainstem disease	
Advanced metabolic/toxic encephalopathy	
Others	Central pontine myelinolysis
Vascular	Vertebrobasilar occlusion
	Vertebrobasilar dissection
	Vertebrobasilar hemorrhage
Tumor	Posterior fossa

Stato Vegetativo

Stato di risveglio senza risposta! I pz emergono dal coma dopo gg o settimane in una condizione con **palpebre aperte** ma **senza consapevolezza di sé, né dell'ambiente, assenza di risposta alle stimolazioni** ("coma da svegli"), presenza di respiro spontaneo e dei riflessi troncali (faringeo, tosse, suzione e deglutizione), cicli sonno-veglia mantenuti.

N.B. No stato vegetativo se ci sono mov volontari, mov oculari ripetuti, fissazione visiva adeguata o risposta a minaccia

SV persistente: se > di 1 mese

SV permanente: > 3 mesi se sofferenza anossico-ischemica

> 12 mesi nei traumatizzati cranici

Minimally conscious state o minimally responsive state

Grave alterazione della coscienza nella quale è dimostrata una **minima, ma sicura prova comportamentale di consapevolezza di sé o dell'ambiente**

Successiva a un coma prolungato, non necessariamente una condizione irreversibile → come nello SV, la prognosi deve tenere conto del fattore causale

Pur se rudimentale ripresa della coscienza, persistono gravi deficit cognitivi e motori

Permanente: se > 12 mesi e la ripresa seppur minima della coscienza si associa alla possibile percezione del dolore

SV *vs* MCS

	Stato vegetativo	MCS
Coscienza	Assenza di evidenze comportamentali di percezione di sé e dell'ambiente	Minima, ma sicura evidenza comportamentale di percezione di sé e dell'ambiente
Cicli sonno veglia	Presenti	Presenti
Motilità	Postura o reazione di allontanamento in rapporto a stimoli nocicettivi; movimenti occasionali afinalistici	Localizzazione degli stimoli nocicettivi; tenere o toccare oggetti in modo adeguato alla misura ed alla loro forma; movimenti automatici
Funzione uditiva	"Startle"; breve localizzazione della fonte di rumore	Localizzazione della fonte del rumore
Funzione visiva	"Startle"; breve fissazione visiva	Fissazione visiva inadeguata; inseguimento prolungato dello stimolo visivo
Comunicazione	assenza di espressione e comprensione, possibili vocalizzazioni	Vocalizzazione non casuale in risposta a stimoli verbali; verbalizzazione e gestualità non appropriata, ma comprensibili
Emotività	Assente; riso e pianto su base riflessa	Riso e pianto appropriato ad una situazione

Mimics del coma

Stato *locked in*

Mutismo acinetico

Patologie psichiatriche: simulazione, catatonia

Mutismo acinetico

Stato di coscienza parzialmente o totalmente integra; il pz ha la capacità di formulare espressioni e pensare ma rimane **virtualmente immobile e muto**

Simile allo stato vegetativo ma il pz si presenta flaccido e non risponde al dolore periferico, mentre nello SVP il tono muscolare è conservato e si possono avere risposte in estensione o in flessione

Eziopatogenesi: ***danno nuclei talamici mediani e lobi frontali o idrocefalo***
-più spesso: gravi traumi cranici, anossia cerebrale, encefalopatie tossiche o da avvelenamento
-più raramente: ictus ischemico o emorragico, encefaliti o meningoencefaliti

Evoluzione: potenzialmente reversibile se origine traumatica prognosi peggiore per le forme anossiche

Locked in syndrome

Pz sveglio e cosciente ma non ha possibilità di produrre la parola o eseguire mov volontari

Conservati i **mov oculari verticali** (con elevazione sinergica delle palpebre superiori) (non i mov orizzontali e altri mov!), anche se talora qualche grado di mov orizzontale degli occhi e di mov faciali, linguali e degli arti è presente, pupille normoreattive, funzioni autonomiche integre; presenti fenomeni involontari, piangere, ridere, trisma, automatismi orali, reazioni al dolore, smorfie faciali, sbadiglio, mioclono palatale, sospiro

Eziopatogenesi: in genere infarto o emorragia ventrale del ponte che interrompe le vie discendenti coricospinali e corticobulbari

Meno frequentemente mielinolisi pontina centrale, traumi, encefalite, tumori, ascessi pontini, sclerosi multipla

Catatonia

Ipomobilità e mutismo come parte di una psicosi grave, di solito schizofrenia o grave depressione

Necessaria ingegnosità dell'esaminatore per dimostrare segnali che il paziente risponde
e.g. innalzamento delle palpebre volontariamente impedito, presente riflesso della minaccia e gli occhi si muovono contemporaneamente alla rotazione della testa
→ segni non compatibili con lesione del cervello

Assenti segni di danno cerebrale: RCP in estensione e ipertono arti

Disturbi dello stato di coscienza: valutazione

Modalità di Presentazione

Livello di Coscienza | **AVPU**

Parametri Vitali
FC, FR, PA, T, SaO_2

EO generale
Temperatura corporea
Stato cute e mucose
Obiettività cardiaca
Obiettività addominale
Obiettività respiratoria
Presenza ferite
Otorrea/otorragia
Liquorrea/rinorragia
Colore urine

Sintomi associati
Febbre
Vomito
Cefalea ……..

Esami urgenti
EGA
ECG
Stick glicemico
Stick urinario
Emocromo e formula
Indici flogosi
Transaminasi, NH3
Elettroliti (anion gap)
Esami tossicologici
Dosaggio farmaci
Neuroimaging → TC/RMN encefalo, eco cerebrale EEG

Antecedenti
Farmaci
Epilessia
Trauma
Sostanze tossiche
Flogosi
……..

EO neurologico
Pupille
Movimenti oculari
FOO
Tipo di respiro
Postura
Segni di lato
Segni meningei
Movimenti patologici associati
Riflessi

EON nelle PDC

Coscienza

Respirazione

Postura, motricità spontanea

Pupille

Movimenti oculari

SIMEUP

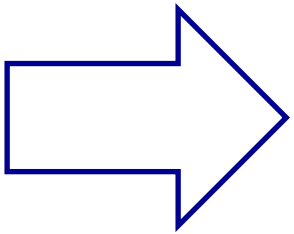
Coscienza

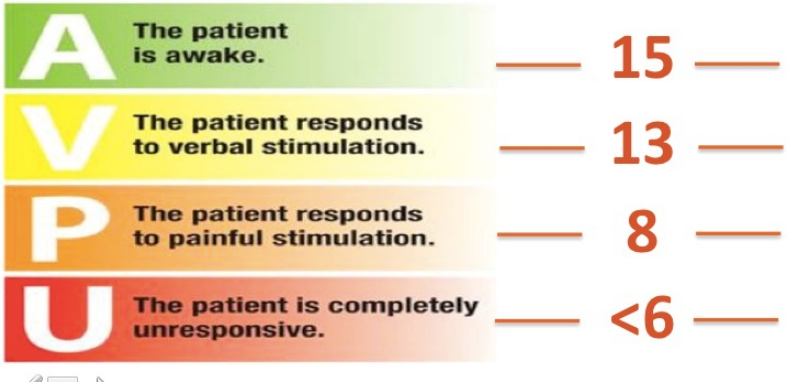
GCS per bambino >2 anni		GCS per bambino <2 anni	
RISPOSTA DI APERTURA DEGLI OCCHI		**RISPOSTA DI APERTURA DEGLI OCCHI**	
Spontanea	4	Spontanea	4
A comando	3	Al rumore	3
Per il dolore	2	Al dolore	2
Nessuna risposta	1	Nessuna risposta	1
RISPOSTA VERBALE		**RISPOSTA VERBALE**	
Orientata	5	Vocalizza, ride	5
Conversazione confusa	4	Piange, è consolabile	4
Parole inappropriate	3	Piange, non è consolabile	3
Suoni incomprensibili	2	Suoni incomprensibili	2
Nessuna risposta	1	Nessuna risposta	1
RISPOSTA MOTORIA		**RISPOSTA MOTORIA**	
Obbedisce al comando	6	Spontanea normale	6
Localizzazione stimolo doloroso	5	Localizzazione stimolo doloroso	5
Si allontana dal dolore	4	Si allontana dal dolore	4
Flessione decorticata	3	Flessione decorticata	3
Estensione decerebrata	2	Estensione decerebrata	2
Nessuna risposta	1	Nessuna risposta	1
Valori normali: >9 (0-6 mesi) ; >11 (6-12 mesi); >12 (1-2 anni); >13 (2-5 anni); >15 (>5 anni)			

