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***Meiner Frau Katja
und unseren Söhnen Lukas und Elias***

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Abkürzungen

ACNS	<i>American Clinical Neurophysiology Society</i>
AED	<i>Antiepileptic drug</i>
ASM	Anfallssuppressive Medikation
cMRT	kraniale Magnetresonanztomographie
CPC	<i>Cerebral Performance Category</i>
CSVD	<i>Cerebral small vessel disease</i>
EEG	Elektroenzephalogramm
ETPs	Epilepsietypische Potenziale
GPDs	Generalisierte periodische Entladungen
HARNES	<i>Harmonized Neuroimaging of Epilepsy Structural Sequences</i>
HIE	Hypoxisch-ischämische Enzephalopathie
ILAE	<i>International League Against Epilepsy</i>
MRT	Magnetresonanztomographie
NCSE	Non-convulsiver Status epilepticus
OR	Odds Ratio
PRISMA	<i>Preferred Reporting Items for Systematic Reviews and Meta-Analyses</i>
KI	Konfidenzintervall
SEP	Sensibel evozierte Potenziale
SUDEP	<i>Sudden unexpected death in epilepsy</i>
ZNS	Zentrales Nervensystem

1. Einleitung

1.1 Epileptische Anfälle

Die Internationale Liga gegen Epilepsien (engl. „*International League Against Epilepsy*“, ILAE) definiert epileptische Anfälle als „*vorübergehendes Auftreten von Zeichen oder Symptomen, die durch eine abnormal gesteigerte oder synchronisierte neuronale Aktivität des Gehirns ausgelöst werden*“ (Fisher et al. 2014, Übersetzung durch den Autor). Es ist davon auszugehen, dass etwa jeder zehnte Mensch im Laufe seines oder ihres Lebens einen epileptischen Anfall erleidet (Hauser et al. 1996). Damit gehören epileptische Anfälle zu den häufigsten Gründen für eine neurologische Behandlung von Patient:innen in einer Notaufnahme (Royle et al. 2010).

Epileptische Anfälle werden nach ihrer Anfallsform und nach ihrer Ursache eingeteilt. Die Einteilung nach Anfallsform wurde von der ILAE in einer *operationalen Klassifikation* festgelegt (Fisher et al. 2017). Demnach können epileptische Anfälle einen fokalen Beginn, d.h. die epileptische Aktivität beginnt in einer Hirnhemisphäre, oder einen generalisierten Beginn, bei dem der Anfall in Netzwerken beider Hemisphären beginnt, haben. Ein Anfall, bei dem nur ein Teil des Verlaufs, nicht aber der Anfallsbeginn bekannt ist, wird als epileptischer Anfall mit unbekanntem Beginn bezeichnet. Für den seltenen Fall, dass zwar Sicherheit hinsichtlich des Vorliegens eines epileptischen Anfalls besteht, es aber keine weiterführenden Informationen zum Anfallsverlauf gibt, ist die Bezeichnung unklassifizierter Anfall vorgesehen (Fisher et al. 2017). Für die Anfallsklassifikation werden klinische Angaben zur Anfallssemiologie und die Ergebnisse apparativer Diagnostik berücksichtigt. Kann (in Anlehnung an den Beta-Fehler) mit einer Wahrscheinlichkeit von $> 80\%$ dem Anfall ein Beginn zugeordnet werden, soll eine entsprechende Klassifizierung hin zu einem fokalen oder generalisierten Anfallsbeginn vorgenommen werden.

Für fokale Anfälle fügt die operationale Klassifikation eine weitere Klassifikationsebene hinsichtlich des iktalen Bewusstseinsgrads hinzu. Fokale Anfälle können demnach bewusst erlebt oder nicht-bewusst erlebt sein. Jedweder fokale Anfall, bei dem der oder die Patient:in sich nicht während der gesamten Anfallsdauer seiner/ihrer selbst und seiner/ihrer Umgebung vollständig bewusst ist, wird als „nicht-bewusst erlebt“ bezeichnet. Da – außer Myoklonien – alle generalisiert beginnenden epileptischen Anfälle sowie fokal zu bilateral tonisch-klonische Anfälle immer mit einer Bewusstseinsstörung einhergehen, wird für diese Anfallsformen der Bewusstseinsgrad nicht angegeben. Alle klassifizierbaren Anfallsformen können schließlich bezüglich ihrer weiteren Semiologie beschrieben werden (Fisher et al. 2017).

