

Azienda Ospedaliero - Universitaria "A. Meyer"
UOC Neurologia Pediatrica - Università degli Studi di Firenze

Direttore Prof. Renzo Guerrini
Viale Pieraccini 24, 50139 Firenze
Tel. +39 055 5662835/2834

BANDO 2019 FONDAZIONE EPILESSIA LICE

Progetto di Ricerca
Firenze, 03/01//2019

• TITOLO DEL PROGETTO

Studio dei predittori di outcome epilettologico e cognitivo dopo chirurgia dell'epilessia del lobo temporale in età pediatrica ed adulta: implicazioni per la strategia chirurgica.

• RESPONSABILE: dott.ssa Carmen Barba, Azienda Ospedaliera Universitaria Anna Meyer-Università di Firenze, Firenze

• GARANTE SCIENTIFICO: dr Carlo Marras, Ospedale Pediatrico Bambino Gesù, coordinatore Commissione Chirurgia della Lice

• SINOSSI (596/ 600 PAROLE)

Nonostante la chirurgia resettiva produca risultati eccellenti nel trattamento dell'epilessia temporale se comparata con il solo trattamento medico, l'outcome post-operatorio a lungo termine rimane insoddisfacente in una significativa proporzione di pazienti. I risultati chirurgici sono migliori nei bambini, per ragioni in parte riconducibili alle differenti eziologie ed alla possibilità di resezioni più ampie. La possibilità di effettuare una valutazione prognostica dei risultati della chirurgia nel singolo paziente è fortemente limitata dai deboli 'odds ratio' associati ai più noti predittori di outcome e dalla elevata variabilità dei risultati nelle diverse serie chirurgiche. Ancora più contraddittori sono i dati relativi all'outcome cognitivo post-operatorio. Queste considerazioni evidenziano l'importanza di condurre studi multicentrici con una metodologia rigorosa di raccolta dati e di analisi statistica. Presentiamo quindi un progetto retrospettivo multicentrico, che coinvolge i principali centri di chirurgia dell'epilessia italiani allo scopo di: **a)** confrontare l'outcome epilettologico e cognitivo post-operatorio ed i relativi predittori in due popolazioni di pazienti: bambini (<16 anni) ed adulti (≥16 anni) sottoposti a chirurgia dell'epilessia del lobo temporale; e **b)** definire eventuali differenze nelle caratteristiche generali, elettrocliniche e di outcome post-operatorio associate alle due varianti istologiche: displasia corticale focale (FCD)IIIa vs sclerosi ippocampale (HS) isolata, in bambini ed adulti sottoposti a chirurgia dell'epilessia del lobo temporale. In relazione al primo obiettivo, abbiamo inviato a tutti i centri partecipanti un database in cui inserire, per ogni paziente incluso nello studio, le seguenti informazioni: dati clinici (sesso, età, antecedenti, frequenza e tipo di crisi, deficit neurologici e cognitivi pre-operatori), elettrografici (EEG intercritico e critico), di neuroimaging (presenza di lesione e di HS) e chirurgici (data e tipo di intervento, istologico, outcome epilettologico e cognitivo a 2 anni ed all'ultimo follow-up, complicanze, completezza della resezione). Sono già stati raccolti i dati in forma anonimizzata di circa 600 pazienti, che rappresenteranno la base per effettuare una analisi statistica volta a individuare eventuali differenze nelle caratteristiche generali, elettrocliniche, e neuroradiologiche, nell'outcome post-operatorio epilettologico e cognitivo e nei relativi predittori tra adulti e bambini. In prima istanza, per tutte le analisi, suddivideremo la popolazione in studio in adulti e bambini sulla base del cut-off di 16 anni, ampiamente utilizzato in letteratura. Successivamente, valuteremo mediante un'analisi di sensibilità se esiste un cut-off di età diverso e più esplicativo rispetto ai 16 anni di età. In relazione al secondo obiettivo, abbiamo inviato a tutti i centri un database relativo al solo sottogruppo di pazienti (adulti e pediatrici) con diagnosi istologica di HS isolata o associata a FCD IIIa (circa 200 pazienti), per i quali abbiamo richiesto informazioni aggiuntive su

Azienda Ospedaliero - Universitaria "A. Meyer"
UOC Neurologia Pediatrica - Università degli Studi di Firenze

Direttore Prof. Renzo Guerrini
Viale Pieraccini 24, 50139 Firenze
Tel. +39 055 5662835/2834

semeiologia delle crisi, migliore caratterizzazione del quadro di RM pre-operatorio (blurring, ipotrofia del polo temporale, etc.), e definizione del tipo della HS. Effettueremo una analisi statistica volta a definire eventuali differenze nelle caratteristiche generali, elettrocliniche e neuroradiologiche, nell'outcome post-operatorio epilettologico e cognitivo e nei relativi predittori tra FCDIIIa ed HS isolata. La definizione dei predittori di outcome potrebbe contribuire a migliorare i criteri di selezione dei candidati alla chirurgia dell'epilessia del lobo temporale e ad individuare quelli in cui è possibile sospendere la terapia dopo chirurgia, con conseguente possibile miglioramento delle capacità cognitive. Inoltre, l'identificazione di un cut-off di età per il verificarsi di eventuali differenze di outcome, potrebbe fornire indicazioni relative ad una finestra di età oltre la quale l'intervento può risultare meno efficace. La definizione delle caratteristiche cliniche e chirurgiche specifiche della FCD IIIa rispetto alla HS isolata potrebbe contribuire a individuarne eventuali differenti meccanismi eziopatogenetici ed influenzare il planning chirurgico nei pazienti con epilessia temporo-mesiale, ad esempio ottimizzando l'estensione della resezione e riducendo il rischio di deficit di memoria o linguaggio.

• RAZIONALE (491/ 500 PAROLE)

Nell'ambito del trattamento chirurgico dell'epilessia, il lobo temporale appare coinvolto nel 71.9% delle procedure (Blumcke et al., N Engl J Med 2017;377:1648-56), anche se con differenze significative tra adulti e bambini. Negli adulti, gli interventi sul lobo temporale rappresentano le procedure più frequenti, mentre sono rari gli interventi multilobari o emisferici (Ryvlin et al., Lancet Neurol 2014;13:1114-26). Al contrario, una survey condotta in USA, Europa, ed Australia (Harvey et al., Epilepsia 2008; 49: 146–55) ha mostrato che nei bambini le procedure multilobari ed emisferiche sono le più frequenti, mentre il lobo temporale è coinvolto solo nel 23% dei casi. Inoltre, negli adulti l'istologia più rappresentata è la sclerosi ippocampale associata o meno a displasia, la cosiddetta FCD IIIa (Blumcke et al., Epilepsia 2011;52:158-74), mentre nei bambini sono più frequenti i tumori e le malformazioni corticali (Blumcke et al., N Engl J Med 2017;377:1648-56).