Coscienza

A	Alert	Paziente vigile
V	Voice	Risponde alla voce
P	Pain	Risponde al dolore
U	Unresponsive	Non risponde agli stimoli

SIMEUP





Behaviour	Response
Eye Opening Response	4. Spontaneously 3. To speech 2. To pain 1. No response
Verbal Response	5. Oriented to time, person and place 4. Confused 3. Inappropriate words 2. Incomprehensible sounds 1. No response
Motor Response	6. Obeys command 5. Moves to localised pain 4. Flex to withdraw from pain 3. Abnormal flexion 2. Abnormal extension 1. No response

Respirazione

Centri del respiro sono situati nella sostanza reticolare della parte caudale del tronco encefalico tra la regione medio-pontina e la giunzione bulbo-midollare

Respiro di Cheynes-Stokes

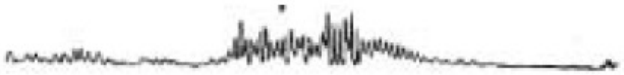
iniziale aumento della profondità e della frequenza degli atti respiratori fino a un picco massimo, poi graduale diminuzione fino a una breve pausa, seguita da una ripresa del ciclo

Cause:
- lesione diencefalica o cerebrale bilaterale
- alterazioni metaboliche
- aumento della pressione intracranica
- ernia tentoriale

Respiro di Kusmaull (iperventilazione)

Cause:
- lesione tra mesencefalo inferiore e ponte
- acidosi metabolica, chetoacidosi, uremia
- intossicazione-etanolo, salicilati
- alterazioni elettrolitiche e della volemia
- ipossia

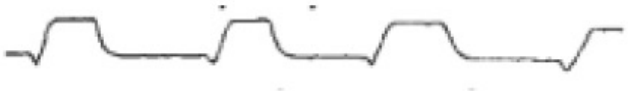
Respiro di Biot o atassico (ritmo e profondità molto irregolari)



Ritmo molto irregolare, alternanza di iperventilazione e apnee

Cause:
- lesione dei centri respiratori bulbari caudali
- lesione del midollo

Respiro apneustico



Fase inspiratoria prolungata e breve fase espiratoria (detto anche “crampo inspiratorio”)

Cause:
- lesioni del tronco e del ponte

Postura e motricità spontanea

Risposte motorie si valutano in risposta a stimoli dolorosi (pressione sovraorbitaria e pizzicotto sul cucullare):

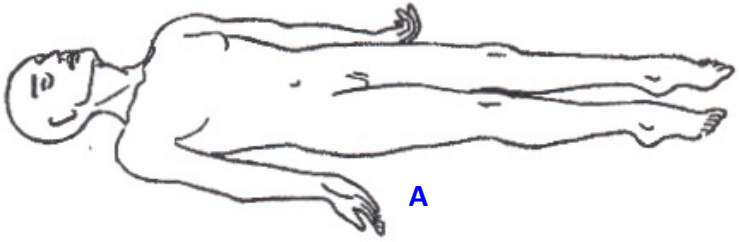
finalistiche: allontanamento del corpo dallo stimolo → vie sensitive e motorie indenni

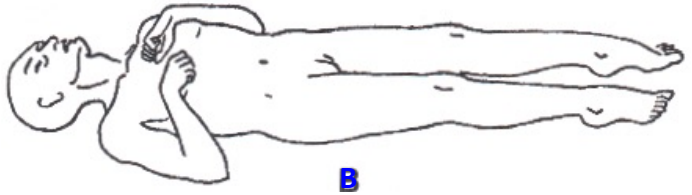
afinalistiche: mancato evitamento dello stimolo

rigidità in decerebrazione (A): risposta in opistotono, denti serrati, arti superiori estesi addotti e iperpronati e arti inferiori estesi con flessione plantare dei piedi (lesione emisferica bilaterale, a lesioni del mesencefalo o medio pontine, ad alterazioni metaboliche, ipoglicemia, ipossia)

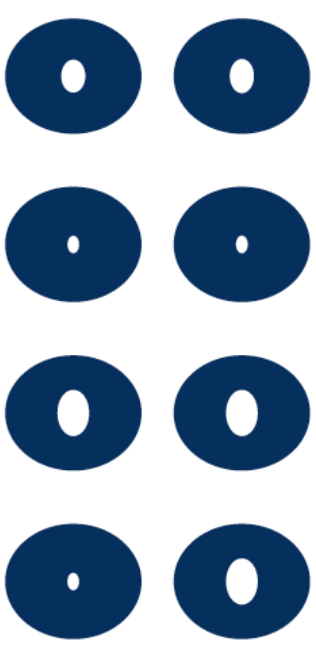
rigidità in decorticazione (B): risposta in flessione del braccio, del polso e delle dita con adduzione degli arti superiori ed estensione, rotazione all'interno e flessione plantare degli arti inferiori (lesione della corteccia o tratto corticospinale adiacente)

risposta motoria assente: si osservano solo reazioni vegetative (midriasi, iperventilazione, tachicardia)





Pupille



Pupille miotiche (2-3 mm), reattive:
lesioni midollari, lesioni diencefaliche, alterazioni metaboliche

Dimensioni e riflesso fotomotore

Pupille a punta di spillo (1-2 mm):
se fisse → lesioni pontine,
se non fisse → intossicazione da oppiacei, barbiturici

Pupille dilatate bilateralmente, fisse:
danno cerebrale irreversibile (shock, emorragia massiva, encefaliti), farmaci anticolinergici (atropina), ipotermia, convulsioni
Pupille dilatate bilateralmente reattive: successivamente a stroke, farmaci anticolinergici

Pupilla dilatata unilateralmente, fissa:
lesione a rapida diffusione omolaterale (emorragia subdurale, tumore), ernia del tentorio, lesione del nucleo del 3° nc, gocce oculari anticolinergiche, convulsioni

Pupilla dilatata (> 6 mm) e non/scarsamente reattiva: compressione o stiramento III NE
Segno pupillare più rilevante: pupille non reattive e dilatate → grave lesione mesencefalica (eg compressione da massa sovratentoriale)

Movimenti oculari

Riflesso oculoencefalico

Riflesso oculovestibolare con stimolazione calorica

Valutazione eventuale deviazione coniugata degli occhi

Segni di paralisi dei NNCC dei mm oculari estrinseci

Riflesso corneale: espressione dell'integrità della via afferente (prima branca del trigemino) e di quella efferente (nervo facciale)