Epileptische Anfälle werden hinsichtlich ihrer Ursache als „akut-symptomatisch“ oder „unprovokiert“ bezeichnet. Akut-symptomatische Anfälle treten in zeitlich definierter – und

damit mutmaßlich ursächlicher – Assoziation zu einer Störung des zentralen Nervensystems (ZNS) auf. Unprovozierte Anfälle hingegen treten ohne nachweisbare ZNS-Störung bzw. außerhalb des für akut-symptomatische Anfälle definierten Zeitintervalls auf (Beghi et al. 2010). Die Unterscheidung zwischen akut-symptomatischen Anfällen und unprovozierten Anfällen ist aus zwei Gründen relevant: Erstens zeigt ein akut-symptomatischer Anfall eine potenziell bedrohliche und zugleich häufig behandelbare Ursache an (Annegers et al. 1995, Reinecke et al. 2022). Zweitens unterscheiden sich akut-symptomatische und unprovozierte Anfälle in einem erheblichen Maß bezüglich des Rezidivrisikos erneuter unprovozierter Anfälle (Hesdorffer et al. 2009). Dies hat unmittelbare Implikationen hinsichtlich der Diagnosestellung einer Epilepsie und Indikation zur anfallssuppressiven Therapie.

1.2 Epilepsien

Die ILAE definiert Epilepsien als *„Hirnerkrankung, die durch eine anhaltende Prädisposition, epileptische Anfälle zu entwickeln, sowie aus den sich daraus ergebenden neurobiologischen, kognitiven, psychologischen und sozialen Konsequenzen charakterisiert ist“*. (Fisher et al. 2014, Übersetzung durch den Autor). Voraussetzung für die Diagnose einer Epilepsie ist das Vorliegen mindestens eines *unprovozierten* epileptischen Anfalls. Nach einem derartigen Anfall kann die Diagnose einer Epilepsie gestellt werden, wenn a) nach frühestens 24 Stunden ein erneuter unprovozierter Anfall auftritt, b) von einem Rezidivrisiko eines erneuten unprovozierten Anfalls in den kommenden 10 Jahren von mindestens 60% auszugehen ist, oder c) ein Epilepsie-Syndrom diagnostiziert werden kann (Fisher et al. 2014). Ein $\geq 60\%$ iges 10-Jahres Rezidivrisiko zeigte sich unter Berücksichtigung des Konfidenzintervalls bei Patient:innen mit unprovoziertem Anfall nach Schlaganfall (Hesdorffer et al. 2009). Obwohl belastbare Daten für andere Ätiologien nicht vorliegen, geht man im klinischen Alltag davon aus, dass nach einem unprovozierten Anfall der Nachweis jedweder epileptogenen Läsion mit einem Überschreiten der 60%-Schwelle assoziiert ist (Holtkamp et al. 2023). Auch wenn im Elektroenzephalogramm (EEG) epilepsietypische Potenziale nachweisbar sind, liegt das Anfallsrezidivrisiko nach erstmaligem unprovoziertem Anfall bei $\geq 60\%$ (Bouma et al. 2016).

Epilepsien haben in der europäischen Bevölkerung eine Prävalenz von ca. 3,3-7,8 pro 1.000 Einwohner (Forsgren et al. 2005, Hirtz et al. 2007). Sie kommen besonders häufig im Kindesalter sowie bei älteren Patient:innen vor, wobei das Alter einen unabhängigen Risikofaktor für das Auftreten von Epilepsien darstellt (Hauser 1992). In sogenannten Niedrigeinkommensländern ist die Prävalenz von Epilepsien mit bis zu 14 pro 1.000 Einwohnern deutlich höher (Fiest et al. 2017).