Le differenze tra popolazione adulta e pediatrica si riflettono anche negli studi di outcome. Mentre nei pazienti adulti la possibilità di ottenere una prolungata libertà da crisi dopo chirurgia dell'epilessia del lobo temporale rimane subottimale (De Tisi et al., Lancet 2011; 378: 1388–95; West et al., Cochrane Database Syst Rev 2015; 7: CD010541), l'outcome è migliore nei bambini, per ragioni in parte riconducibili alle differenti eziologie ed alla possibilità di resezioni più ampie (Spencer & Huh, Lancet Neurol 2008; 7: 525–37). In generale, la nostra capacità di predire l'outcome chirurgico nel singolo paziente rimane ancora limitata dai deboli 'odds ratio' associati ai più noti predittori di insuccesso (Tonini et al., Epilepsy Res 2004; 62: 75–87). Studi recenti hanno messo in dubbio il ruolo della evidenza di sclerosi ippocampale alla RM encefalo come fattore predittivo di outcome favorevole, mentre appare confermato il ruolo negativo del residuo ippocampale post-operatorio, a sottolineare la rilevanza del dato istologico (McIntosh et al., Epilepsia 2012; 53:970–78; Blumcke et al., N Engl J Med 2017;377:1648-56). Deleo, Garbelli e colleghi (Epilepsia 2016;57:306-15) hanno evidenziato come il tipo di sclerosi ippocampale isolata o associata ad altre lesioni possa predire il rischio di recidiva delle crisi dopo chirurgia del lobo temporale.

Ancora più contrastanti appaiono poi i dati relativi all'outcome cognitivo post-operatorio (Van Schooneveld & Braun, Brain Dev 2013;35:721–9). La relativa rarità della popolazione in studio, la mancanza di protocolli condivisi e di gruppi di controllo rendono problematico il panorama sperimentale, anche se l'evidenza recente suggerisce che le performance cognitive possano migliorare dopo chirurgia, soprattutto in caso di sospensione dei farmaci (Moosa & Wyllie, Semin Pediatr Neurol

Azienda Ospedaliero - Universitaria "A. Meyer"
UOC Neurologia Pediatrica - Università degli Studi di Firenze

Direttore Prof. Renzo Guerrini
Viale Pieraccini 24, 50139 Firenze
Tel. +39 055 5662835/2834

2017;24:331-39). Inoltre, mentre appare dubbio il ruolo della eziologia, la libertà da crisi e la breve durata di malattia sembrano fattori predittivi significativi di stabilità o miglioramento cognitivo dopo chirurgia (Freitag & Tuxhorn, *Epilepsia* 2005;46:561-7; Sibilis et al., *Epilepsy Behav* 2017;73:23-30). Il counseling ai pazienti è reso ancora più difficile dalla elevata variabilità dei risultati nelle diverse serie chirurgiche, da cui l'importanza di condurre studi multicentrici con una rigorosa metodologia di raccolta dati e di analisi statistica.

• **OBIETTIVI (83/ 200 PAROLE)**

Obiettivo primario: confrontare l'outcome epilettologico e cognitivo post-operatorio ed i relativi predittori in due popolazioni di pazienti: bambini (<16 anni all'intervento) ed adulti (≥16 anni all'intervento) sottoposti a chirurgia dell'epilessia del lobo temporale in otto centri di chirurgia dell'epilessia italiani.

Obiettivo secondario: definire eventuali differenze nelle caratteristiche generali, elettrocliniche e di outcome epilettologico e cognitivo post-operatorio associate alle due varianti istologiche: FCD IIIa vs sclerosi ippocampale isolata nei pazienti sottoposti a chirurgia dell'epilessia del lobo temporale in otto centri di chirurgia dell'epilessia italiani.

• **PAROLE CHIAVE (MAX 5)**

Epilessia del lobo temporale, chirurgia dell'epilessia, outcome post-operatorio, età all'intervento, sclerosi dell'ippocampo

• **METODI (989/ 1000 PAROLE)**

Disegno dello studio: studio retrospettivo multicentrico nazionale

Centro ospitante: Centro Eccellenza Neuroscienze, AOU Meyer, Firenze

Il centro di eccellenza Neuroscienze dell'AOU Meyer si occupa della diagnosi e cura delle patologie neurologiche in età pediatrica, ed in particolare delle epilessie rare e complesse. Alla struttura afferiscono due unità sanitarie e di ricerca ad alta specializzazione, laboratori in ambito neurofisiologico e genetico ed un servizio di neuropsicologia dedicato all'età evolutiva. Dal 2007 è attivo un programma di chirurgia dell'epilessia che prevede un bilancio prechirurgico non invasivo ed invasivo e dal 2016 anche la possibilità di effettuare impianti di elettrodi intracerebrali robot-assistiti. Sono stati sviluppati database dedicati per la chirurgia dell'epilessia e la genetica delle epilessie rare e complesse. Il centro di Eccellenza Neuroscienze ha condotto o partecipato a numerosi progetti di ricerca in ambito nazionale ed europeo relativamente alle epilessie rare e complesse. In particolare, il Responsabile di questo progetto è stato coordinatore di un progetto di Ricerca Finalizzata in ambito di chirurgia dell'epilessia (RF-2010-2309954, 2012-2016) e responsabile di WP per il progetto europeo DESIRE (grant agreement 602531, 2013-2018).

Centri partecipanti

Centro Chirurgia dell'Epilessia 'Claudio Munari', ASST Grande Ospedale Metropolitano Niguarda, Milano

Epilettologia Clinica e Neurofisiologia Sperimentale, IRCCS Besta, Milano

IRCCS Neuromed, Pozzilli, Isernia

Dipartimento Neuroscienze, Ospedale Pediatrico Bambino Gesù, Roma

Neuropsichiatria Infantile, Azienda Ospedaliera Universitaria G Salesi, Ancona

Neuropsichiatria Infantile, Università Cattolica del Sacro Cuore, Roma

UOC Neurochirurgia, IRCCS Istituto Giannina Gaslini, Genova

Azienda Ospedaliero - Universitaria "A. Meyer"
UOC Neurologia Pediatrica - Università degli Studi di Firenze

Direttore Prof. Renzo Guerrini
Viale Pieraccini 24, 50139 Firenze
Tel. +39 055 5662835/2834

I centri partecipanti, tutti con dimostrato expertise nell'ambito della chirurgia dell'epilessia, garantiscono la possibilità di reclutare un numero elevato di pazienti sia adulti che pediatrici. L'analisi statistica sarà effettuata con il supporto del Dipartimento di Statistica dell'Università di Firenze.

Criteri di inclusione:

- a) pazienti sottoposti ad intervento di chirurgia dell'epilessia del lobo temporale nei centri partecipanti tra Gennaio 2011 e Dicembre 2016, con almeno 2 anni di follow-up.
- b) Istologia, EEG e Risonanza Magnetica encefalo pre- e post-operatori disponibili per revisione.

Criteri di esclusione:

- a) pazienti sottoposti ad interventi con estensione extratemporale della resezione.

