Resoconto attività Gruppo di Studio (GdS) Epilessie Disimmuni per il triennio 2015-2017

Membri del GdS: Flavio Villani (chairman), Stefano Sartori (chairman), Carlo Antozzi, Elena Freri, Antonio Gambardella, Sara Matricardi, Roberto Michelucci, Luigi Zuliani

Obiettivi del GdS

Il GdS Epilessie disimmuni si è costituito con i seguenti obiettivi:

- Identificare i fenotipi epilettici a possibile genesi autoimmune
- Analizzare la presentazione clinica, gli aspetti diagnostici e il trattamento di tali forme
- Delineare l'attuale condotta diagnostica e terapeutica dei Centri italiani per l'epilessia
- Formulare raccomandazioni per l'approccio diagnostico e terapeutico a tali forme
- Formulare PDTA condivisi a livello nazionale
- Diffondere la conoscenza su questo argomento

Attività del GdS

- Incontri scientifici e organizzativi
- Attività di raccolta dati
- Attività di diffusione dei risultati fino a qui ottenuti

A) Incontri

1. Il primo incontro è avvenuto il 21 Aprile 2015 presso la Fondazione I.R.C.C.S. Istituto Neurologico Carlo Besta, con il seguente ordine del giorno:

- *Razionale, obiettivi, organizzazione e progetti del gruppo di studio*

- *Presentazioni scientifiche*

Presenti: Flavio Villani, Stefano Sartori, Carlo Antozzi, Elena Freri, Antonio Gambardella, Sara Matricardi, Roberto Michelucci, Luigi Zuliani, Francesco Deleo, Giuseppe Didato, Raffaele Iorio. Ospite Sarosh Irani.

Programma della giornata:

Sessione mattino

h. 10:30-11:30 Introduzione: razionale, obiettivi e organizzazione del GdS (Sartori e Villani)

h. 11:30-13:00 Seminario Sarosh Irani e discussione

h. 13:00-14:00 Intervallo pranzo

Sessione pomeriggio

h. 14:00-14:30 Linee guida, percorsi diagnostici e terapeutici nell'ambito delle encefaliti autoimmuni: la necessità della condivisione sul territorio nazionale (Zuliani)

h. 14:30-14:50 Il problema dei casi non definiti (Matricardi)

h. 14:50-15:05 Caso clinico esemplificativo (Freri)

h. 15:05-15:20 Caso clinico esemplificativo (Deleo)

h. 15:20-16:20 Progetti (PDTA, banche dati e materiale biologico) (moderazione: Antozzi, Gambardella, Michelucci)

h. 16:20-16:30 Discussione generale, varie e saluti

Sommario dei contenuti dell'incontro:

Durante l'incontro si è discussa la definizione del tema oggetto di studio, in particolare dell'equivalenza della terminologia "epilessia autoimmune" ed "encefalite autoimmune", sottolineando l'importanza di una "definizione" per l'epilettologo e l'immunologo come supplemento d'indagine e base per lavori prospettici.

L'epilessia autoimmune viene, quindi, intesa come entità clinica distinta, ma strettamente connessa con l'encefalite autoimmune, nella quale l'epilessia rappresenta il sintomo predominante, ma non esclusivo, del quadro neurologico. Si è pertanto sottolineata l'importanza di delineare criteri diagnostici condivisi per individuare quadri clinici con epilessia a possibile genesi disimmune, definendo altresì un algoritmo diagnostico e terapeutico.

È stata sottolineata l'opportunità di coinvolgere altri centri ed estendere collaborazioni nazionali e internazionali, al fine di costituire banche dati che includano retrospettivamente pazienti con diagnosi di epilessia disimmune con o senza encefalopatia associata, e diagnosi anticorpale sia positiva che negativa. Oltre alla raccolta retrospettiva dei casi già diagnosticati, fine del gruppo di studio è anche quello di strutturare un lavoro prospettico, includendo pazienti con epilessia di nuova diagnosi a possibile genesi disimmune secondo i criteri diagnostici definiti e condivisi, e la creazione di un registro (sul modello delle PME). Si evidenzia, inoltre, la necessità di creare banche locali di campioni biologici secondo protocolli condivisi di raccolta e conservazione dei materiali biologici.

Obiettivo del gruppo di studio è, infine, quello di stilare Raccomandazioni per l'epilettologo per la diagnosi e il trattamento di forme di epilessia ad eziologia disimmune.

2. Il secondo incontro è stato effettuato il 14 dicembre 2015 presso la Clinica Pediatrica dell'Università di Padova.

Presenti: Flavio Villani, Stefano Sartori, Elena Freri, Luigi Zuliani e Sara Matricardi.

Odg: sviluppo di progetti collaborativi multicentrici in base alla "call" ministeriale. Aggiornamento scientifico.

Sommario contenuti dell'incontro:

Il primo punto discusso ha riguardato il tipo di progetto che vorremmo mettere in cantiere: a tale proposito abbiamo tutti concordato che un progetto di Rete ha le caratteristiche più adatte a mettere insieme i diversi gruppi di ricerca che compongono il nostro GdS. La complessità e la necessità di coordinare diversi gruppi di ricerca rendono la concorrenza meno pesante rispetto ai progetti convenzionali. Ovviamente, in merito a tale scelta, attendiamo il parere di tutti i membri del GdS.

I progetti di Rete presuppongono l'organizzazione di Workpackages (WP) autonomi e coordinati che abbiano ciascuno un progetto specifico. Ogni WP avrà quindi "aims" specifici che dovranno essere raggiunti in autonomia rispetto agli altri WP, ma che concorreranno al raggiungimento degli obiettivi generali del progetto. La stesura della Lettera d'Intenti (LOI) comprenderà quindi una parte generale con obiettivi e quadro economico generale, e parti specifiche in numero pari ai WP. Per esperienza diretta (ma questo punto può essere discusso) riteniamo che tre WP possano essere sufficienti e non tali da complicare troppo il coordinamento. Ogni WP avrà il proprio PI e potrà aggregare altri gruppi di ricerca.