Die Klassifikation der Epilepsien baut auf der Klassifikation der Anfallsformen (Fisher et al. 2017) auf. Nach Klassifizierung der Anfallsform wird die Art der Epilepsie definiert (Scheffer et

al. 2017). Diese wird unterteilt in fokale, generalisierte, kombiniert fokale/generalisierte sowie unklassifizierte Epilepsie. Als letzte Klassifikationsstufe kann unter Berücksichtigung demografischer, semiologischer, bildgebender und elektroenzephalographischer Informationen die Zuordnung zu einem spezifischen Epilepsiesyndrom erfolgen (Scheffer et al. 2017). Die ILAE-Klassifikation der Epilepsien erlaubt zudem die Zuordnung der Epilepsie zu einer spezifischen Ätiologie.

1.3 Ätiologien von akut-symptomatischen Anfällen und von Epilepsien

Sowohl akut-symptomatischen Anfällen als auch Epilepsien kann eine spezifische Ätiologie zugeordnet werden. Akut-symptomatische Anfälle können strukturelle und nicht-strukturelle (also systemische) Ursachen haben. Eine weiterführende ätiologische Einteilung umfasst strukturelle, metabolische, toxische, infektiöse und entzündliche Ursachen (Beghi et al., 2010). Je nach Art der Ursache unterscheidet sich das Zeitintervall zwischen akuter ZNS-Störung und Anfall, in dem von einem akut-symptomatischen Anfall gesprochen werden kann. Dieses liegt für strukturell bedingte akut-symptomatische Anfälle bei 7 Tagen und für akut-symptomatische Anfälle systemischer (nicht-struktureller) Genese i.d.R. bei 24-48 Stunden (Beghi et al. 2010). Schlaganfälle gelten als die häufigsten strukturellen Ursachen, Alkoholentzug als die häufigste Ursache nicht-strukturell bedingter akut-symptomatischer Anfälle (Herzig-Nichtweiß et al. 2023, Reinecke et al. 2022). Bei akut-symptomatischen Anfällen struktureller Ätiologie besteht ein erheblich größeres Risiko für das Auftreten unprovoked Anfälle im Verlauf als bei nicht-strukturellen Ursachen (Herzig-Nichtweiß et al. 2023). Kann hingegen einem unprovoked Anfall eine spezifische Ätiologie zugeordnet werden, liegt definitionsgemäß bereits eine Epilepsie vor (s.o.).

In der ILAE-Klassifikation werden sechs Ätiologien von Epilepsien beschrieben: Genetisch, strukturell, metabolisch, infektiös, immunvermittelt und unbekannt (Scheffer et al. 2017). In Europa sind Epilepsien struktureller (37%), unbekannter (36%) und genetischer (20%) Ursache am häufigsten (Syvertsen et al. 2015). In anderen Teilen der Welt weicht die oben beschriebene Häufigkeitsverteilung deutlich ab, wobei infektiöse Ursachen in ressourcenarmen Ländern eine hervorgehobene Rolle spielen (Preux et al. 2005). In der Epilepsiechirurgie gilt die Ätiologie als wichtiger Prädiktor für das Outcome hinsichtlich postoperativer Anfallsfreiheit (Englot et al. 2012, Jones et al. 2016, McIntosh et al. 2001, Tonini et al. 2004). In der medikamentösen Therapie war dieser Zusammenhang bislang nicht ausreichend belegt.

1.4 Status epilepticus

Üblicherweise sistieren epileptische Anfälle spontan innerhalb weniger Minuten (Jenssen et al. 2006, Dobesberger et al. 2015). Bei länger dauernder epileptischer Aktivität, wenn also