Studio sperimentale: obiettivo primario

Abbiamo inviato a tutti i centri partecipanti un database redatto in forma di foglio elettronico, con la richiesta di riempire un record per ciascun caso che soddisfacesse i criteri di inclusione. Le informazioni richieste, organizzate per codici predeterminati o per testo libero, includevano: dati clinici (sesso, età, antecedenti, frequenza e tipo di crisi, deficit neurologici e cognitivi progressi), elettrografici (EEG intercritico e critico), di neuroimaging (presenza di lesione e/o di HS alla RM preoperatoria) e chirurgici (data e tipo di intervento, istologico, outcome epilettologico e cognitivo a 2 anni ed all'ultimo follow-up, complicanze neurologiche o chirurgiche, completezza della resezione). Sono stati raccolti retrospettivamente ed in forma anonimizzata i dati di circa 600 pazienti che rappresenteranno la base per effettuare una analisi statistica volta a definire eventuali differenze nelle caratteristiche generali, elettrocliniche e neuroradiologiche, nell'outcome epilettologico e cognitivo post-operatorio e nei relativi predittori tra adulti e bambini. Tutti i dati raccolti saranno analizzati con tecniche di statistica descrittiva al fine di caratterizzare il campione in studio. Saranno utilizzati appropriati test d'ipotesi (test sull'uguaglianza delle medie e delle proporzioni) per valutare le differenze nei due gruppi (bambini e adulti) per tutti gli outcome e le variabili di interesse. Inoltre, per tener conto della natura gerarchica dei dati (i pazienti che appartengono allo stesso centro possono presentare caratteristiche comuni), e per valutare la presenza di potenziali confondenti e identificare eventuali interazioni, saranno effettuate analisi di regressione multivariata multilivello, dove il livello sarà definito dall'appartenenza al centro. In prima istanza, per tutte le analisi, suddivideremo la popolazione in studio in adulti e bambini sulla base del cut-off di età all'intervento di 16 anni, ampiamente utilizzato in letteratura. Successivamente, valuteremo mediante un'analisi di sensibilità se esiste un cut-off di età diverso e più esplicativo rispetto ai 16 anni di età.

Studio sperimentale: obiettivo secondario

Abbiamo inviato ai centri partecipanti un secondo database, che includeva solo il sottogruppo di pazienti adulti e pediatrici con diagnosi istologica di HS isolata o FCD IIIa (circa 200 pazienti), per i quali abbiamo richiesto, sempre in forma anonimizzata, informazioni aggiuntive relative a semeiologia delle crisi, migliore caratterizzazione del quadro di RM pre-operatorio (blurring e/o ipotrofia del polo temporale, etc), e indicazione del sottotipo istologico della HS (Blumcke et al, Epilepsia 2013;54:1315-29).

Effettueremo una analisi statistica volta a definire eventuali differenze nelle caratteristiche generali, elettrocliniche e neuroradiologiche, nell'outcome epilettologico e cognitivo post-operatorio e nei relativi predittori tra FCD IIIa e HS isolata, anche in rapporto alle diverse fasce di età. Per tener conto della natura gerarchica dei dati, valutare la presenza di potenziali confondenti ed identificare eventuali interazioni, saranno effettuate analisi di regressione multivariata multilivello, dove il livello sarà definito dall'appartenenza al centro.

Azienda Ospedaliero - Universitaria "A. Meyer"
UOC Neurologia Pediatrica - Università degli Studi di Firenze

Direttore Prof. Renzo Guerrini
Viale Pieraccini 24, 50139 Firenze
Tel. +39 055 5662835/2834

I dati inviati dai centri saranno raccolti in un database centralizzato presso AOU Meyer; responsabile protezione dati: dott.ssa Carmen Barba.

Cronologia dello studio

M1: kick-off meeting con i centri partecipanti, completamento procedure comitato etico (già avviato presso AOU Meyer)

M2-5: completamento raccolta dati, analisi statistiche preliminari, meeting per valutazione dati dubbi di neuroimaging o istologia

M6-8: completamento analisi statistica; meeting con i centri per discussione finale dei risultati

M9-12: preparazione manoscritto (indicazione della Fondazione nella pubblicazione) e disseminazione attraverso convegni regionali e nazionali (referente disseminazione: dott.ssa Carmen Barba)

Milestone del progetto

M6: analisi preliminare dei dati e relazione intermedia

M12: completamento analisi dei dati, preparazione manoscritto e relazione finale

Analisi dei rischi dello studio

Per quanto riguarda l'obiettivo primario, esiste una bassa possibilità che le analisi statistiche non determinino risultati statisticamente significativi, nonostante l'elevato numero di pazienti già inclusi nello studio. In questo caso utilizzeremo metodiche statistiche alternative. Per quanto riguarda l'obiettivo secondario, i dati raccolti potrebbero essere insufficienti in relazione alla disponibilità di un dato istopatologico precisamente definito in base ai criteri della classificazione ILAE, a causa delle differenze di approccio allo studio dell'ippocampo tra i vari centri. In questo caso, sarà effettuato un incontro tra neuropatologi afferenti ai vari centri, già in contatto tramite la Commissione Chirurgia della LICE, per la revisione dei casi dubbi.

• **RISULTATI ATTESI (392/ 400 PAROLE)**

1) La definizione dei predittori di outcome potrebbe contribuire a ottimizzare i criteri di selezione dei candidati alla chirurgia dell'epilessia del lobo temporale. La definizione di un profilo prognostico individualizzato potrebbe contribuire alla gestione post-operatoria della terapia farmacologica, la cui sospensione potrebbe preludere al miglioramento delle performance cognitive. Inoltre, l'identificazione di un cut-off di età per il verificarsi di eventuali differenze di outcome post-operatorio e quindi di una finestra di età oltre la quale l'intervento risulta meno efficace, potrebbe fornire indicazioni importanti per l'ottimizzazione del timing chirurgico.

2) La migliore definizione delle caratteristiche cliniche e chirurgiche associate alla FCD IIIa rispetto alla HS isolata potrebbe contribuire a individuare eventuali differenze nei meccanismi eziopatogenetici e ad influenzare il planning chirurgico nei pazienti con epilessia temporo-mesiale, permettendo, ad esempio, di meglio definire l'estensione della resezione e ridurre il rischio di deficit di memoria o linguaggio.

Il presente progetto ha un approccio innovativo rispetto agli studi precedenti per le seguenti ragioni:

a) è uno studio multicentrico che coinvolge tutti i principali centri di chirurgia dell'epilessia di una unica nazione, che operano secondo PDTA e raccomandazioni nazionali ed internazionali condivise. Questo garantirà la possibilità di reclutare un elevato numero di pazienti adulti e pediatrici con sufficiente omogeneità nella raccolta dati; b) saranno confrontate popolazione adulta e pediatrica in modo da definire in maniera precisa il ruolo di predittori di outcome come l'istologia e l'età all'intervento. Questo potrebbe contribuire ad influenzare le priorità di selezione dei candidati chirurgici dei centri partecipanti, attraverso l'identificazione precoce dei pazienti con maggiore probabilità di guarigione dalle crisi e di miglioramento delle capacità cognitive dopo chirurgia. Inoltre,

Azienda Ospedaliero - Universitaria "A. Meyer"
UOC Neurologia Pediatrica - Università degli Studi di Firenze

Direttore Prof. Renzo Guerrini
Viale Pieraccini 24, 50139 Firenze
Tel. +39 055 5662835/2834

potrebbe emergere il profilo di pazienti con minori possibilità di beneficio post-chirurgico, o non suscettibili di trattamento curativo. Di conseguenza, questi ultimi, che andrebbero esclusi da indagini neurofisiologiche o di neuroimaging costose e time-consuming, potrebbero essere avviati precocemente alla chirurgia palliativa o ad approfondimenti diagnostici in ambiti diversi, ad esempio di tipo genetico. In generale, i risultati ottenuti potrebbero migliorare il counseling ai pazienti ed alle famiglie e, a lungo termine, incrementare il numero di pazienti operati in età evolutiva. Il reclutamento già avvenuto di 600 pazienti, il supporto di un centro di alta specializzazione per l'analisi statistica, l'esistenza di precedenti collaborazioni di ricerca tra i centri partecipanti attraverso la Commissione Chirurgia della LICE, rappresentano garanzie di successo dello studio nei tempi previsti dal Bando.