Valutazione deviazione degli occhi

Deviazione coniugata degli occhi *nella lesione cerebrale*:

verso la lesione distruttiva in caso di lesione inattiva

verso il lato opposto della lesione irritativa in caso di lesione attiva (es. focolaio contusivo)

Deviazione coniugata degli occhi *nella lesione tronco cerebrale*:

lontano dalla lesione distruttiva

Gli occhi guardano dallo stesso lato di una lesione emisferica

e dal lato opposto di una lesione del tronco encefalico

NNCC dei mm oculari estrinseci

Nervo cranico	Muscoli innervati	Segni di paralisi del nervo	Cause di paralisi
3°	Muscolo retto superiore, retto inferiore, retto mediale, obliquo inferiore, elevatore delle palpebre	• Strabismo divergente • Difetto di rotazione dell'occhio verso l'interno, l'alto e il basso • Diplopia orizzontale • Midriasi fissa omolaterale	• Ernia cerebrale • Compressione (ad es. frattura del cranio) • Lesione intrinseca (es. diabete) • Compressione (aneurisma, tumore)
4°	Muscolo obliquo superiore	• Inclinazione compensatoria della testa verso il lato opposto all'occhio con un muscolo paretico • Slivellamento dei globi oculari sul piano orizzontale • Difetto di rotazione dell'occhio in basso e in dentro • Diplopia verticale	• Aumento della pressione endocranica • Infezione meningea • Lesione pontina • Trauma, neoplasia
6°	Muscolo retto esterno	• Strabismo convergente • Difetto di rotazione dell'occhio verso l'esterno • Diplopia orizzontale	

Riflesso oculoencefalico e oculovestibolare

Riflesso oculoencefalico (degli occhi di bambola)	**Risposta normale**	**Risposta patologica**
Con gli occhi aperti si gira velocemente la testa da una parte all'altra (N.B. valutare prima la colonna cervicale!)	In un paziente vigile cosciente la mobilizzazione passiva laterale del capo è accompagnata da concomitante movimento laterale degli occhi	• paziente in coma con tronco encefalico intatto: il movimento degli occhi è in direzione opposta al lato in cui viene girata la testa, come se continuasse a fissare la posizione iniziale • **paziente in coma con lesioni del mesencefalo o del ponte:** il movimento è random
Riflesso oculovestibolare con stimolazione calorica:	**Risposta normale:**	**Risposta patologica:**
con la testa sollevata di 30° si inietta acqua ghiacciata nel canale auricolare per mezzo di un piccolo catetere (dopo essersi accertati che il tronco sia integro)	nel soggetto vigile cosciente l'irrigazione con acqua fredda di un orecchio comporta un nistagmo con fase lenta ipsilaterale alla irrigazione	• paziente in coma con tronco cerebrale intatto: deviazione coniugata degli occhi verso l'orecchio irrigato • paziente in coma con lesioni al tronco cerebrale: nessuna reazione

Esame clinico generale – 1/2

alito: può odorare di alcool, chetoni o presentare foetor epatico o renale

mucose: cianosi, anemia, ittero, colore rosso rubino da intossicazione CO

abrasioni di mastoide e delle regioni orbitali: fratture temporali, orbitali o della base del cranio (così come sangue nel meato uditivo esterno)

punture nella fossa antecubitale: overdose da opioidi (adolescenti)

cute: rash di petecchie o porpora: setticemia meningococcica, da Pseudomonas, Stafilococco, endocardite; lesioni maculopapulari: meningoencefalite virale, endocardite, infezione fungina; rash vescicolare: herpes simplex, varicella; lesioni bollose: intossicazione da barbiturici; petecchie ed ecchimosi: anomalie della coagulazione da trauma, uso di steroidi, coagulopatia da insufficienza epatica, CID, porpora trombotica trombocitopenica; iperpigmentazione: porfiria, chemioterapia

ipertermia: di norma sepsi; crisi tireotossiche, colpo di calore, iperpiressia maligna; ipertermia neurogena centrale

ipotermia: può essere di per sé causa di coma; generalmente associata con cause ambientali (ipotermia accidentale) o metaboliche, endocrine (ipopituitarismo, ipotiroidismo), farmaci (barbiturici)

Esame clinico generale – 2/2

ipertensione: per lo più da ipertensione endocranica

ipotensione: shock emorragico, tamponamento cardiaco, sepsi, intossicazioni, diabete

tachicardia: tachiaritmia, ipovolemia, febbre, tossine, intossicazione da farmaci

bradicardia: bradiaritmia, ipertensione endocranica, farmaci

meningismo: meningite infettiva o carcinomatosa, ernia centrale o tonsillare, ESA

respiro: tipi particolari in caso di ernia cerebrale, intossicazioni, acidosi, diabete

FO: papilledema da ipertensione endocranica

orecchio: otorrea o emotimpano da frattura della base cranica, oto-rino-liquorrea

cuore: aritmia, cardiopatia , valvulopatia, endocardite

fegato: epatomegalia da scompenso cardiaco, ipertensione portale

linfadenopatia: infezioni, tumori

Diagnostica

Esami ematochimici: *emocromo, chimica generale con prove emocoagulative, Screening tossicologico. Se sospetta origine metabolica: lattati, aminoacidi plasmatici e urinari, acidi grassi plasmatici, funzionalità tiroidea*

Rx torace

ECG

EGA

TC/RMN cerebrale

Esame liquorale

Monitoraggio EEG

Box 2
Initial and core management of nontraumatic coma and increased ICP

ABC (airway, blood pressure, circulation) or CAB (circulation, airway, blood pressure) as appropriate

Rule out and treat: hypoglycemia and electrolyte disturbance

Evaluate for clinical features of increased ICP/herniation syndromes

Investigate for cause and complications

CSF examination is an important investigation if meningitis, encephalitis, or certain IEM are under consideration but please consider if any contraindications to LP

Neuroradiologic investigations (especially MRI) high on the list

EEG (high on the list); may need continuous EEG monitoring

Treat seizures (do not mistake nonepileptic phenomena for seizures)

Specific treatment of underlying cause (eg, infective)

Maintain age-appropriate CPP

Maintain normothermia

Maintain normoxia and normocarbia

Head in the midline and avoid obstruction to venous outflow (neck)

Elevate head end of the bed to 20° to 30° if increased ICP suspected

Repeat investigations as clinically necessary; however, avoid unnecessary radiographs (including CT scans) because of the cumulative radiation dosing for children

Abbreviations: CPP, cerebral perfusion pressure; CSF, cerebrospinal fluid; CT, computed tomography; EEG, electroencephalogram or electroencephalographic; ICP, intracranial pressure; IEM, inborn error/s of metabolism; LP, lumbar puncture; MRI, magnetic resonance imaging.

Data from Tatman A, Warren A, Williams, A, et al. Development of a modified pediatric coma scale in intensive care clinical practice. Arch Dis Child 1997; 77:519–21.