Al momento avremmo identificato 3 possibili WP: WP 1 Besta (Villani); WP 2 Padova (Sartori); WP 3 Bologna (Michelucci).

Nel corso della riunione abbiamo tentato di abbozzare un titolo e gli obiettivi generali del progetto:

Towards the recognition of autoimmune epilepsy in children and adult patients. A prospective cohort study for the characterization of biological markers of immune activation and advanced non-conventional 3T MRI analysis in different forms of new onset epilepsies.

Aim 1: To determine the prevalence of known anti-neuronal antibodies in an adult and pediatric cohort of patients with new onset epilepsies.

Aim 2: To identify a subgroup of patients with possible autoimmune epilepsies by means of clinical and paraclinical criteria defined on the basis of an extensive literature search.

Aim 3: To define the diagnostic gain of an advanced neuroimaging analysis (3T MRI) compared to conventional neuroimaging in the subsample of patients with possible autoimmune epilepsy.

Infine è stato discussa l'organizzazione della raccolta e della gestione dei dati (registro, piattaforma, analisi biostatistica), senza giungere ad una definizione conclusiva.

Aggiornamento clinico-scientifico:

Scopi: definire il ruolo dell'immunità (infiammazione) nelle epilessie di nuova diagnosi.

- Criteri di reclutamento: pazienti (di ogni età) con epilessia di nuova diagnosi (Classificazione ILAE)

- Consenso

1) Diagnosi di epilessia

2) Inquadramento clinico (anamnesi, Es. Obiettivo, EEG, RM, ecc… altre indagini laboratoristiche e strumentali a seconda del contesto clinico)

3) Raccolta di siero di tutti i pz reclutati (+/- liquor) e ricerca Ab noti

4) Prima stratificazione eziologica in base ai dati raccolti:

- Epi idiopatiche
- Epi sintomatiche ad eziologia nota
- Epi non idiopatiche ad eziologia non nota (→ indagini utili a stabilire una possibile natura autoimmune – Liquor, ecc…-)

5) Seconda stratificazione: eziologia autoimmune sospettata in base a:

Criteri di letteratura…. Es:

- Epilessia ad esordio acuto o subacuto;
- Epilessia come sintomo esclusivo o predominante il quadro clinico
- Epi responsiva alla Tp. Immunomodulante
- Evidenza di infiammazione SNC
- Altri segni liquorali, clinici (es. comportamentali)
- Ecc…

(Definizione criteri di probabilità)

3. Il terzo incontro si è tenuto in occasione del Policentrico di quest'anno, il 26 gennaio 2017.

Presenti: Flavio Villani, Stefano Sartori, Elena Freri, Sara Matricardi, Roberto Michelucci, Antonio Gambardella, Patrizia Riguzzi.

Sommario contenuti dell'incontro:

l'obiettivo è sempre l'identificazione di fenotipi epilettici accomunati da una possibile eziologia autoimmune. La letteratura, pur ipotizzando l'esistenza di condizioni epilettiche autoimmuni in cui la sintomatologia critica è predominante rispetto al quadro clinico complessivo, non fornisce dati

conclusivi per una loro sicura identificazione e, di conseguenza, non dà indicazioni condivise rispetto al loro possibile trattamento.

Il quesito a cui vorremmo dare una risposta necessita di un'iniziale "fotografia" dell'attuale condotta diagnostica e terapeutica in questo ambito in Italia. In particolare, quali casi vengono inquadrati come "Epilessia Autoimmune" e perché? Quale trattamento farmacologico (antiepilettico e/o immunomodulante) viene utilizzato in acuto e in cronico in tali pazienti?

A tale scopo riteniamo utile effettuare una prima raccolta retrospettiva della casistica afferente ai Centri Epilessia riconosciuti dalla LICE o ai servizi di neurologia sparsi sul territorio nazionale. Vi invitiamo pertanto a ripensare ai casi in cui avete ravvisato una possibile genesi autoimmune dell'epilessia. Allo scopo di facilitare l'identificazione dei casi inviamo una lista di criteri d'inclusione/esclusione nella casistica. Alleghiamo inoltre una scheda per agevolare la raccolta dei dati.

	DATI ANAGRAFICI
Iniziali	
Data di nascita	
Genere	
	ANAMNESI FAMILIARE
Familiarità per patologie neurologiche (No/Sì-quali)	
Familiarità per patologie immuno-mediate (No/Sì-quali)	
	ANAMNESI PERSONALE
Patologie neurologiche (No/Sì-quali)	
Patologie immuno-mediate (No/Sì-quali)	
Neoplasie (No/Sì-quali)	
Infezioni recenti (No/Sì-quali)	
	DATI CLINICI ED EPILETTOLOGICI ALL'ESORDIO
Età d'esordio	
Tipo di crisi (Focali, focali limbiche, distoniche facio-brachiali, Multifocali, generalizzate, EPC)	(Eventuale descrizione)
Frequenza (quotidiana, settimanale, mensile, annuale)	
Durata crisi	
Stati di male	
EEG (attività di fondo, anomalie lente, anomalie epilettiformi, eventuali pattern critici,	

organizzazione del sonno se disponibile)	
MRI	
Liquor (Leucociti, proteine, bande OC)	
Auto-anticorpi (siero e liquor): immunità "classica", anticorpi onconeuronali e antigeni intracellulari, anticorpi anti-antigeni di superficie neuronale	
Altri segni o sintomi associati (cognitivi, psichiatrici, neurologici)	
Terapia con AEDs (quali AEDs – risposta)	
Terapia immunomodulante (tipo – risposta)	
	DATI CLINICI ED EPILETTOLOGICI AL FOLLOW-UP
Durata Follow-up	
Tipo di crisi (Focali, focali limbiche, distoniche facio-brachiali, Multifocali, generalizzate, EPC)	(Eventuale descrizione)
Frequenza (quotidiana, settimanale, mensile, annuale)	
Durata	
Stati di male	
EEG (attività di fondo, anomalie lente, anomalie epilettiformi, eventuali pattern critici, organizzazione del sonno se disponibile)	
MRI	
Liquor (Leucociti, proteine, bande OC)	
Auto-anticorpi (siero e liquor): immunità "classica", anticorpi onconeuronali e antigeni intracellulari, anticorpi anti-antigeni di superficie neuronale	
Altri segni o sintomi associati (cognitivi, psichiatrici, neurologici)	