• PIANO ECONOMICO RELATIVO AL PROGETTO IN TOTO

Totale richiesto: 15000 euro così suddivisi:

A- (attrezzature e programmi), **3000 euro (20% spese del progetto)**: 1 computer portatile per gestione database ed analisi statistica; 1 programma per gestione dati (eventuali licenze aggiuntive in base ad esigenze del progetto);

B- (personale non strutturato) **9000 euro (60% spese del progetto)**: fondi da destinare ai centri partecipanti per la acquisizione di personale per attività di ricerca connesse al progetto (gestione database e raccolta dati) in misura commisurata al numero di pazienti reclutati;

C- 0

D (spese correnti)- **1500 euro (10% budget totale)**: spese correnti AOU Meyer

E- (Altre spese gestionali) **1500 euro (10% budget totale)**: missioni e partecipazioni a congressi da parte di ricercatori coinvolti nel progetto, meeting tra i partner, spese per pubblicazione manoscritti (figure, open access).

• Specificare in modo dettagliato le eventuali collaborazioni e cofinanziamenti

Il progetto al momento non prevede collaborazioni internazionali o cofinanziamenti. Tuttavia, dopo aver concluso questo primo studio multicentrico italiano, ci proponiamo di estendere il progetto a livello europeo tramite l'ERN per le epilessie rare e complesse: EpiCare di cui il Responsabile scientifico, dott.ssa Carmen Barba è membro dello steering committee e del WP Research.

Azienda Ospedaliero - Universitaria "A. Meyer"
UOC Neurologia Pediatrica - Università degli Studi di Firenze
Viale Pieraccini 24, 50139 Firenze
Tel. +39 055 5662835/2834

Project

FONDAZIONE LICE

Firenze, 03/01/2019

TITLE

Analysis of predictors of seizure and cognitive outcome after temporal lobe epilepsy surgery in children and adults: implications for surgical strategy.

PI: dr Carmen Barba, Children's Hospital Anna Meyer-University of Florence, Firenze

SCIENTIFIC GUARANTOR: dr Carlo Marras, Coordinator, Epilepsy Surgery Commission, Italian League against Epilepsy

SUMMARY (531/600 WORDS)

Resective surgery has proved to be an effective treatment option for drug-resistant temporal lobe epilepsy (TLE) compared to medical treatment only. However, the proportion of adult patients enjoying long-term post-operative seizure freedom remains suboptimal. Better outcomes were reported in children, possibly owing to different etiologies and the possibility to carry out more extended resections. Individual prediction of seizure relapse is hampered by the weak odds ratios associated with known predictors of TLE surgery and by the level of unexplained heterogeneity across epilepsy surgery series. Available evidence about post-operative cognitive outcome is even more controversial. These issues highlight the need for multicenter studies using rigorous experimental protocols and robust statistical methods.

This retrospective multicenter study has involved the main Italian epilepsy surgery centers with the following aims: **a)** to compare post-operative seizure and cognitive outcomes and their predictors in children (<16 years) and adults (≥16 years) submitted to TLE surgery; and **b)** to identify possible differences in the general and electroclinical features and post-operative outcomes associated with two histologic variants: Focal Cortical Dysplasia (FCD) IIIa and isolated hippocampal sclerosis (HS). Concerning the primary aim, we asked all participating centers to fill in a database including the following information from each patient included in the study: general characteristics (sex, age at surgery, antecedents, seizure frequency and type, pre-existing neurological and cognitive deficits), ictal and interictal EEG, neuroimaging (MRI visible lesion and HS) and surgical findings (type of surgery, histology, seizure and cognitive outcome 2 years after surgery and at last follow-up, complications, completeness of the resection). We have already collected anonymized information from about 600 patients. Based on this data collection, we will carry out a statistical analysis aimed at defining possible differences of general, electroclinical and neuroimaging features, post-operative seizure and cognitive outcomes and their predictors between adults and children. For all analyses, we will first distinguish adults and children based on a cut-off age of 16 years at surgery. Subsequently, we will test through sensitivity analyses whether a different and more explanatory cut-off age exists. Concerning the secondary aim, we sent to all participating centers a database including only the subgroup of patients with either isolated HS or FCD IIIa (about 200 patients) to be filled in with additional information on seizure semeiology, neuroimaging features (i.e. temporal pole blurring, hypotrophy, etc.), and histology characterization of HS. We will carry out a statistical analysis to define possible differences of general, electroclinical and neuroimaging features, post-operative seizure and cognitive outcomes and their predictors between FCD IIIa and isolated HS.

The identification of outcome predictors might contribute to improve the selection criteria of candidates to TLE surgery and identify those in which drug withdrawal could be achieved, with

Azienda Ospedaliero - Universitaria "A. Meyer"
UOC Neurologia Pediatrica - Università degli Studi di Firenze
Viale Pieraccini 24, 50139 Firenze
Tel. +39 055 5662835/2834

subsequent possible improvement of cognitive performances. In addition, the definition of a cut-off age for the occurrence of possible differences of outcome, might indicate a temporal window beyond which surgery is less effective. The better definition of the clinical and surgical features specifically associated with FCD IIIa in comparison to isolated HS might contribute to identify possible different etiopathogenetic mechanisms, and influence surgical planning in patients with temporo-mesial epilepsy, i.e. optimizing the extent of the resection and reducing the risk for post-operative memory or language deficits.

BACKGROUND (488/ 500 WORDS)

In the context of the surgical treatment of epilepsy, the temporal lobe is involved in 71.9% of operations (Blumcke et al., *N Engl J Med* 2017;377:1648-56), with significant differences between adults and children. In adults, most procedures are temporal lobe resections, with very few multilobar procedures or hemispherectomies (Ryvlin et al., *Lancet Neurol* 2014;13:1114-26). By contrast, a survey of pediatric epilepsy surgery in the USA, Europe, and Australia showed most procedures to be multilobar or hemispheric, with temporal lobe resections accounting for only 23% of cases (Harvey et al., *Epilepsia* 2008; 49: 146–55). Hippocampal sclerosis (HS) associated or not with focal cortical dysplasia (FCD) IIIa is the most common histopathological diagnosis among adults, while tumors and malformations of cortical development are the most common diagnoses among children (Blumcke et al., *N Engl J Med* 2017;377:1648-56).