Nontraumatic Coma in Children and Adolescents: Diagnosis and Management

Shashi S. Seshia, MD (Bombay), FRCPC&E[a,*], William T. Bingham, MD, FRCPC[b], Fenella J. Kirkham, MD, FRCPCH[c,d], Venkatraman Sadanand, PhD, MD, FRCSC[e]

Neurol Clin 29 (2011) 1007–1043

Box 3
Management of unresponsive patient in a trauma situation

Airway or **Breathing**: oxygenation, make sure the airways are clear

Circulation: monitor and keep the blood pressure within normal range if possible; cervical-spine precautions if necessary

Glucose: check or administer; if unknown circumstances, keep in mind that the patient may have fallen following hypoglycemia

ICP: if signs it is raised (pupil asymmetry), lower by administrating mannitol or 3% saline

Stop seizures

Restore electrolytes and acid-base balance

Adjust body temperature

Thiamine, because the patient might have fallen due to alcohol influence and have a chronic condition

Specific antidotes if the cause of the trauma is unclear and the patient might be under some drug influence

Trauma and Impaired Consciousness

Sandrine de Ribaupierre, MD

Disturbi dello stato di coscienza: eziologia

A – Alcohol, Abuse (Physical or Substance)

E – Encephalopathy, Electrolytes

I – Insulin, Intussusception, Inborn errors

O – Overdose, Oxygen deficiency (Lung or Systemic, Hemoglobinopathy)

U – Uremia, Nephropathy, Heart Failure

T – Trauma, Temperature abnormality, Tumor

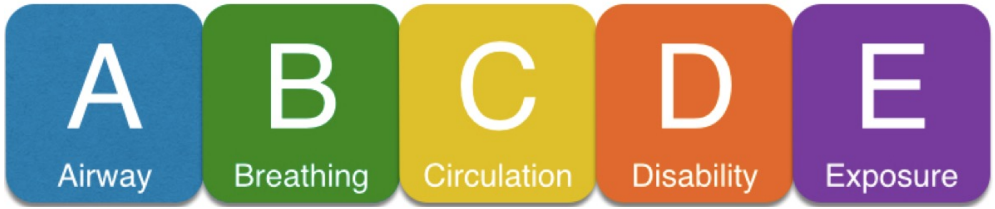
I – Infection (Systemic or Neurological)

P – Poisoning, Psychiatric, Psychogenic

S – Shock, Stroke, Seizures, Shunt

Trattamento del paziente in coma

Stabilizzazione:



Trattamenti in emergenza:

- correzione ipoglicemia
- naloxone o flumazenil in caso di sospetta overdose di oppioidi o benzodiazepine
- correzione di squilibri elettrolitici ed acido/base
- trattamento epilessia

Alterazione dello stato di coscienza

Transitoria

Sincope

- Breath holding spells
- Cardiogena
- Sindrome da tachicardia posturale ortostatica

Non sincope o Pseudo-sincope

- Metaboliche (ipo-O2 e ipo-glic)
- Intossicazione farmaci
- Neurologiche (epilessia, cefalea, traumi, stroke)
- Psicogene (somatizzazione/conversione)

Persistente

Continuum di stati di veglia ridotta fino al coma

Outline di oggi

- Alterazioni stato di coscienza (transitorie e persistenti)
- Encefalopatia

Outline del futuro meeting

- Ipertensione endocranica
- Edema cerebrale
- Perdita acuta della vista (neurite ottica)
- Disturbi acuti della deambulazione e atassia
- Sindrome di Guillain Barré
- Miastenia Gravis
- Disturbi movimenti oculari

Encephalitis

Encephalitis is a broad term encompassing any inflammatory disease process of the brain that manifests clinically with alterations of consciousness and/or behavioral changes (neuropsychiatric symptoms)

Associated signs and symptoms of encephalitis may include (but are not limited to):

- seizures
- movement abnormalities (e.g., dyskinesias, choreoathetosis)
- Ataxia
- Dysautonomia
- focal neurological deficits

Encephalitis may occur as the result of:

- primary infection of the CNS
- autoimmune process (nonparaneoplastic autoantibodies (i.e., those formed without an associated neoplasm) to neuronal surface antigens) triggered by an infection, vaccine, or occult neoplasm (paraneoplastic autoantibodies (i.e., antibodies formed in association with a neoplasm)

J.N. Brenton, H.P. Goodkin. Pediatric Neurology 2016

Cellucci T, et al. Clinical approach to the diagnosis of autoimmune encephalitis in the pediatric patient. Neurol Neuroimmunol Neuroinflamm. 2020.

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Review Article

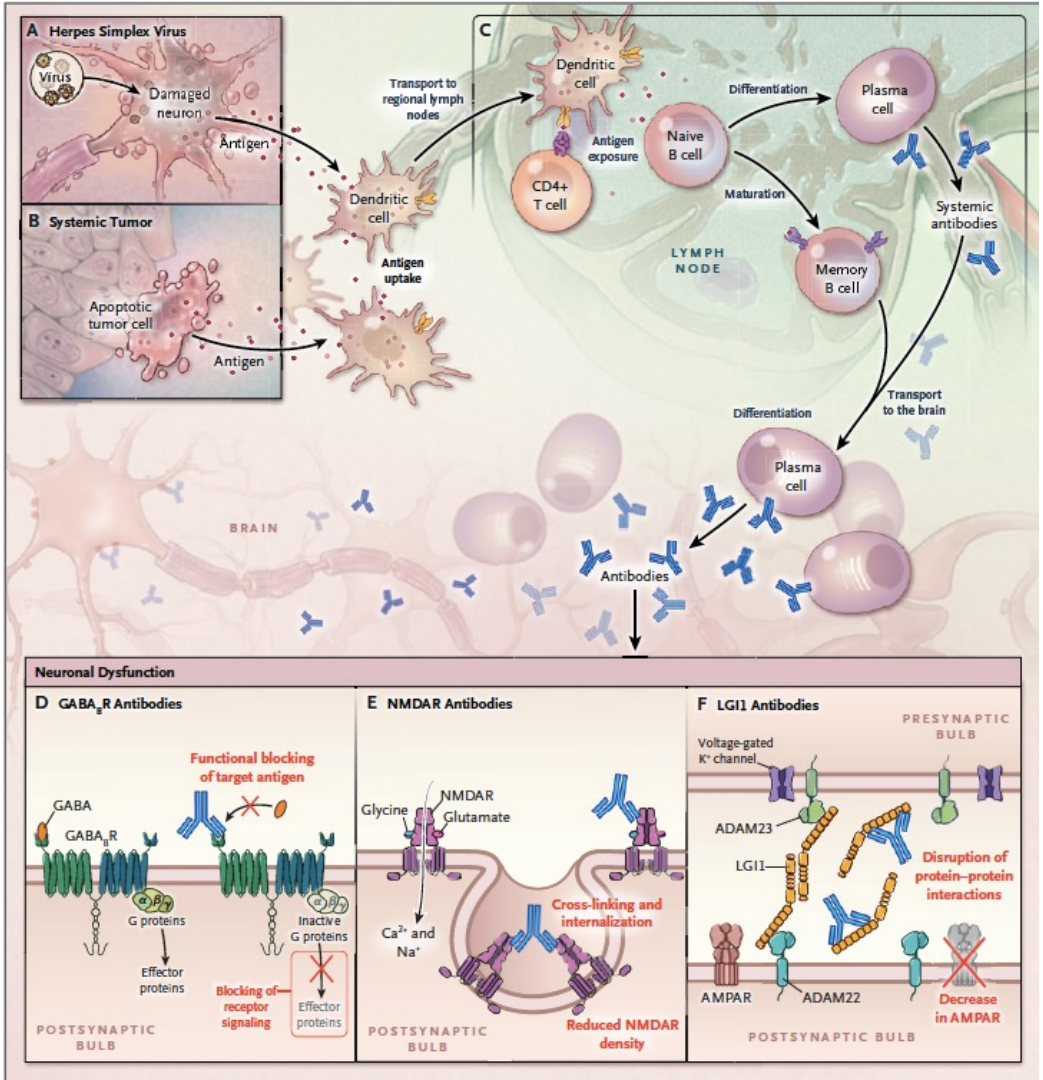
Pediatric Autoimmune Encephalitis and Its Relationship With Infection

Pathogenesis of AE is not clear, and immune system disorders after infection likely play an important role.