Terapia con AEDs (quali AEDs – risposta)	
Terapia immunomodulante (tipo – risposta)	

CRITERI D'INCLUSIONE

- Esordio acuto/subacuto crisi
- Crisi: sintomo esclusivo o predominante
- Esclusione altre eziologie
- Almeno 1 tra i 3 criteri:
    - **Risposta a Tp immunomodulante**
    - **Storia personale recente per sintomi prodromici simil-influenzali**
    - **Segni di Infiammazione** agli esami strumentali e laboratoristici (CSF: Aum proteinorrachia, pleiocitosi, bande oligoclonali; MRI: iperintensità T2, presa di contrasto gadolinio, restricted diffusion, coinvolgimento limbico)

CRITERI SUPPORTIVI

- Crisi focali/multifocali/limbiche/FBDS
- Elevata frequenza critica
- Farmacoresistenza
- Risposta a Tp immunomodulante
- Storia personale o familiare positiva per patologie immuno-mediate
- Storia personale recente o pregressa per neoplasia
- Storia personale recente per sintomi prodromici simil-influenzali
- Segni di Infiammazione agli esami strumentali e laboratoristici (CSF: Aum proteinorrachia, pleiocitosi, bande oligoclonali; MRI: iperintensità T2, presa di contrasto gadolinio, restricted diffusion, coinvolgimento limbico)
- *Eventuale positività per Anticorpi specifici*

CRITERI DI ESCLUSIONE

- Epilessia ad eziologia definita
- Segni e sintomi di processi infettivi (virali, batterici, fungini) alla base della infiammazione cerebrale
- Alterazioni metaboliche (renali, epatiche, ipo/iperglicemia grave, …)
- Alterazioni cerebrali strutturali (stroke, tumori, lesioni traumatiche, eterotopie, alterazioni della migrazione neuronale, sclerosi temporale mesiale, malformazioni vascolari, ascessi cerebrali, …)

B) Attività di raccolta dati: dal febbraio 2017 è iniziata la raccolta multicentrica di dati retrospettivi.

Hanno aderito alla raccolta dati: *S. Matricardi[1], T Granata[1], AT. Giallonardo[2], R. Michelucci[3], E. Freri[1], F. Ragona[1], E. Ferlazzo[4], A. C. Di Bonaventura[2], G. Di Gennaro[5], S. Casciato[2], La Neve[6], M. Tappatà[6], V. Belcastro[7], P. Riguzzi[3], I. Pappalardo[8], G. Didato[8], C. Pastori[8], S. Sartori[9], M. Nosadini[9], L. Zuliani[10], C. Antozzi[11], A. Gambardella[12], F. Villani[8]*

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C) Attività di diffusione conoscenze e risultati fino a qui ottenuti: si allegano documento sulle Epilessie autoimmuni (Margherita Nosadini) e abstract presentato alla LICE 2017 che riassume i dati fino ad ora raccolti dal GdS.

FENOTIPI EPILETTICI A POSSIBILE GENESI AUTOIMMUNE: UNO STUDIO RETROSPETTIVO DEL GRUPPO DI STUDIO LICE SULLE EPILESSIE DISIMMUNI

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Razionale e obiettivi: Identificazione di fenotipi epilettici a possibile eziopatogenesi autoimmune, per tentare una classificazione per gruppi omogenei e per delineare in tale ambito l'attuale condotta diagnostica e terapeutica dei Centri italiani per l'epilessia.

Metodi: Sono stati retrospettivamente arruolati 113 pazienti (18 bambini, 95 adulti) in cui le crisi epilettiche erano il sintomo d'esordio o predominante il quadro clinico, e per i quali è stata identificata (positività di anticorpi antineuronali) o ipotizzata (sulla base dei dati clinici e paraclinici suggestivi di infiammazione del SNC, o della risposta alla terapia immunomodulante) una eziopatogenesi autoimmune.

Risultati: I pazienti sono stati seguiti per un periodo di almeno 24 mesi. Le crisi focali, farmacoresistenti nell' 82% dei casi, erano il tipo di crisi più frequente. La frequenza delle crisi era elevata, soprattutto all'esordio nel 73% dei casi, con episodi di stato epilettico nel 45%. Nel 36% dei casi, la ricerca per anticorpi specifici è risultata positiva su siero e/o su liquor. Nella maggior parte dei pazienti erano presenti anche altri segni e sintomi di coinvolgimento del SNC. La terapia immunomodulante (con farmaci di I e II linea) ha determinato una riduzione significativa della frequenza critica nel 60 % dei casi. Sono state confrontate le caratteristiche cliniche e paracliniche, nonché la risposta alla terapia dei pazienti con e senza anticorpi.

Conclusioni: Il ruolo patogenetico dell'infiammazione nel determinare e sostenere l'attività critica è riconosciuto. Una più certa classificazione dei fenotipi clinici e la definizione di modelli di trattamento possono migliorare la prognosi di condizioni potenzialmente trattabili.

Bibliografia:

1 Toledano M, Pittock SJ. Autoimmune Epilepsy. Semin Neurol. 2015;35(3):245-58
2 Spatola M, Dalmau J. Seizures and risk of epilepsy in autoimmune and other inflammatory encephalitis. Curr Opin Neurol 2017;22. [Epub ahead of print]

AUTOIMMUNE EPILEPSY

INTRODUZIONE

Activation of the immune system is observed in many disease processes of the CNS, although discriminating a primary (causal) immune response from a secondary (reactive) immune response to tissue damage is not straightforward. There is a large and complex literature describing the presence of inflammation and immune activation in seizures and epilepsy [Suleiman, 2015].