Disparities between adult and pediatric surgical candidates are observed also in the outcome studies. The proportion of adult patients enjoying long-term post-operative seizure freedom following temporal lobe epilepsy (TLE) surgery remains suboptimal (De Tisi et al., *Lancet* 2011; 378: 1388–95; West et al., *Cochrane Database Syst Rev* 2015; 7: CD010541), while better outcomes were reported in children, possibly owing to different etiologies and the possibility to carry out more extended resections (Spencer & Huh, *Lancet Neurol* 2008; 7: 525–37).

In general, individual prediction of seizure relapse is hampered by the weak odds ratios associated with known predictors of TLE surgery (Tonini et al., *Epilepsy Res* 2004; 62: 75–87). Some recent studies have challenged the classic view that MRI signs of hippocampal sclerosis are associated with greater chances of post-operative seizure freedom following anterior temporal lobectomy, while confirming hippocampal remnant to be one the main predictors of surgical failures (McIntosh et al., *Epilepsia* 2012; 53:970–78; Blumcke et al., *N Engl J Med* 2017;377:1648-56). These findings highlight the relevance of histology in predicting epilepsy surgery outcome. Accordingly, Deleo, Garbelli and colleagues (*Epilepsia* 2016;57:306-15) suggested that HS subtypes and associated pathologies may predict the risk of seizure recurrence after TLE surgery.

Available evidence about post-operative cognitive outcome is even more controversial (Van Schooneveld & Braun, *Brain Dev* 2013;35:721–9). The small sample size, the flaws in the methodology and the lack of adequate control groups have precluded drawing firm evidence-based conclusions on post-operative neuropsychological changes. However, recent studies have suggested the cognitive performances can improve after epilepsy surgery, especially in case of antiepileptic drug withdrawal (Moosa & Wyllie, *Semin Pediatr Neurol* 2017;24:331-39). In addition, the role of etiology is still matter of debate, while seizure freedom and short duration of epilepsy seem to be associated with improved or stable cognitive function after surgery (Freitag & Tuxhorn, *Epilepsia* 2005;46:561-7; Sibilia et al., *Epilepsy Behav* 2017;73:23-30).

The level of unexplained heterogeneity across epilepsy surgery series continues to pose a

Azienda Ospedaliero - Universitaria "A. Meyer"
UOC Neurologia Pediatrica - Università degli Studi di Firenze
Viale Pieraccini 24, 50139 Firenze
Tel. +39 055 5662835/2834

difficult challenge for counseling patients and families on post-operative seizure and cognitive outcome, thus highlighting the need for multicenter studies using rigorous experimental protocols and robust statistical methods.

Aims (68/200 words)

Primary aim: to compare post-operative seizure and cognitive outcomes and their predictors in children (<16 years at surgery) and adults (≥ 16 years at surgery) submitted to TLE surgery in eight Italian epilepsy surgery centers.

Secondary Aim: to identify possible differences in the general and electroclinical features and post-operative seizure and cognitive outcomes associated with two histologic variants: FCD IIIa and isolated HS in eight Italian epilepsy surgery centers.

KEYWORDS (max 5)

Temporal lobe epilepsy, epilepsy surgery, post-operative outcome, age at surgery, hippocampal sclerosis

METHODS (931/1000 words)

Study Design: retrospective multicenter nationwide study

Host center: Neuroscience Department, Children's Hospital Anna Meyer, Firenze

The Neuroscience Department at Children's Hospital Meyer provides multidisciplinary care for children with neurological disorders, in particular with rare and complex epilepsies. It includes two pediatric neurology and psychiatry inpatient wards, neurophysiology and neurogenetics laboratories and a dedicated pediatric neuropsychology team. Since 2007, an epilepsy surgery program has been established including invasive and non-invasive presurgical evaluation protocols; navigated and robotically-assisted neurosurgery procedures have been set up for the epilepsy treatment. Dedicated databases are available for the epilepsy surgery program and genetics of complex and rare epilepsies. The Neuroscience Department at Children's Hospital Meyer has participated to or led several national and European projects on the topic of rare and complex epilepsies. In particular, the PI has led a multicenter project on the topic of epilepsy surgery funded by the Italian Ministry of Health and Tuscany Region (RF-2010-2309954, 2012-2016) and she has been WP coordinator of the project DESIRE funded by the European FP7 Programme (grant agreement 602531, 2013-2018).

Participating Centers

Epilepsy Surgery Center 'Claudio Munari', ASST Grande Ospedale Metropolitano Niguarda, Milano
Clinical Epileptology and Experimental Neurophysiology Unit, IRCCS Besta, Milano
IRCCS Neuromed, Pozzilli, Isernia

Neuroscience Department, Ospedale Pediatrico Bambino Gesù, Roma

Child Neurology and Psychiatry Unit, Azienda Ospedaliera Universitaria G. Salesi, Ancona

Child Neurology and Psychiatry Unit, Università Cattolica del Sacro Cuore, Roma

Neurosurgery Unit, IRCCS Istituto Giannina Gaslini, Genova

The participating centers, which all have a well-known expertise in the field of epilepsy surgery, guarantee the possibility to recruit a great number of adult and pediatric surgical candidates.

Statistical analyses will be carried out with the help of the Department of Statistics, University of Florence.

Inclusion criteria:

Azienda Ospedaliero - Universitaria "A. Meyer"
UOC Neurologia Pediatrica - Università degli Studi di Firenze
Viale Pieraccini 24, 50139 Firenze
Tel. +39 055 5662835/2834

- a) TLE surgery between January 2011 and December 2016 at the participating centers, with at least 2 years of follow-up
- b) Histology, pre and post-operative EEG and brain MRI available for review

Exclusion criteria:

- a) Surgery extended beyond the limits of the temporal lobe

Experimental design: primary aim

We sent a database for all participating centers to fill in with the following information from each patient included in the study: general characteristics (sex, age at surgery, antecedents, seizure frequency and type, previous neurological and cognitive deficits), ictal and interictal EEG, neuroimaging (possible MRI visible lesion and HS) and surgical findings (type of surgery, histology, seizure and cognitive outcome 2 years after surgery and at last follow-up, complications, completeness of the resection).

We have already collected information on about 600 patients. Based on this, we will carry out a statistical analysis aimed at defining possible differences of general, electroclinical and neuroimaging features, post-operative seizure and cognitive outcomes and their predictors between adults and children. In order to characterize the sample, we will analyze all collected data using descriptive statistics. We will focus on hypothesis testing (equality test for means and proportion) in order to assess possible differences between the two groups (children and adults) for all outcomes and variables of interest. In addition, to take in account the hierarchical nature of the data (patients belonging to the same center can share common characteristics) and to assess the presence of potential confounders and identify possible interactions, we will carry out multilevel multivariate regression analyses, where the level will be defined by the center to which data belong. For all analyses, we will first distinguish adults and children based on a cut-off age of 16 years at surgery, which has been largely utilized in previous studies. Then, we will test through sensitivity analyses whether a different and more explanatory cut-off age exists.

Experimental design: secondary aim

We asked all participating centers to fill in a database including only the subgroup of patients with either isolated HS or FCD IIIa with additional information on seizure semeiology, neuroimaging features (i.e. temporal pole blurring, hypotrophy, etc), and histology characterization of HS (Blumcke et al, Epilepsia 2013;54:1315-29).