endogene anfallsterminierende Prozesse nicht erfolgreich sind oder anfallsverlängernde Mechanismen greifen, liegt ein Status epilepticus vor (Trinka et al. 2015a). Gemäß der S2k-Leitlinie „Status epilepticus im Erwachsenenalter“ der Deutschen Gesellschaft für Neurologie sollte jedweder epileptische Anfall mit einer Dauer von >5 Minuten (oder ≥ 2 aufeinanderfolgende Anfälle ohne ein zwischenzeitliches Wiedererlangen des präiktalen neurologischen Zustands) als Status epilepticus definiert und entsprechend therapiert werden (Rosenow et al. 2020). Die aktuelle ILAE-Definition des Status epilepticus (Trinka et al. 2015a) führt zwei relevante Zeitpunkte an: Der Zeitpunkt t_1 , ab dem der Anfall als pathologisch verlängert gilt und mit einem spontanen Sistieren nicht mehr zu rechnen ist, sowie der Zeitpunkt t_2 , ab dem mit der Schädigung von Nervenzellen oder neuronalen Netzwerken zu rechnen ist. Dabei markiert der Zeitpunkt t_1 (5 Minuten bei tonisch-klonischem Status epilepticus und 10 Minuten bei fokalem Status epilepticus) den empfohlenen Beginn einer Status-durchbrechenden Therapie. Vom Zeitpunkt t_2 (30 Minuten bei tonisch-klonischem Status epilepticus und > 60 Minuten bei fokalem Status epilepticus) hängt ab, wie aggressiv diese Therapie implementiert werden sollte (Trinka et al. 2015a).

In Europa liegt die Inzidenz des Status epilepticus zwischen 8,5-36/100.000/Jahr (Ascoli et al. 2021). Semiologisch werden Status epileptici bezüglich des Vorliegens motorischer Symptome eingeteilt. Weitere Klassifikationsachsen umfassen die Ätiologie, Veränderungen im EEG sowie das Alter der Patient:innen (Trinka et al. 2015a).

Der non-convulsive Status epilepticus (engl. *nonconvulsive status epilepticus*, NCSE) stellt eine diagnostische Herausforderung dar, weil er nur mit Hilfe des EEGs von Bewusstseinsstörungen anderer Ätiologien abgegrenzt werden kann (Bauer et al. 2010). Zur Vereinheitlichung der Diagnosestellung liegen die Salzburg-Kriterien vor, die neben der Frequenz periodischer Entladungen auch deren räumliche und örtliche Ausbreitung, das Vorliegen subtiler iktaler Phänomene und das Ansprechen auf ASM beinhalten (Beniczky et al. 2013, Leitinger et al. 2015). Der Bewusstseinsstörung beim Status epilepticus liegt einerseits die anhaltende epileptische Aktivität, andererseits eine zunehmende funktionelle und auch strukturelle Hirnschädigung zu Grunde. Der Anteil der strukturellen Komponente nimmt mit zunehmendem Grad der Bewusstseinsstörung zu (Bauer et al. 2010, Leitinger et al. 2021). Die hypoxisch-ischämische Enzephalopathie (HIE) stellt dabei einen Sonderfall dar, bei dem zwischen epileptischer Hirnfunktionsstörung und struktureller zerebraler Schädigung häufig nur schwer unterschieden werden kann (Trinka et al. 2015b).

1.5 cMRT in der Epilepsiediagnostik

Das MRT gilt als das bildgebende Verfahren der Wahl zur Diagnosestellung einer Epilepsie nach erstmaligem unprovokierten Anfall (s.o., Abschnitt 1.2) sowie zur Klärung der Ätiologie.

Die deutschsprachige S2k-Leitlinie empfiehlt die Durchführung eines cMRTs innerhalb weniger Tage nach erstmaligem epileptischen Anfall (Holtkamp et al. 2023).

Bei ca. 20% der Erwachsenen Patient:innen mit neu aufgetretenen epileptischen Anfällen kann im MRT eine epileptogene Läsion identifiziert werden (Hakami et al. 2013, Craven et al. 2012). Epileptogene Läsionen sind häufig subtil und werden durch ein Standard-MRT-Protokoll teilweise nur unzureichend erfasst (Von Oertzen et al. 2002). Daher wird für die MRT-Bildgebung in der Epilepsiediagnostik ein Epilepsie-Protokoll empfohlen, das dünn-schichtige, dreidimensionale T1- und T2-gewichtete Sequenzen mit isotropen Voxeln enthält, wie z.B. das HARNESS (Harmonized Neuroimaging of Epilepsy Structural Sequences)-Protokoll (Bernasconi et al. 2019). Von herausgehobener Bedeutung für die Identifizierung epileptogener Läsionen ist zudem die Befundung des MRTs durch in der Epilepsie-Diagnostik erfahrene Untersucher:innen (Mann et al. 2023). Die Sensitivität für den Nachweis epileptogener Läsionen im MRT kann zudem durch Post-Processing erhöht werden (Urbach et al. 2023). Durch MRT-Scanner mit einer Feldstärke von 7 Tesla kann die diagnostische Präzision weiter erhöht werden. So kann bei bis zu 40% der Patient:innen mit bislang als non-läsionell eingeschätzter Epilepsie durch eine 7 Tesla MRT-Untersuchung doch eine mutmaßliche epileptogene Läsion identifiziert werden, deren vollständige operative Entfernung dann bei einer Mehrheit der Patient:innen zu Anfallsfreiheit führt (Wang et al. 2020). 7 Tesla MRTs werden in der Epilepsie-Diagnostik derzeit noch nicht routinemäßig eingesetzt.