Although epilepsy is one of the most common neurologic disorders affecting millions of people worldwide, in a substantial number of individuals the etiology remains unknown [Bien and Scheffer, 2011].

Over the last few years there has been increasing support for the hypothesis that some forms of epilepsy may have an autoimmune component. Circumstantial evidence in support of this idea includes the apparent association of seizures with certain autoimmune diseases (e.g., systemic lupus erythematosus and Hashimoto's encephalopathy) and, in some patients, an acute or subacute onset of the seizures, a rapidly progressive course, and a favourable response to immunotherapy [Bien and Scheffer, 2011].

A large population-based study (n>2,000,000) showed that patients with autoimmune disease constituted 17.5% of patients with epilepsy, and that the presence of an autoimmune disorder may contribute to a fourfold increased risk of epilepsy [Ong, 2014].

Recently, clinically relevant autoantibodies have been detected in a number of CNS disorders that often present with recurrent seizures [Bien and Scheffer, 2011]. The confident diagnosis of autoimmune encephalitis and epilepsy has improved substantially owing to the discovery of pathogenic autoantibodies that seem to be discriminating biomarkers of disease [Suleiman, 2015].

Specific neuronal auto-antibodies with pathogenic potential may be present in a subset of patients with epilepsy. Importantly, it has recently been shown that some patients with these serum auto-antibodies are often refractory to treatment with standard anti-epileptic drugs (AEDs) and, in contrast, may respond well to immunomodulatory therapies [Irani, 2011].

AUTOIMMUNE ENCEPHALITIS WITH SEIZURES

Seizures are a common feature of autoimmune encephalitis, where patients characteristically have other clinical features such as encephalopathy, behavioural alteration, and movement disorders, in addition to seizures [Suleiman, 2015].

Autoimmune encephalitis can be broadly separated into focal (i.e. limbic encephalitis), multifocal (i.e. (anti-GABAAR encephalitis), or diffuse processes (i.e. anti-NMDAR encephalitis).

Autoantibodies to neuronal surface antigens described in autoimmune encephalitis associated with seizures are reported in Table 1.

Epilessia e anticorpi anti-antigeni di superficie neuronale

Tipo di anticorpo	Descrizione del fenotipo	Descrizione di crisi epilettiche (in presenza o	Descrizione di epilessia isolata (o come

		meno di altre manifestazioni, es encefalite) in pazienti con anticorpi positivi	prevalente manifestazione) in pazienti con anticorpi positivi
NMDAR	Anti-NMDAR encephalitis (multiphasic disease with behavioural and psychiatric changes, movement disorders, seizures, hyporesponsive state and dysautonomia)	Yes	Yes
LGI1	Limbic encephalitis (confusion, agitation, memory loss and seizures) Isolated epilepsy (faciobrachial dystonic seizures) Progressive encephalomyelitis with rigidity and myoclonus Isolated chorea Hemianaesthesia Neurocardiac prodromes	Yes	Yes [Quek, 2012; Irani, 2013] (adults)
Caspr2	Limbic encephalitis Morvan's syndrome Neuromyotonia Isolated epilepsy Encephalopathy	Yes	Yes [Irani, 2010; Lancaster, 2011; Sunwoo, 2015] (adults)
AMPAR	Limbic encephalitis Other encephalitis (multifocal/diffuse encephalopathy, hyponatremia, limbic encephalitis preceded by motor deficits, or a predominantly psychiatric syndrome)	Yes	No
GABAAR	Limbic encephalitis Other encephalitis Isolated epilepsy Isolated psychiatric disturbances Isolated cognitive impairment Stiff-person-syndrome Opsoclonus myoclonus ataxia syndrome	Yes	Yes [Pettingill, 2015] (children and adults)
GABABR	Limbic encephalitis Cerebellar ataxia Rapidly progressive encephalomyelopathy Opsoclonus myoclonus ataxia syndrome Isolated epilepsy	Yes	Yes [Höftberger, 2013] (children and adults)
GlyR	Limbic encephalitis Epileptic encephalopathy Isolated epilepsy Progressive encephalomyelitis with rigidity and myoclonus Stiff-person-syndrome Cerebellar ataxia Optic neuritis	Yes	Yes [Brenner, 2013; Ekizoglu, 2014; Gresa-Arribas 2015] (children and adults)
DPPX	Encephalitis Progressive encephalomyelitis with rigidity and myoclonus	No	No
IgLON5	Syndrome with atypical sleep disorder with abnormal sleep movements and behaviour, obstructive sleep apnoea, dysautonomia, movement disorder	No	No
D2R	Basal ganglia encephalitis (encephalopathy, movement disorder, psychiatric symptoms, sleep disorder)	No	No
mGluR5	Ophelia syndrome (Hodgkin lymphoma and limbic encephalitis) Limbic encephalitis and prosopagnosia, without tumour	Yes	No

Tabella 1. Presenza di crisi epilettiche (in presenza o meno di altre manifestazioni, ad esempio encefalite), e di epilessia isolata in pazienti con positivita' per anticorpi anti antigeni di superficie neuronale.

AUTOIMMUNE EPILEPSY WITHOUT ENCEPHALITIS (paragrafo tratto da [Suleiman, 2015])

There are now many reports and accumulating data to define a group of patients with an autoimmune basis for their seizures including those *without* typical 'autoimmune encephalitis' phenotype both in adults and in children. These patients present primarily with seizures in the absence of other features of encephalitis such as encephalopathy, although the seizures and electrographic abnormalities might be severe enough to produce an 'epileptic' encephalopathy.