We will carry out a statistical analysis aimed at defining possible differences of general, electroclinical and neuroimaging features, post-operative seizure and cognitive outcomes and their predictors between FCD IIIa and isolated HS. In order to take into account the hierarchical nature of the data (patients belonging to the same center can share common characteristics) and to assess the presence of potential confounders and identify possible interactions, we will carry out multilevel multivariate regression analyses, where the level will be defined by the center to which data belong.

All collected data will be stored in a centralized database at Meyer Hospital. Dr. Carmen Barba will be responsible for data protection.

Timeline

M1: kick-off meeting with the participating centers, ethics committee approval (ongoing at Meyer Hospital)

M2-5: data collection completed, preliminary statistical analysis, meeting with the participating centers to evaluate doubtful neuroimaging and histology findings.

M6-8: statistical analysis completed; meeting with the participating centers to discuss final results

Azienda Ospedaliero - Universitaria "A. Meyer"
UOC Neurologia Pediatrica - Università degli Studi di Firenze
Viale Pieraccini 24, 50139 Firenze
Tel. +39 055 5662835/2834

M9-12: manuscript preparation (acknowledgment of the Fondazione Lince funding), dissemination through local and national meetings (responsible for dissemination: dr Carmen Barba)

Milestones

M6: preliminary statistical analyses and intermediate report

M12: statistical analyses completed, manuscript preparation and final report

Risk analysis

Concerning the primary aim, there is a low possibility that our results will not reach statistical significance, despite the large amount of data already collected. In this case, we will utilize alternative statistical methods. Concerning the secondary aim, histopathology findings might be insufficient for a robust analysis due to the observer-related variability in the approach to the study of hippocampus in the different centers. In this case, a meeting will be organized through the Commission of Epilepsy Surgery, in order to allow pathologists from different centers to review doubtful cases.

EXPECTED RESULTS (344/400)

1) The definition of the predictors of post-operative seizure and cognitive outcome might contribute to improve the selection criteria of candidates to TLE surgery and identify those in which drug withdrawal could be achieved, with subsequent possible improvement of cognitive performances (Boshuisen et al, 2015). In addition, the definition of a cut-off age for the occurrence of possible differences of outcome, might indicate a temporal window beyond which surgery is less effective and possibly contribute to optimize the timing of intervention.

2) The better definition of clinical and surgical features associated with FCD IIIa in comparison to isolated HS might contribute to identify possible different etiopathogenetic mechanisms and influence surgical planning in patients with temporo-mesial epilepsy i.e. optimizing the extent of the resection and reducing the risk for post-operative memory or language deficits.

The innovative approach of the present project is related to the following issues:

a) this multicenter study involves the main Italian epilepsy surgery centers, all of which follow national and international recommendations and consensus in their clinical practice. This will help including in the study a great number of adults and children with TLE while ensuring adequate homogeneity in data collection; b) we will compare adult and pediatric patients in order to precisely identify post-operative outcome predictors such as histology and age at surgery. This might influence the selection criteria of surgical candidates in the participating centers, through early identification of patients with higher probability to be cured and to improve cognitive function after surgery. On the other side, it would be possible to early identify patients unsuitable for surgery, thus avoiding expensive and time-consuming neurophysiology and neuroimaging investigations, and opt for palliative surgery or alternative investigations, such as genetic analyses.

In general, our results might improve counseling to patients and families and, in the long-term, increase the number of patients operated during childhood.

The recruitment of 600 patients, the availability of a highly specialized center for statistical analysis, previous collaborations between the participating centers through the Commission of Epilepsy Surgery, will guarantee success for this study during the planned period of funding.

• **BUDGET**

Total budget: 15000 euro subdivided as follows:

Azienda Ospedaliero - Universitaria "A. Meyer"
UOC Neurologia Pediatrica - Università degli Studi di Firenze
Viale Pieraccini 24, 50139 Firenze
Tel. +39 055 5662835/2834

A- 3000 euro (20% total budget): 1 laptop for the database management system and to carry out the statistical analyses; 1 software for the database management system (possible additional licenses based on the project's needs)

B- 9000 euro (60% total budget): funding for the participating centers to hire personnel for collecting data and managing the local database, according to the number of recruited patients in each center.

C- 0

D - 1500 euro (10% total budget): overheads for Children's Hospital Meyer

E- 1500 euro (10% total budget): meetings between partners, dissemination through participation to medical conferences, publications (figures, open access).

• **COLLABORATIONS AND CO-FUNDING**

This project does not include international collaborations and partnerships or co-funding at this stage. However, after this first multicenter Italian study, we aim to develop the project at the European level through the ERN for rare and complex epilepsies: EpiCARE, of which the PI, dr Carmen Barba, is member of the steering committee and of the WP Research.

Azienda Ospedaliero - Universitaria "A. Meyer"
UOC Neurologia Pediatrica - Università degli Studi di Firenze
Viale Pieraccini 24, 50139 Firenze
Tel. +39 055 5662835/2834

Project

FONDAZIONE LICE

Firenze, 03/01/2019

TITLE

Analysis of predictors of seizure and cognitive outcome after temporal lobe epilepsy surgery in children and adults: implications for surgical strategy.

PI: dr Carmen Barba, Children's Hospital Anna Meyer-University of Florence, Firenze

SCIENTIFIC GUARANTOR: dr Carlo Marras, Coordinator, Epilepsy Surgery Commission, Italian League against Epilepsy

SUMMARY (531/600 WORDS)

Resective surgery has proved to be an effective treatment option for drug-resistant temporal lobe epilepsy (TLE) compared to medical treatment only. However, the proportion of adult patients enjoying long-term post-operative seizure freedom remains suboptimal. Better outcomes were reported in children, possibly owing to different etiologies and the possibility to carry out more extended resections. Individual prediction of seizure relapse is hampered by the weak odds ratios associated with known predictors of TLE surgery and by the level of unexplained heterogeneity across epilepsy surgery series. Available evidence about post-operative cognitive outcome is even more controversial. These issues highlight the need for multicenter studies using rigorous experimental protocols and robust statistical methods.

This retrospective multicenter study has involved the main Italian epilepsy surgery centers with the following aims: **a)** to compare post-operative seizure and cognitive outcomes and their predictors in children (<16 years) and adults (≥ 16 years) submitted to TLE surgery; and **b)** to identify possible differences in the general and electroclinical features and post-operative outcomes associated with two histologic variants: Focal Cortical Dysplasia (FCD) IIIa and isolated hippocampal sclerosis (HS). Concerning the primary aim, we asked all participating centers to fill in a database including the following information from each patient included in the study: general characteristics (sex, age at surgery, antecedents, seizure frequency and type, pre-existing neurological and cognitive deficits), ictal and interictal EEG, neuroimaging (MRI visible lesion and HS) and surgical findings (type of surgery, histology, seizure and cognitive outcome 2 years after surgery and at last follow-up, complications, completeness of the resection). We have already collected anonymized information from about 600 patients. Based on this data collection, we will carry out a statistical analysis aimed at defining possible differences of general, electroclinical and neuroimaging features, post-operative seizure and cognitive outcomes and their predictors between adults and children. For all analyses, we will first distinguish adults and children based on a cut-off age of 16 years at surgery. Subsequently, we will test through sensitivity analyses whether a different and more explanatory cut-off age exists. Concerning the secondary aim, we sent to all participating centers a database including only the subgroup of patients with either isolated HS or FCD IIIa (about 200 patients) to be filled in with additional information on seizure semeiology, neuroimaging features (i.e. temporal pole blurring, hypotrophy, etc.), and histology characterization of HS. We will carry out a statistical analysis to define possible differences of general, electroclinical and neuroimaging features, post-operative seizure and cognitive outcomes and their predictors between FCD IIIa and isolated HS.