Many studies have reported that patients with herpes simplex virus encephalitis develop anti-NMDA-R encephalitis after antiviral treatment.

It is critical to recognize pediatric AE early and to distinguish it from infectious forms because AE is treatable and responsive to immunotherapies

Q. Li, N. Fu, Y. Han et al. Pediatric Neurology 120 (2021)



Dalmau J, Graus F. Antibody-Mediated Encephalitis. N Engl J Med. 2018 Mar 1;378(9):840-851. doi: 10.1056/NEJMra1708712. PMID: 29490181.

Pediatric AE	Clinical Features	EEG	Brain MRI	CSF	Infection	Associated Disease
Anti-NMDAR encephalitis	Prodromal symptoms, movement disorder, seizures, psychiatric symptoms, language disorders, sleep dysfunction (mainly insomnia), and autonomic instability	Generalized slowing and focal epileptic activity, focal slowing, or "prolonged spindles/ delta brush pattern"	More than 65% of patients are normal or show increased T2/ FLAIR signals in the cortex, white matter, cerebellum, or basal ganglia; reversible cerebral atrophy is a late finding	CSF pleocytosis, positive oligoclonal bands	HSV, HHV-6, enterovirus,	Teratoma
Anti-GAD65 encephalitis	Subacute headache, epilepsy, memory loss, psychiatric symptoms, cerebellar ataxia, development delay, behavioral changes, severe intractable autonomic imbalance, brainstem symptoms	Slowing; epileptiform discharges may be multifocal	Normal, or showing lesions in the limbic system, cortices, and cerebellum	Normal, or mildly increased leukocytosis and positive oligoclonal bands	/	Type 1 diabetes mellitus, stiff-person syndrome, immune deficiency
Anti-dopamine-2 receptor encephalitis	Prodromal symptoms (infection, vaccination), lethargy, drowsy, movement disorder (dystonia, parkinsonism), psychiatric symptoms, encephalopathy, reduced consciousness or confusion, seizures	Normal or showing nonspecific slowing compatible with encephalopathy	50% are normal or show an increased T2/FLAIR signal in the basal ganglia	75% are abnormal	β-Hemolytic streptococcus, mycoplasma pneumonia, and enterovirus	Basal ganglia encephalitis
Anti-VGKC encephalitis Anti-LGI1 encephalitis Anti-CASPR2 encephalitis	Encephalopathy, memory loss, seizures, neuropathic pain, sleep disturbances, limbic encephalitis, abnormal neuropsychiatric, Morvan syndrome (neuromyotonia, memory loss and confusion, sleep disturbances, autonomic instability)	Normal or approximately 50% abnormal (epileptiform discharges, slowing)	Increased signal in medial temporal lobes	Normal or 42% abnormal among pediatric patients	/	Thymoma, rare in children
Anti-$GABA_A$ receptor encephalitis	Decreased level of consciousness, neuropsychiatric symptoms, movement disorders, hemiparesis, seizures, reduced verbal output, insomnia, stiff-person syndrome	Multifocal T2/FLAIR high signal	Abnormal EEG including slowing and ictal activity	CSF leukocytosis	/	/
Anti-$GABA_B$ receptor encephalitis	Prominent seizures, memory loss, consciousness disorder, OMS, cerebellar ataxia	More than half had multifocal hyperintensities	Slowing and epileptiform discharges	74% of patients had abnormal CSF	/	Small-cell lung cancer in adults and no tumors in children

(continued on next page)

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Encephalitis -Childhood versus adulthood

Presentation with an autoimmune encephalitis **in childhood is often subacute**

In anti-NMDAR encephalitis, children are more likely to have a neurologic-based presentation (consisting of movement abnormalities and/or seizures) than are adults, who tend to present with psychiatric features

In adults, autoimmune encephalitis is commonly paraneoplastic (presence of an occult tumor)

J.N. Brenton, H.P. Goodkin. Pediatric Neurology 2016

Cellucci T, et al. Clinical approach to the diagnosis of autoimmune encephalitis in the pediatric patient. Neurol Neuroimmunol Neuroinflamm. 2020.

Autoimmune encephalitis

AE refers to an **increasingly recognized** group of inflammatory brain diseases

Many AE associate with **Ab directed toward extracellular antigens (**synaptic receptors and ion channels) that are generally pathogenic, whereas antibodies that bind **intracellular antigens are not considered pathogenic**, instead general markers of autoimmunity

The most common Ab in children target:

- the N-methyl-D-aspartate receptor (NMDAR)
- myelin oligodendrocyte glycoprotein (MOG)
- glutamic acid decarboxylase 65 (GAD65)

It is also recognized that not all children have a known Ab

The treatment of AEconsists of immunomodulatory therapy. The duration of therapy depends on the AEin question and the patient's clinical response. **Outcome in childhood is generally good** but may depend on the pathogenic Ab and neuronal target involved, in addition to the time from symptom onset to treatment initiation

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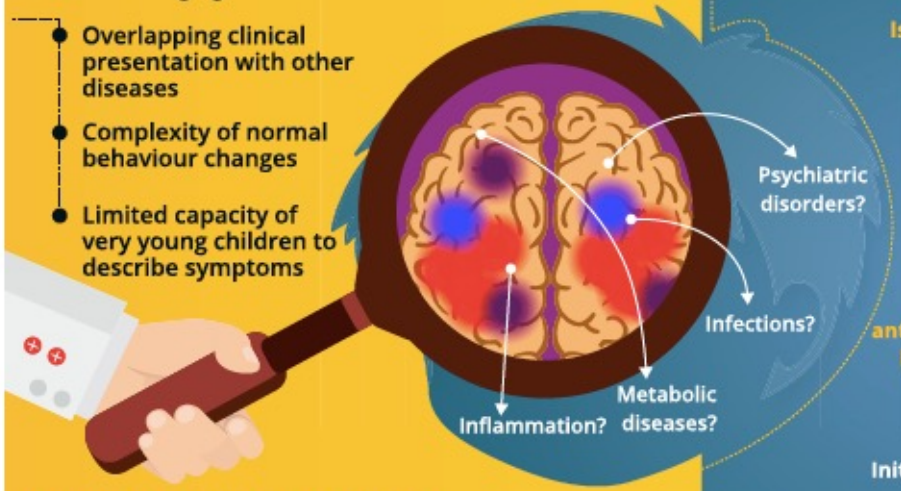
Clinical Guidelines for the Diagnosis of Pediatric Autoimmune Encephalitis

Diagnosis of autoimmune encephalitis (AE) in a developing child is challenging because of