Neuronal autoantibodies are found in many reports of adults and children with epilepsy, supporting the hypothesis that the epilepsy is 'autoimmune' in these cases. The emerging theme in these reports suggests that autoantibodies are more likely to be found in patients with focal seizures, particularly those who are refractory to antiepileptic drugs, and those previously classified as having 'unknown

cause' [Quek, 2012; Brenner, 2013; Ekizoglu , 2014].

In an adult study of two epilepsy cohorts (established, n=235; new onset, n=181), neuronal autoantibodies were found in 11% of patients [Brenner, 2013] (Tabella 2). There were no differences in antibody prevalence between established and new cohorts, or patients with focal or generalized epilepsy. The authors explored the aetiology for patients with focal epilepsy only and found that antibodies were more common in patients with unknown cause than those with a known structural or metabolic cause for their focal epilepsy.

Another adult study investigated the prevalence of neuronal autoantibody in patients with focal epilepsy of unknown cause and in patients with mesial temporal lobe epilepsy with hippocampal sclerosis [Ekizoglu, 2014] (Tabella 2). Neuronal autoantibodies were found in 13 out of 81 of the total cohort (16%), including 7 out of 55 of the group with focal epilepsy of unknown cause (12.7%) and 6 out of 26 with mesial temporal lobe epilepsy with hippocampal sclerosis (23%).

In a paediatric study of children with new-onset epilepsy (n=114), neuronal autoantibodies were found in 9.7% of the total cohort. Neuronal autoantibodies were found more commonly in children with an unknown cause (21%) than in those who had a known structural or metabolic cause (3%). In the antibody-positive patients with unknown cause, the seizures were mostly focal (4/7) [Suleiman, 2013] (Tabella 2).

Prevalenza di autoanticorpi in pazienti con epilessia

STUDI SULLA PREVALENZA DI AUTANTICORPI IN CASISTICHE DI PAZIENTI CON EPILESSIA				
Autore, anno **Titolo**	**Criteri di inclusione**	**N° ed eta' dei casi**	**% (N°) di casi con auto-anticorpi** **Tipo di autoanticorpi**	**Altre osservazioni**
Brenner, 2013 Prevalence of neurologic autoantibodies in cohorts of patients with new and established epilepsy	Adults (≥16 years) with either established epilepsy (n = 235) or new-onset epilepsy (n = 181)	416 (235 + 181) adults	11% (46/416) 20/416: VGKC 11/416: GlyR 7/416: GAD 7/416: NMDAR 1/416: VGKC and GlyR	There was no difference in the prevalence of antibodies, individually or collectively, between patients with established and newly diagnosed epilepsy or with generalized or focal epilepsy. There was, however, a significantly higher prevalence of positive antibody titers in patients with focal epilepsy of unknown cause than in those with structural/metabolic focal epilepsy (14.8% vs. 6.3%; $p < 0.02$). Newly diagnosed antibody-positive patients were less likely to achieve adequate seizure control with initial treatment than antibody- negative patients, but this difference failed to reach statistical significance. Significance: The presence of autoantibodies is equally common in newly diagnosed and established epilepsy, it is therefore unlikely to be an epiphenomenon of long-standing refractory seizures.
Suleiman, 2013 Autoantibodies to neuronal antigens in children with new onset seizures classified according to the revised ILAE organization of seizures and epilepsies	Children aged 2 months to 16 years with new-onset seizures (presenting to the Children's Hospital at Westmead Hospital, Sydney between September 2009 and November 2011).	114 children	9.7% (11/114) 4/114: VGKC complex 3/114: CASPR2 2/114: NMDAR 2/114: VGKC complex and NMDAR	The classification of "unknown cause" was higher in the antibody positive (7/10; 70%) compared with the antibody negative subjects (23/86; 26.7%; $p = 0.0095$, Fisher's exact test). Furthermore, 4 of these 7 patients with epilepsy (57.1%) were classified as having predominantly focal seizures compared with 12 of the 86 antibody-negative patients (13.9%; $p = 0.015$). Significance: Because autoantibodies were more frequent in pediatric patients with new-onset epilepsy of "unknown cause," often with focal epilepsy features, this group of children may benefit most from autoantibody screening and consideration of immune therapy.

Ekizoglu, 2014 Investigation of neuronal autoantibodies in two different focal epilepsy syndromes	Consecutive adult patients diagnosed with focal epilepsy of unknown cause (FEoUC) or mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE-HS), followed for more than 1 year	81 adults	16% (13/81) 5/81: GlyR 4/81: CASPR2 2/81: NMDAR 2/81: : VGKC complex	Psychotic attacks and nonspecific MRI white matter changes showed significant associations in seropositive patients ($p = 0.003$ and $p = 0.03$, respectively). Poor drug-response rates and total seizure counts were also higher in the seropositive patients but without reaching statistical significance. Three seropositive patients with previous epilepsy surgery showed typical histopathologic results for MTLE-HS, but not inflammatory changes. Moreover, some patients harbouring these antibodies partly benefited from immunotherapy. Significance: We detected neuronal antibodies in one sixth of patients with focal epilepsy, GLY-R antibodies being the leading one. Psychosis or nonspecific MRI WMCs were frequent in the seropositive group. Our results suggested that relevant antibodies should be screened for a treatment possibility in these groups.
Wright, 2016	Children (aged 1 month to 16 years) were enrolled into the Dutch Study of Epilepsy in Childhood (DSEC) from four participating centers in The Netherlands between 1988 and 1992. Children with a presumed "acute symptomatic" etiology for their epilepsy were excluded.	178 children	9.5% (17/178) 7/178: NMDAR 4/178: CASPR2 3/178: VGKC complex 2/178: Contactin-2	Seventeen patients (9.5%) were positive for VGKC complex (n = 3), NMDAR (n = 7), CASPR2 (n = 4), and contactin-2 (n = 3), compared to three (3/112; 2.6%) healthy controls (VGKC complex [n = 1], NMDAR [n = 2]; $p = 0.03$; Fisher's exact test). Low levels of neuronal antibodies are present in ~10% of patients with pediatric epilepsy at onset but are not associated with poor long-term outcomes or treatment intractability Antibodies can develop during the course of epilepsy and are not likely to be the sole cause of epilepsy in pediatric patients However, if associated with clinical features suggestive of autoimmune encephalitis, this "secondary inflammation" may be immunotherapy responsive as seen in other antibody-mediated diseases

Tabella 2. Studi sulla prevalenza di autoanticorpi in pazienti con epilessia.