The identification of outcome predictors might contribute to improve the selection criteria of candidates to TLE surgery and identify those in which drug withdrawal could be achieved, with

Azienda Ospedaliero - Universitaria "A. Meyer"
UOC Neurologia Pediatrica - Università degli Studi di Firenze
Viale Pieraccini 24, 50139 Firenze
Tel. +39 055 5662835/2834

subsequent possible improvement of cognitive performances. In addition, the definition of a cut-off age for the occurrence of possible differences of outcome, might indicate a temporal window beyond which surgery is less effective. The better definition of the clinical and surgical features specifically associated with FCD IIIa in comparison to isolated HS might contribute to identify possible different etiopathogenetic mechanisms, and influence surgical planning in patients with temporo-mesial epilepsy, i.e. optimizing the extent of the resection and reducing the risk for post-operative memory or language deficits.

BACKGROUND (488/ 500 WORDS)

In the context of the surgical treatment of epilepsy, the temporal lobe is involved in 71.9% of operations (Blumcke et al., *N Engl J Med* 2017;377:1648-56), with significant differences between adults and children. In adults, most procedures are temporal lobe resections, with very few multilobar procedures or hemispherectomies (Ryvlin et al., *Lancet Neurol* 2014;13:1114-26). By contrast, a survey of pediatric epilepsy surgery in the USA, Europe, and Australia showed most procedures to be multilobar or hemispheric, with temporal lobe resections accounting for only 23% of cases (Harvey et al., *Epilepsia* 2008; 49: 146–55). Hippocampal sclerosis (HS) associated or not with focal cortical dysplasia (FCD) IIIa is the most common histopathological diagnosis among adults, while tumors and malformations of cortical development are the most common diagnoses among children (Blumcke et al., *N Engl J Med* 2017;377:1648-56).

Disparities between adult and pediatric surgical candidates are observed also in the outcome studies. The proportion of adult patients enjoying long-term post-operative seizure freedom following temporal lobe epilepsy (TLE) surgery remains suboptimal (De Tisi et al., *Lancet* 2011; 378: 1388–95; West et al., *Cochrane Database Syst Rev* 2015; 7: CD010541), while better outcomes were reported in children, possibly owing to different etiologies and the possibility to carry out more extended resections (Spencer & Huh, *Lancet Neurol* 2008; 7: 525–37).

In general, individual prediction of seizure relapse is hampered by the weak odds ratios associated with known predictors of TLE surgery (Tonini et al., *Epilepsy Res* 2004; 62: 75–87). Some recent studies have challenged the classic view that MRI signs of hippocampal sclerosis are associated with greater chances of post-operative seizure freedom following anterior temporal lobectomy, while confirming hippocampal remnant to be one the main predictors of surgical failures (McIntosh et al., *Epilepsia* 2012; 53:970–78; Blumcke et al., *N Engl J Med* 2017;377:1648-56). These findings highlight the relevance of histology in predicting epilepsy surgery outcome. Accordingly, Deleo, Garbelli and colleagues (*Epilepsia* 2016;57:306-15) suggested that HS subtypes and associated pathologies may predict the risk of seizure recurrence after TLE surgery.

Available evidence about post-operative cognitive outcome is even more controversial (Van Schooneveld & Braun, *Brain Dev* 2013;35:721–9). The small sample size, the flaws in the methodology and the lack of adequate control groups have precluded drawing firm evidence-based conclusions on post-operative neuropsychological changes. However, recent studies have suggested the cognitive performances can improve after epilepsy surgery, especially in case of antiepileptic drug withdrawal (Moosa & Wyllie, *Semin Pediatr Neurol* 2017;24:331-39). In addition, the role of etiology is still matter of debate, while seizure freedom and short duration of epilepsy seem to be associated with improved or stable cognitive function after surgery (Freitag & Tuxhorn, *Epilepsia* 2005;46:561-7; Sibilia et al., *Epilepsy Behav* 2017;73:23-30).

The level of unexplained heterogeneity across epilepsy surgery series continues to pose a

Azienda Ospedaliero - Universitaria "A. Meyer"
UOC Neurologia Pediatrica - Università degli Studi di Firenze
Viale Pieraccini 24, 50139 Firenze
Tel. +39 055 5662835/2834

difficult challenge for counseling patients and families on post-operative seizure and cognitive outcome, thus highlighting the need for multicenter studies using rigorous experimental protocols and robust statistical methods.

Aims (68/200 words)

Primary aim: to compare post-operative seizure and cognitive outcomes and their predictors in children (<16 years at surgery) and adults (≥ 16 years at surgery) submitted to TLE surgery in eight Italian epilepsy surgery centers.

Secondary Aim: to identify possible differences in the general and electroclinical features and post-operative seizure and cognitive outcomes associated with two histologic variants: FCD IIIa and isolated HS in eight Italian epilepsy surgery centers.

KEYWORDS (max 5)

Temporal lobe epilepsy, epilepsy surgery, post-operative outcome, age at surgery, hippocampal sclerosis

METHODS (931/1000 words)

Study Design: retrospective multicenter nationwide study

Host center: Neuroscience Department, Children's Hospital Anna Meyer, Firenze

The Neuroscience Department at Children's Hospital Meyer provides multidisciplinary care for children with neurological disorders, in particular with rare and complex epilepsies. It includes two pediatric neurology and psychiatry inpatient wards, neurophysiology and neurogenetics laboratories and a dedicated pediatric neuropsychology team. Since 2007, an epilepsy surgery program has been established including invasive and non-invasive presurgical evaluation protocols; navigated and robotically-assisted neurosurgery procedures have been set up for the epilepsy treatment. Dedicated databases are available for the epilepsy surgery program and genetics of complex and rare epilepsies. The Neuroscience Department at Children's Hospital Meyer has participated to or led several national and European projects on the topic of rare and complex epilepsies. In particular, the PI has led a multicenter project on the topic of epilepsy surgery funded by the Italian Ministry of Health and Tuscany Region (RF-2010-2309954, 2012-2016) and she has been WP coordinator of the project DESIRE funded by the European FP7 Programme (grant agreement 602531, 2013-2018).

Participating Centers

Epilepsy Surgery Center 'Claudio Munari', ASST Grande Ospedale Metropolitano Niguarda, Milano
Clinical Epileptology and Experimental Neurophysiology Unit, IRCCS Besta, Milano
IRCCS Neuromed, Pozzilli, Isernia

Neuroscience Department, Ospedale Pediatrico Bambino Gesù, Roma

Child Neurology and Psychiatry Unit, Azienda Ospedaliera Universitaria G. Salesi, Ancona

Child Neurology and Psychiatry Unit, Università Cattolica del Sacro Cuore, Roma

Neurosurgery Unit, IRCCS Istituto Giannina Gaslini, Genova

The participating centers, which all have a well-known expertise in the field of epilepsy surgery, guarantee the possibility to recruit a great number of adult and pediatric surgical candidates.