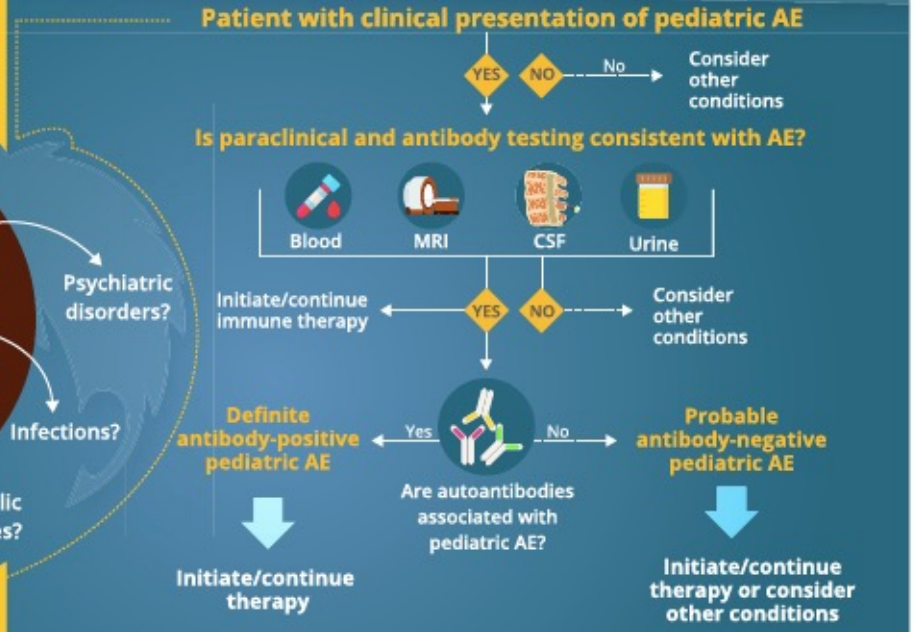
- Overlapping clinical presentation with other diseases
- Complexity of normal behaviour changes
- Limited capacity of very young children to describe symptoms



Adult guidelines are not applicable in children due to differences in

- Clinical presentations and paraclinical findings
- Autoantibody profiles

International Autoimmune Encephalitis Working Group has modified existing criteria for adult AE to propose new criteria and an algorithm to guide early diagnosis of pediatric AE



Pediatric AE should be diagnosed based on clinical history as well as paraclinical and autoantibody testing

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Annual incidence of pediatric AIE and ADEM

Year	AIE—incidence children/million (95%-CI)	ADEM—incidence children/million (95% CI)	No. of Dutch pediatric inhabitants
2015	1.46 (0.47–3.40)	2.62 (1.20–4.98)	3.429.193
2016	1.76 (0.64–3.82)	2.05 (0.82–4.22)	3.416.581
2017	1.76 (0.65–3.84)	3.23 (1.16–5.78)	3.404.098
2018	1.18 (0.32–3.02)	2.07 (0.83–4.26)	3.386.096
2015–2018	1.54 (0.95–2.35)	2.35 (1.61–3.31)	3.408.992

Abbreviations: AIE = autoimmune encephalitis, ADEM = acute disseminated encephalomyelitis.

Pediatric autoimmune encephalitis, Neurol Neuroimmunol Neuroinflamm 2020

Antibodies that are commonly identified in pediatric AE

Antibody target (localization)	Typical clinical features in children	
GAD65[10–12] (intracellular)	Frequency	Common in AE, but only pathologic if high titers in serum and present in CSF
	Clinical	Encephalitis with memory loss, cognitive impairment, cerebellar ataxia, and temporal lobe seizures
	MRI	May be normal initially often progresses to lesions in the limbic system, cerebellum, and cortices with possible atrophy
	EEG	Epileptiform discharges may be multifocal
	Other	CSF leukocytosis may be mild with oligoclonal bands Associated personal or family history of autoimmunity Often resistant to immunotherapy
MOG[8,9,42,45–47] (extracellular)	Frequency	Common in AE
	Clinical	Acute disseminated encephalomyelitis including encephalopathy, optic neuritis, or transverse myelitis (but not typical MS); cortical encephalitis with seizures; brainstem encephalitis; and meningoencephalitis without demyelination
	MRI	Focal or multifocal white matter lesions, longitudinally extensive myelitis and optic neuritis
	EEG	Nonspecific slowing
	Other	Serum antibody testing preferable to CSF Higher titers of antibodies in younger children Persistent antibodies in relapsing disease
NMDAR[5–7] (extracellular)	Frequency	Most common antibody target in pediatric AE
	Clinical	Encephalitis with movement disorder, seizures, psychiatric symptoms, reduced verbal output/mutism, developmental regression (in younger children), sleep dysfunction (mainly insomnia), and autonomic instability
	MRI	Normal in at least 65% of patients; T2/FLAIR lesions may be identified in the cortex, white matter, cerebellum, or basal ganglia; reversible cerebral atrophy is a late finding
	EEG	Abnormal in over 90% of patients—most have generalized slowing, but may see focal epileptic activity, focal slowing, or "prolonged spindles/delta brush pattern"
	Other	CSF antibody testing preferable to serum Increased association with tumors in females and in patients older than 12 y

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Antibodies that are identified less frequently in pediatric AE

Antibody target (localization)	Typical clinical features in children	
Dopamine-2 receptor[13] **(extracellular)**	Frequency	Very uncommon
	Clinical	Encephalitis with predominant movement disorders, psychiatric symptoms, sleep disturbance, mutism, and decreased consciousness
	MRI	Abnormal in 50% of patients, usually symmetric selective involvement of basal ganglia
	EEG	No consistent pattern reported
	Other	Variable CSF findings, sometimes lymphocytic pleocytosis or oligoclonal bands
$GABA_A$ receptor[14,15] **(extracellular)**	Frequency	Uncommon
	Clinical	Encephalitis with refractory seizures, status epilepticus, or epilepsia partialis continua
	MRI	Multifocal T2/FLAIR lesions in cortical/subcortical areas
	EEG	Epileptiform activity and generalized slowing
	Other	Most patients have CSF leukocytosis Often associated with GAD or thyroid autoantibodies
GABA-B receptor[16,17] **(extracellular)**	Frequency	Very uncommon
	Clinical	Encephalitis with focal or generalized seizures and mixed movement disorder
	MRI	Abnormal in over 50% with increased T2/FLAIR signal in the medial temporal lobe (may be multifocal and may be associated with changes on diffusion-weighted imaging)
	EEG	Diffuse slowing and epileptiform discharges
	Other	CSF abnormal in up to 90% with lymphocytic pleocytosis Pediatric cases not linked to infection or tumor
Glycine receptor[18,19] **(extracellular)**	Frequency	Uncommon
	Clinical	Progressive encephalomyelitis with rigidity and myoclonus; encephalitis; and other brainstem syndromes
	MRI	Frequently normal (70% reported cases)
	EEG	Abnormal in approximately 70%, usually slowing
	Other	Variable CSF findings of lymphocytosis, elevated protein, and oligodonal bands May be associated with antibodies to other targets (e.g., GAD)
m-GluR5[20,21] **(extracellular)**	Frequency	Very uncommon
	Clinical	Encephalitis with psychiatric symptoms
	MRI	Variable MRI findings, often T2/FLAIR
	EEG	Variable EEG findings, typically absent epileptiform discharges
	Other	CSF lymphocytic pleocytosis

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Antibody-Associated Encephalitides in Childhood