QUANDO SOSPETTARE UN'EPILESSIA AUTOIMMUNE?

Despite increased recent research interest, no clear guidelines exist for the diagnosis or management of autoimmune epilepsy [Dubey, 2015]. Different studies have adopted slightly different operative definitions for autoimmune encephalitis (see next paragraph, "Definizioni operative", and relative Table). Guidelines for the recognition of autoimmune epilepsy have been proposed in children [Suleiman, 2013], based on modified guidelines for the recognition, of suspected autoimmune CNS disorders by Zuliani et al [Zuliani, 2012] (see paragraph "Proposed modified guidelines for the recognition of autoimmune epilepsy in children").

- The features of autoimmune epilepsy include acute or subacute onset of seizures, usually in the context of encephalopathy, and inflammation of the central nervous system on testing cerebrospinal fluid or magnetic resonance imaging. Neuronal antibodies associated with autoimmune encephalitis and seizures in children include NMDAR, voltage-gated potassium channel complex, glycine receptor, c-Aminobutyric acid type A receptor (GABAAR), c-Aminobutyric acid type B receptor (GABABR), and glutamic acid decarboxylase antibodies. These antibodies support the diagnosis of autoimmune epilepsy, but are not essential for diagnosis [Suleiman, 2015].
- Autoimmune epilepsy is increasingly recognized in the spectrum of neurological disorders characterized by detection of neural autoantibodies in serum or spinal fluid and responsiveness to immunotherapy. An autoimmune cause is suspected based on frequent or medically intractable seizures and the presence of at least one neural antibody, inflammatory changes indicated in serum or spinal fluid or on MRI, or a personal or family history of autoimmunity. It is essential that an autoimmune etiology be considered in the initial differential diagnosis of new onset epilepsy, because early immunotherapy assures an optimal outcome for the patient [Greco, 2015].

Definizioni operative di sospetta epilessia autoimmune adottate ed anticorpi identificati in alcune delle maggiori casistiche di pazienti con sospetta epilessia autoimmune

Le casistiche di pazienti con epilessia autoimmune utilizzano generalmente una definizione di epilessia autoimmune basata su una combinazione dei seguenti criteri di inclusione ed esclusione (dettagliati nella tabella sottostante):

Criteri di inclusione:

- Epilepsy as the exclusive or predominant presenting concern [anche se in alcune casistiche questo non appare invece tra i criteri di inclusione]
- Epilepsy with an acute or subacute onset
- Epilepsy that responded well to steroids or immunomodulatory agents
- Autoimmune pathogenesis suspected by the treating physicians based on:
    - Detection of a neural autoantibody in serum or CSF which have been associated with autoimmune encephalitis (any neuronal nuclear/cytoplasmic antibody such as anti-Hu or anti-CRMP-5, any neuronal membrane antibody including anti-VGKC, anti- NMDA-R, anti-GABAB-R, anti-ganglionic AChR, or anti-glutamic acid decarboxylase (GAD) antibody),
    - Inflammatory CSF (leucocytosis, elevated proteins, or CSF-exclusive oligoclonal immunoglobulin bands)
    - MRI characteristics suggesting inflammation (T2 hyperintensities, contrast enhancement on gadolinium studies, and/or restricted diffusion; limbic involvement).

Criteri di esclusione: presenza di altra eziologia che possa spiegare l'epilessia:

- Presence of CSF viral/bacterial/fungal antigens or antibodies or DNA PCR which could explain underlying acute inflammatory brain parenchymal changes,
- Presence of metabolic abnormalities which could have precipitated seizures (severe renal or hepatic failure, malignant hypertension, severe hypo/ hyperglycemia),
- Presence of brain structural lesions such as stroke, tumor, traumatic lesions, heterotopias, neuronal migration anomalies, mesial temporal sclerosis, vascular malformation, abscess or infectious lesion which could have precipitated the presenting seizure
- Presence of genetic backgrounds epilepsies (e.g., SCN1A mutations),
- Possibility of side effects to drugs

CASISTICHE DI PAZIENTI CON SOSPETTA EPILESSIA AUTOIMMUNE			
Autore, anno **Titolo**	**Definizione operativa di sospetta epilessia autoimmune**	**N° ed eta' dei casi**	**% (N°) di casi con auto-anticorpi** **Tipo di autoanticorpi**
Quek, 2012 Autoimmune Epilepsy: Clinical Characteristics and Response to Immunotherapy	Autoimmune epilepsy was defined as (1) epilepsy as the exclusive (n=11) or predominant (n=21) presenting concern and (2) autoimmune pathogenesis suspected by the treating physicians based on detection of a neural autoantibody, inflammatory cerebrospinal fluid (CSF) (leukocytosis or CSF-exclusive oligoclonal immunoglobulin bands), or magnetic resonance imaging (MRI) characteristics suggesting inflammation (T2 hyperintensities, contrast enhancement on gadolinium studies, and/or restricted diffusion).	32 children and adults	91% (29/32) 18/32: VGKC complex (14 Lgi1, 1 Caspr2, and 3 were of unknown specificity) 7/32: GAD 2/32: CRMP-5 1/32: Ma 1/32: NMDAR 1/32: neuronal nicotinic acetylcholine receptor, ganglionic type
Bektaş, 2015 Epilepsy and Autoimmunity in Pediatric Patients	The patients were chosen from among epilepsy patients with undetermined etiology and susceptible autoimmunity who were referred or followed. Patients who met one of the following *inclusion criteria* were included in this study: (1) epilepsy that responded well to steroids or immunomodulatory agents and (2) epilepsy with an acute or subacute (<12 weeks) onset of symptoms whose underlying cause could not be determined. *Exclusion criteria* included neuronal migration anomalies, genetic backgrounds epilepsies (e.g., SCN1A mutations), diabetes (GAD Abs can be elevated), oncologic diseases, metabolic diseases, stroke, rheumatologic disease (e.g., systemic lupus erythematosus [SLE]), and side effects to drugs.	80 children	45% (36/80) 15/80: ANA 3/80: TPO 3/80: Antiphospholipid 1/80: Anticardiolipine 7/80: GAD 2/80: Ma2 2/80: Yo 13/80: VGKC complex