Statistical analyses will be carried out with the help of the Department of Statistics, University of Florence.

Inclusion criteria:

Azienda Ospedaliero - Universitaria "A. Meyer"
UOC Neurologia Pediatrica - Università degli Studi di Firenze
Viale Pieraccini 24, 50139 Firenze
Tel. +39 055 5662835/2834

- a) TLE surgery between January 2011 and December 2016 at the participating centers, with at least 2 years of follow-up
- b) Histology, pre and post-operative EEG and brain MRI available for review

Exclusion criteria:

- a) Surgery extended beyond the limits of the temporal lobe

Experimental design: primary aim

We sent a database for all participating centers to fill in with the following information from each patient included in the study: general characteristics (sex, age at surgery, antecedents, seizure frequency and type, previous neurological and cognitive deficits), ictal and interictal EEG, neuroimaging (possible MRI visible lesion and HS) and surgical findings (type of surgery, histology, seizure and cognitive outcome 2 years after surgery and at last follow-up, complications, completeness of the resection).

We have already collected information on about 600 patients. Based on this, we will carry out a statistical analysis aimed at defining possible differences of general, electroclinical and neuroimaging features, post-operative seizure and cognitive outcomes and their predictors between adults and children. In order to characterize the sample, we will analyze all collected data using descriptive statistics. We will focus on hypothesis testing (equality test for means and proportion) in order to assess possible differences between the two groups (children and adults) for all outcomes and variables of interest. In addition, to take in account the hierarchical nature of the data (patients belonging to the same center can share common characteristics) and to assess the presence of potential confounders and identify possible interactions, we will carry out multilevel multivariate regression analyses, where the level will be defined by the center to which data belong. For all analyses, we will first distinguish adults and children based on a cut-off age of 16 years at surgery, which has been largely utilized in previous studies. Then, we will test through sensitivity analyses whether a different and more explanatory cut-off age exists.

Experimental design: secondary aim

We asked all participating centers to fill in a database including only the subgroup of patients with either isolated HS or FCD IIIa with additional information on seizure semeiology, neuroimaging features (i.e. temporal pole blurring, hypotrophy, etc), and histology characterization of HS (Blumcke et al, Epilepsia 2013;54:1315-29).

We will carry out a statistical analysis aimed at defining possible differences of general, electroclinical and neuroimaging features, post-operative seizure and cognitive outcomes and their predictors between FCD IIIa and isolated HS. In order to take into account the hierarchical nature of the data (patients belonging to the same center can share common characteristics) and to assess the presence of potential confounders and identify possible interactions, we will carry out multilevel multivariate regression analyses, where the level will be defined by the center to which data belong.

All collected data will be stored in a centralized database at Meyer Hospital. Dr. Carmen Barba will be responsible for data protection.

Timeline

M1: kick-off meeting with the participating centers, ethics committee approval (ongoing at Meyer Hospital)

M2-5: data collection completed, preliminary statistical analysis, meeting with the participating centers to evaluate doubtful neuroimaging and histology findings.

M6-8: statistical analysis completed; meeting with the participating centers to discuss final results

Azienda Ospedaliero - Universitaria "A. Meyer"
UOC Neurologia Pediatrica - Università degli Studi di Firenze
Viale Pieraccini 24, 50139 Firenze
Tel. +39 055 5662835/2834

M9-12: manuscript preparation (acknowledgment of the Fondazione Lince funding), dissemination through local and national meetings (responsible for dissemination: dr Carmen Barba)

Milestones

M6: preliminary statistical analyses and intermediate report

M12: statistical analyses completed, manuscript preparation and final report

Risk analysis

Concerning the primary aim, there is a low possibility that our results will not reach statistical significance, despite the large amount of data already collected. In this case, we will utilize alternative statistical methods. Concerning the secondary aim, histopathology findings might be insufficient for a robust analysis due to the observer-related variability in the approach to the study of hippocampus in the different centers. In this case, a meeting will be organized through the Commission of Epilepsy Surgery, in order to allow pathologists from different centers to review doubtful cases.

EXPECTED RESULTS (344/400)

1) The definition of the predictors of post-operative seizure and cognitive outcome might contribute to improve the selection criteria of candidates to TLE surgery and identify those in which drug withdrawal could be achieved, with subsequent possible improvement of cognitive performances (Boshuisen et al, 2015). In addition, the definition of a cut-off age for the occurrence of possible differences of outcome, might indicate a temporal window beyond which surgery is less effective and possibly contribute to optimize the timing of intervention.

2) The better definition of clinical and surgical features associated with FCD IIIa in comparison to isolated HS might contribute to identify possible different etiopathogenetic mechanisms and influence surgical planning in patients with temporo-mesial epilepsy i.e. optimizing the extent of the resection and reducing the risk for post-operative memory or language deficits.

The innovative approach of the present project is related to the following issues:

a) this multicenter study involves the main Italian epilepsy surgery centers, all of which follow national and international recommendations and consensus in their clinical practice. This will help including in the study a great number of adults and children with TLE while ensuring adequate homogeneity in data collection; b) we will compare adult and pediatric patients in order to precisely identify post-operative outcome predictors such as histology and age at surgery. This might influence the selection criteria of surgical candidates in the participating centers, through early identification of patients with higher probability to be cured and to improve cognitive function after surgery. On the other side, it would be possible to early identify patients unsuitable for surgery, thus avoiding expensive and time-consuming neurophysiology and neuroimaging investigations, and opt for palliative surgery or alternative investigations, such as genetic analyses.

In general, our results might improve counseling to patients and families and, in the long-term, increase the number of patients operated during childhood.

The recruitment of 600 patients, the availability of a highly specialized center for statistical analysis, previous collaborations between the participating centers through the Commission of Epilepsy Surgery, will guarantee success for this study during the planned period of funding.

• **BUDGET**

Total budget: 15000 euro subdivided as follows:

Azienda Ospedaliero - Universitaria "A. Meyer"
UOC Neurologia Pediatrica - Università degli Studi di Firenze
Viale Pieraccini 24, 50139 Firenze
Tel. +39 055 5662835/2834

A- 3000 euro (20% total budget): 1 laptop for the database management system and to carry out the statistical analyses; 1 software for the database management system (possible additional licenses based on the project's needs)

B- 9000 euro (60% total budget): funding for the participating centers to hire personnel for collecting data and managing the local database, according to the number of recruited patients in each center.

C- 0

D - 1500 euro (10% total budget): overheads for Children's Hospital Meyer

E- 1500 euro (10% total budget): meetings between partners, dissemination through participation to medical conferences, publications (figures, open access).

• **COLLABORATIONS AND CO-FUNDING**

This project does not include international collaborations and partnerships or co-funding at this stage. However, after this first multicenter Italian study, we aim to develop the project at the European level through the ERN for rare and complex epilepsies: EpiCARE, of which the PI, dr Carmen Barba, is member of the steering committee and of the WP Research.