Autoimmune Encephalitis	Ages Described*	Clinical Manifestations	Associated Tumor	Risk of Relapse	Long-Term Outcomes
NMDAR	20 mo-17 yr	Seizures, behavioral disturbance, aphasia, psychosis, orofacial dyskinesias, catatonia	30% of females with ovarian teratoma	Up to 25% when causative tumor is not identified and removed	80% or greater have full recovery
VGKC	10 mo-17 yr	Seizures, behavioral disturbance, movement disorders, dysarthria, developmental regression	Neuroblastoma in one case (patient with multiple autoantibodies)	Unknown; reported in single case series as 25% relapse rate in childhood	Unknown, but most reported patients show marked to full recovery
GlyR	1-14 yr	PERM, seizures, ADEM with ON	None currently reported in childhood	Unknown; reported in single case series as 25% relapse rate in childhood	Unknown; generally considered to have good outcomes
$GABA_A$	2-17 yr	Seizures, cognitive and memory alterations, movement abnormalities	Hodgkin's lymphoma predating encephalitis in one patient	Unknown, but reported in a single pediatric case	Unknown; most have good recovery but residual seizures
$GABA_B$	3-18 yr	Seizures, movement disorders, memory loss, delirium, psychosis	None currently reported in childhood	Unknown in childhood	Unknown; majority reported show full recovery
AMPA	7-8 yr	Seizures, memory loss, behavioral changes	None currently reported in childhood	Unknown in childhood	Unknown
D2R	4 mo-15 yr	Seizures, lethargy, psychiatric symptoms, dystonia, parkinsonism, chorea, ataxia	None currently reported in childhood	Unknown; reported in case series as 25% relapse rate in childhood	Unknown; a single case series reports full recovery in 40%
mGluR5 (Ophelia syndrome)	Adolescence	Memory loss, depression, hallucinations, behavior abnormalities	Hodgkin's lymphoma	Uncommon if treated appropriately	Full recovery with appropriate treatment
Hu	1-15 yr	Behavioral changes, seizures, posterior cord syndrome, ataxia	Estimated 25% associated with neuroblastoma	Unknown in childhood	Reported patients with continued seizures despite treatment
Ma1 and *Ma2*	2-14 yr	Seizures, behavioral changes, memory loss, speech changes	None currently reported in childhood	Unknown in childhood	Reported patients with poor outcomes
GAD	2-17 yr	Seizures, cognitive decline, psychosis, memory loss, stiff-person syndrome, progressive developmental delay	None currently reported in childhood	Unknown in childhood	Variable outcome potentially related to rapidity of treatment

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Recommended investigations for children with suspected AE

A. Initial investigations for patients with possible AE	
Diagnostic imaging	Brain MRI with gadolinium (including T1, T2, FLAIR, and diffusion-weighted sequences)
	Consider adding spine MRI if neurologic abnormalities potentially mediated by spinal cord involvement
Blood tests	Complete blood cell count and differential
	Erythrocyte sedimentation rate, C-reactive protein, and ferritin
	Vitamin B12 level and vitamin D level
	Serum lactate
	Thyroid-stimulating hormone, free thyroxine, and thyroid autoantibodies (e.g., antithyroid peroxidase, antithyroglobulin, and anti–thyroid-stimulating hormone receptor)
	Serologic testing for infectious causes (dependent on regional epidemiology)
	Consider antinuclear antibodies and specific antinuclear antibodies (e.g., anti–double-stranded DNA and anti-Smith) if indicated by clinical presentation
	Consider serum complement and immunoglobulin levels if personal or family history of autoimmunity or immune deficiency
Urine tests	Testing for recreational drugs (e.g., marijuana, cocaine, and opioids)
Lumbar puncture	Opening pressure
	CSF cell counts, protein, lactate, oligoclonal bands, and neopterin (if available)
	Infectious testing dependent on regional epidemiology, but often includes PCR for enterovirus, herpes simplex virus, and varicella zoster viruses
	Save 5–10 mL of CSF for future testing
Respiratory tests	Nasopharyngeal swab for respiratory viruses and mycoplasma PCR
EEG	Assess for focal or generalized seizures, epileptiform discharges, and changes in background activity
B. More specific investigations for patients with possible AE	
Blood tests	Serum testing for antibodies associated with AE[a]
Lumbar puncture	CSF testing for antibodies associated with AE[a]
Neurocognitive tests	Assess for cognitive deficits affecting memory, attention, problem solving, language, and cognitive processing
	Consider using symbol digit modalities test to screen for cognitive dysfunction
Other tests	Consider if available and/or if required based on initial investigations: PET and SPECT

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MRI Findings in Antibody-Mediated Encephalitis

A. Anti-NMDAR encephalitis, normal MRI findings or mild signal abnormalities on FLAIR images.

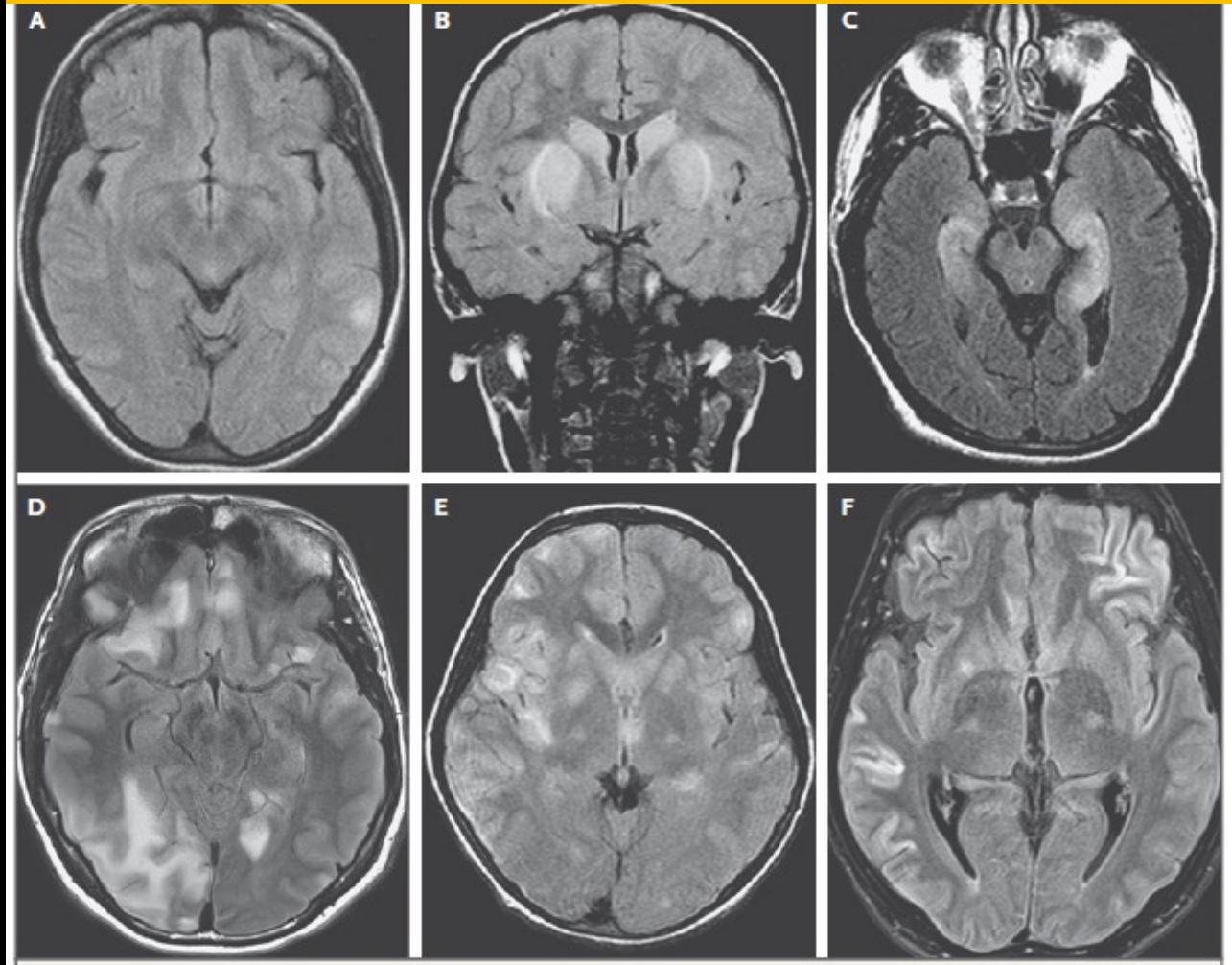
B. Basal ganglia encephalitis associated with **dopamine 2 receptor antibodies** typically affects the striatum.