Dubey, 2015 Retrospective case series of the clinical features, management and outcomes of patients with autoimmune epilepsy	*Cases included* were patients presenting with new onset electrographic seizure activity, plus ≥2 of the following: (1) CSF findings consistent with inflammation (elevated CSF protein >50 and/or lymphocytic pleocytosis), (2) brain MRI showing signal changes consistent with limbic encephalitis, (3) autoimmune/paraneoplastic antibodies in serum or CSF which have been associated with autoimmune encephalitis in previous studies (any neuronal nuclear/cytoplasmic antibody such as anti-Hu or anti-CRMP-5, any neuronal membrane antibody including anti-VGKC, anti- NMDA-R, anti-GABAB-R, anti-ganglionic AChR, or anti-glutamic acid decarboxylase (GAD) antibody), (4) new onset seizure responding to immunomodulatory therapies. *Cases were excluded* if there was evidence of another identified cause of the patient's seizures: (1) Presence of CSF viral/bacterial/fungal antigens or antibodies or DNA PCR which could explain underlying acute inflammatory brain parenchymal changes, (2) Presence of metabolic abnormalities which could have precipitated seizures (severe renal or hepatic failure, malignant hypertension, severe hypo/ hyperglycemia), (3) Presence of brain structural lesions such as stroke, tumor, traumatic lesions, heterotopias, mesial temporal sclerosis, vascular malformation, abscess or infectious lesion which could have precipitated the presenting seizure	34 adults	76.5% (26/34) 8/34: VGKC 7/34: NMDAR 4/34: GAD 2/34: GABAB 5/34: Anti-thyroid

Tabella 3. Definizione operativa di epilessia autoimmune utilizzata in alcune recenti casistiche

Proposed modified guidelines for the recognition of autoimmune epilepsy in children (paragrafo e Tabelle tratti da [Suleiman, 2013])

Zuliani et al. proposed guidelines for the recognition, testing, and treatment of suspected autoimmune CNS disorders. They used clinical criteria, supportive features, neuronal antibody testing, and the response to immune therapy to classify patients into categories of definite, probable, and possible NSAS [Zuliani, 2012].

To improve recognition and diagnosis of children with suspected autoimmune epilepsy, we modified the guidelines proposed by Zuliani et al. for identification of children with neuronal surface antibodies syndromes (Table 1). Then, based on antibody testing and the response to immunotherapy (when given), we proposed five categories for classification (in descending order of likelihood of autoimmune epilepsy) including definite, probable, possible, unlikely, or unknown autoimmune epilepsy.

Table 1. Criteria and supportive features to suspect autoimmune epilepsy in children with seizures

The following two clinical criteria are used to suspect autoimmune epilepsy associated with NSAbs and GAD antibodies (both are needed)

1 Acute or subacute (<12 weeks) onset of symptoms.
2 Exclusion of other causes (CNS infection, trauma, toxic, tumor, metabolic, previous CNS disease).

The following supportive features would strengthen the suspicion of autoimmune epilepsy (patients should have at least 1 of the following):

1 The presence of a well-defined clinical syndrome such as NMDAR or limbic encephalitis
2 CNS inflammation manifested by at least one of:
  a CSF pleocytosis (defined as >5 white cells/mm^3) or presence of oligoclonal bands, elevated IgG index, or elevated neopterin (defined as >30 nM)
  b MRI abnormality compatible with an inflammatory or autoimmune encephalitis including increased signal in the mesiotemporal lobe (LE – like syndrome)
  c Inflammatory neuropathology on biopsy
3 History of other antibody mediated condition (e.g., myasthenia gravis), organ specific autoimmunity or other autoimmune disorders.[a]
4 Response to immunotherapy

[a]It is recognized that epilepsy is more common in many autoimmune disorders including multiple sclerosis, systemic lupus erythematosus, type 1 diabetes mellitus (T1DM), celiac disease, and autoimmune thyroid disease (Vincent & Crino, 2011).

Table 2. Classification categories of suspected autoimmune epilepsy in children identified using the criteria and supportive features in Table 1 (Zuliani et al., modified)

Classification categories expressing the likelihood of autoimmune epilepsy based on the presence of NSAbs and GAD Abs and the response to immunotherapy (see Fig. 1):

Definite autoimmune epilepsy is present if:
  Known NSAbs are present in serum or CSF
  AND there is response to immunotherapy
Probable autoimmune epilepsy is present if
  Known NSAbs are present and no immunotherapy responsiveness demonstrated (immunotherapy unsuccessful or not given)
  OR GAD antibodies are present AND there is response to immunotherapy
Possible autoimmune epilepsy is present if known NSAbs are negative and
  GAD antibodies are present and no immunotherapy responsiveness demonstrated (unsuccessful or not given)
  OR GAD antibodies are negative and there is a response to immunotherapy
Unlikely autoimmune epilepsy is present if
  Known NSAbs and GAD are negative and there is no response to immunotherapy
Unknown autoimmune epilepsy[a] is present if
  Known NSAbs and GAD are negative and immunotherapy is not given

[a]Patients in this category may move to a different category if they receive immunotherapy, such as "possible" if they respond or "unlikely" if they did not respond to immunotherapy.