C. Limbic encephalitis is typically indicated by FLAIR signal increases in the medial temporal lobes.

D. Encephalitis with **antibodies against GABAAR** is usually associated with multiple cortical and subcortical FLAIR signal changes.

E. ADEM with antibodies against MOG, extensive, bilateral FLAIR signal abnormalities

F. large thymoma, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) antibodies, and MRI findings that suggested widespread cortical damage and a poor prognosis



Proposed classification criteria for possible, definite antibody-positive and probable antibody-negative pediatric AE

Categorical features of AE	Specific diagnostic features	Diagnostic categories		
		Possible AE	Probable antibody-negative AE	Definite antibody-positive AE
1. Evidence of acute or subacute symptom onset	Onset of neurologic and/or psychiatric symptoms over ≤3 mo in a previously healthy child	Yes	Yes	Yes
2. Clinical evidence of neurologic dysfunction	Features include:	≥2 features present	≥2 features present	≥2 features present
	Altered mental status/level of consciousness or EEG with slowing or epileptiform activity (focal or generalized)			
	Focal neurologic deficits			
	Cognitive difficulties[a]			
	Acute developmental regression			
	Movement disorder (except tics)			
	Psychiatric symptoms			
	Seizures not explained by a previously known seizure disorder or other condition			
3. Paraclinical evidence of neuroinflammation	Features include:	Not available	≥1 features present	≥1[b] features present
	CSF inflammatory changes (leukocytosis >5 cells/mm^3 and/or oligoclonal banding)			
	MRI features of encephalitis			
	Brain biopsy showing inflammatory infiltrates and excluding other disorders			
4. AE serology	Presence in serum and/or CSF of well-characterized autoantibodies associated with AE	Not available	No	Yes
5. Exclusion of other etiologies	Reasonable exclusion of alternative causes, including other causes of CNS inflammation	Yes	Yes	Yes

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Differential diagnosis of AE in childhood

Differential Diagnosis of Encephalopathy and Encephalitis of Childhood

Infectious etiologies

Viral Encephalitis (e.g., EBV, HHV-6, VZV, HSV, HIV, enterovirus, arbovirus, parechovirus)
Bacterial encephalitis (e.g., *Bartonella*, *Mycoplasma*, *Rickettsia*)
Spirochetal encephalitis (e.g., *Borrelia*)

Toxic

Neuroleptic malignant syndrome
Drug Ingestion (e.g., alcohol, ketamine, phencyclidine, organophosphates)

Epileptic disorders

Nonconvulsive status epilepticus
Fever-induced refractory epileptic encephalopathy in school-aged children (FIRES)

Vascular disorders

Posterior reversible encephalopathy syndrome (PRES)
Inflammatory vasculitis (e.g., primary CNS vasculitis, systemic lupus erythematosus with neuropsychiatric features, Bechet's)
Migraine (e.g. acute confusional migraine)

Miscellaneous disorders

Autism spectrum disorders
Kleine–Levin syndrome

Genetic and metabolic disorders

Inherited disorders and inborn errors of metabolism (e.g., Wilson disease, PKAN, glutaric aciduria type I, Lesch–Nyhan syndrome, creatine transport deficiencies, urea cycle disorders)
Mitochondrial disorders (e.g., Leigh syndrome)

Psychiatric disorders

Brief reactive psychosis
Major depressive disorder with psychotic episode(s)
Conversion disorder

Autoimmune and inflammatory disorders

Demyelinating disease (MS, NMO, ADEM)
Sydenham chorea
Opsoclonus–myoclonus ataxia syndrome
Steroid-responsive encephalopathy associated with autoimmune thyroiditis (SREAT)
Antibody-mediated encephalitides

Structural disease

Neoplasm (e.g., gliomatosis cerebri)
Hydrocephalus

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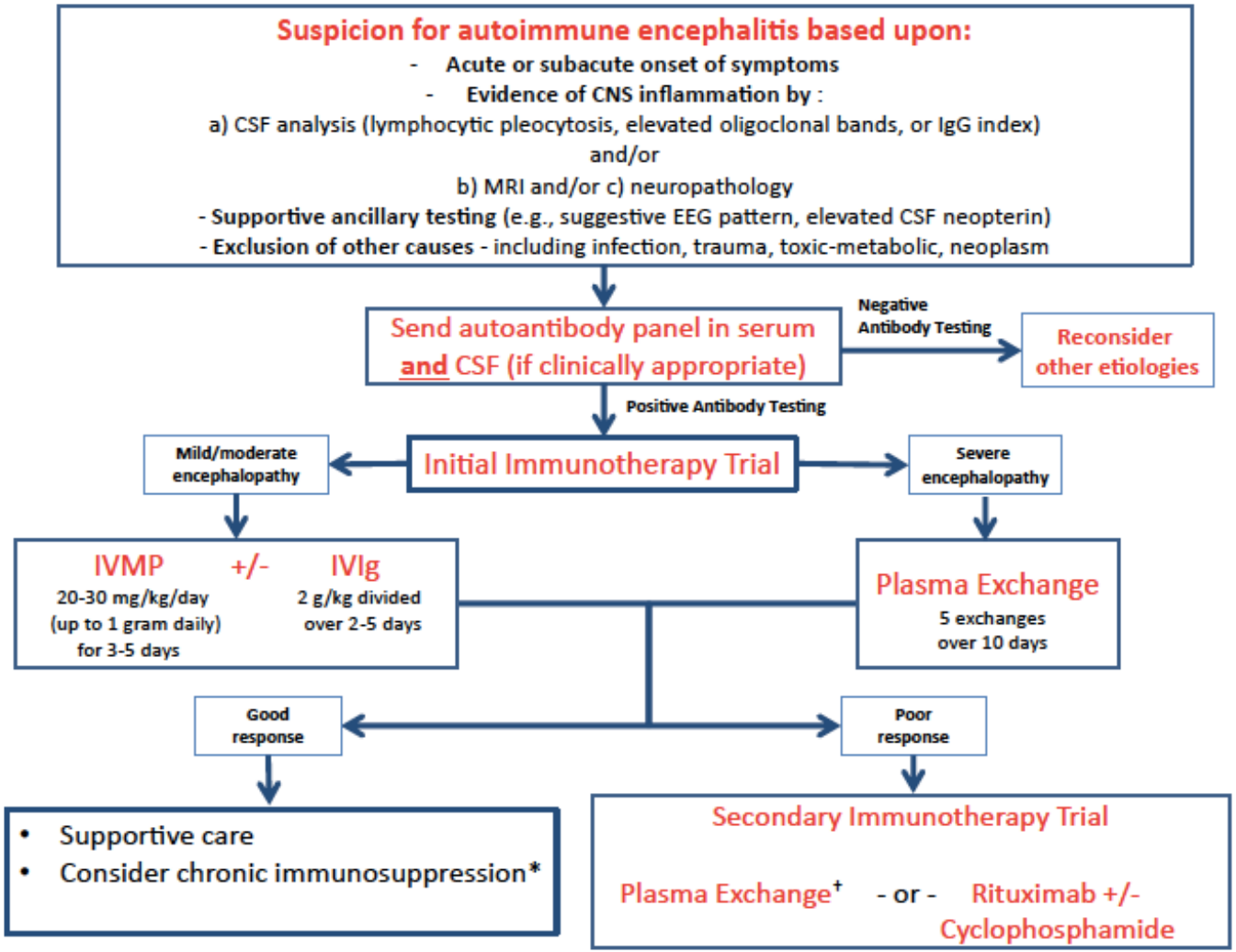

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