Tabelle tratte da [Suleiman, 2013]

ALTRE OSSERVAZIONI

Le caratteristiche EEG permettono di differenziare epilessia autoimmune da non autoimmune?

Le caratteristiche EEG non consentono di effettuare la distinzione tra epilessie autoimmuni e non autoimmune [Baysal-Kirac, 2015].

In uno studio condotto su 20 pazienti adulti con epilessia e autoanticorpi (in alcuni casi epilessia isolata, in altri in corso di encefalite autoimmune) (anticorpi anti NMDAR, GlyR, Caspr2, VGKC, GAD, Hu, amfifisina), e 21 controlli seronegativi: non differenze significative nell'EEG dei pazienti seropositive e seronegativi. Altri dati emersi da questo studio:

- Onset con stato di male non convulsivo (NCSE) o con stato di male focale motorio: 20% dei pazienti seorpositivi, 0% di quelli seronegativi
- Ritmo theta e delta continuo: in 71% pazienti seropositivi, e in 25% di quelli seronegativi
- Frontal intermittent rhythmic delta activity (FIRDA): in 40% pazienti seropositivi, e in 24% di quelli seronegativi [Baysal-Kirac, 2015]

Efficacia dell'immunoterapia nelle epilessie autoimmuni

Articolo	N° ed eta' dei casi	Tipo di pazienti	Risultati e osservazioni
Quek, 2012#	32 adulti	Exclusive (n=11) or predominant (n=21) seizure presentation in whom an autoimmune etiology was suspected (on the basis of neural autoantibody, inflammatory CSF, or MRI suggesting inflammation) Autoantibodies in 91% (29/32)	After a median interval of 17 months (range, 3–72 months), 22 of 27 (81%) reported improvement post-immunotherapy; 18 were seizure free. The median time from seizure onset to initiating immunotherapy was 4 months for responders and 22 months for nonresponders (P<.05). All voltage-gated potassium channel complex antibody–positive patients reported initial or lasting benefit (P<.05). One voltage-gated potassium channel complex antibody–positive patient was seizure free after thyroid cancer resection; another responded to antiepileptic drug change alone. **When clinical and serological clues suggest an autoimmune basis for medically intractable epilepsy, early-initiated immunotherapy may improve seizure outcome.**
Irani, 2013*#	10 adulti	Facio-brachial dystonic seizures (cognitive impairment in 8/10) Autoantibodies in 100% (10%)	**Facio-brachial dystonic seizures were controlled more effectively with immunotherapy than anti-epileptic drugs (P = 0.006).** Strikingly, in the nine cases who remained anti-epileptic drug refractory for a median of 30 days (range 11–200), the addition of corticosteroids was associated with cessation of faciobrachial dystonic seizures within 1 week in three and within 2 months in six cases. VGKC antibodies persisted in the four cases with relapses of faciobrachial dystonic seizures during corticosteroid withdrawal. Time to recovery of baseline function was positively correlated with time to immunotherapy (r = 0.74; P = 0.03) but not time to anti-epileptic drug administration (r = 0.55; P = 0.10). Of 10 cases, the eight cases who received anti-epileptic drugs (n = 3) or no treatment (n = 5) all developed cognitive impairment. By contrast, the two who did not develop cognitive impairment received immunotherapy to treat their faciobrachial dystonic seizures (P = 0.02). In eight cases without clinical magnetic resonance imaging evidence of hippocampal signal change, cross-sectional volumetric magnetic resonance imaging post-recovery, after accounting for age and head size, revealed cases (n = 8) had smaller brain volumes than healthy controls (n = 13) (P50.001).
Dubey, 2015#	34 adulti	Hospitalized patients who presented predominantly due to seizures with concern for autoimmune etiology Autoantibodies in 76.5% (26/34)	**Time from symptom onset to diagnosis (p < 0.005) and symptom onset to immunomodulation (p < 0.005) was significantly lower among patients who achieved responder rate (RR).** Conclusion: This study highlights certain important clinical and electrographic aspects of autoimmune epilepsy, and the significance of early diagnosis and initiation of immunomodulatory therapy.

Tabella 4. Efficacia dell'immunoterapia rispetto ai farmaci antiepilettici nelle epilessie autoimmune, e beneficio di immunoterapia precoce rispetto a tardiva.

Legenda: *L'immunoterapia e' piu' efficace degli AED nelle epilessie autoimmuni (con significativita' statistica); #Beneficio di immunoterapia early vs late (con significativita' statistica)

Tra gli anticorpi anti antigeni intraneuronali, crisi epilettiche (in presenza o meno di altre manifestazioni) sono state frequentemente descritte anche nei pazienti con anticorpi anti-GAD (associati alle seguenti sindromi cliniche: limbic encephalitis, stiff-person-syndrome; cerebellar ataxia; downbeat nystagmus; palatal tremor; brainstem dysfunction; isolated epilepsy (mostly temporal lobe epilepsy). Epilessia isolata o come prevalente manifestazione e' stata descritta

in pazienti con positivita' per anticorpi anti-GAD [Liimatainen, 2010; Lilleker, 2014; Bektaş, 2015; Akaishi, 2015- (not exhaustive) (children and adults)]

In un recente articolo su anticorpi anti-GAD ed epilessia, viene descritto nessun miglioramento delle crisi nei pazienti trattati con immunoterapia [Lilleker, 2014]. Five patients received immunotherapy. No improvement in seizures was observed in any. One patient with equivocal MRI evidence of hippocampal sclerosis and concordant video EEG and PET scan, achieved 12 months seizure freedom following temporal lobectomy. Conclusions: The relevance of GAD Abs to epilepsy remains uncertain. Our experience does not support the routine use of immunotherapy in patients with epilepsy and GAD Abs [Lilleker, 2014].

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