1.6 EEG in der Epilepsiediagnostik

Im Oberflächen-EEG werden Spannungsunterschiede des Kortex auf der Kopfoberfläche abgeleitet, die sich überwiegend aus den Summationspotenzialen erregender und inhibitorischer postsynaptischer Potenziale zusammensetzen (Timofeev et al. 2004). Neben dem MRT ist das EEG die einzige spezifische Untersuchungsmethode zur Diagnosestellung einer Epilepsie nach erstmaligem unprovokierten Anfall (Fisher et al. 2014). Hierfür dient der Nachweis epilepsietypischer Potenziale (ETPs) in einer qualitativen – also visuellen – Auswertung. ETPs sind nur im Zusammenhang mit dem Auftreten epileptischer Anfälle als pathologisch zu werten und treten auch bei ca. 1% der gesunden Bevölkerung auf (Aschner et al. 2023). Die Sensitivität des EEGs hinsichtlich Detektion interiktaler ETPs ist umso größer, je früher das EEG nach einem Anfall durchgeführt wird (Sofat et al. 2016, King et al. 1998). Die Sensitivität von EEG-Untersuchungen kann zudem durch eine längere Ableitdauer, durch wiederholte EEG-Messungen nach einem Anfall und durch Ableitung im Schlaf erhöht werden (Salinsky et al. 1987, Badry 2013, Rowan et al. 1982). ETPs können regional oder generalisiert auftreten und damit Hinweise auf das zu Grunde liegende Epilepsiesyndrom geben. Allerdings treten auch bei Patient:innen mit generalisierten Epilepsien fokale ETPs auf und (wenngleich

seltener) umgekehrt (Usui et al. 2005, Tezer et al. 2009). Insgesamt ist die örtliche Diskriminationsfähigkeit des EEGs eher als gering einzuschätzen. So zeigt sich vor allem bei Patient:innen mit Läsionen außerhalb des Temporallappens eine Inkongruenz zwischen der Lokalisation von ETPs im EEG und der Hirnregion im cMRT detektierter Läsionen (Rémi et al. 2011).

Neben der Diagnostik und Zuordnung von epileptischen Anfällen und Epilepsien ist das EEG auch ein wichtiges prognostisches Werkzeug. Bei generalisierten Epilepsien kann das EEG Auskunft über die Wirksamkeit der ASM geben (Kamitaki et al. 2022). Es ist zudem eine Vielzahl von quantitativen und qualitativen EEG-Parametern beschrieben, die mit dem funktionellen Outcome und mit Komplikationen nach Schlaganfällen assoziiert sind (Dörrfuß et al. 2020a, Dörrfuß et al. 2020b, Lasek-Bal et al. 2023). Eine besonders herausgehobene Rolle spielt das EEG zudem in der Prognoseabschätzung nach Reanimation.

1.7 EEG-Veränderungen nach Reanimation

Im Jahr 2022 kam es zu knapp 19.000 Fällen außerklinischer Reanimationen in Deutschland. Ein Drittel dieser Patient:innen erreichte ein Krankenhaus mit wiederhergestelltem Spontankreislauf. Ca. 10% der Patient:innen nach außerklinischer Reanimation wurden lebend entlassen (Fischer et al. 2023). Nach innerklinischer Reanimation überleben ca. 20% der Patient:innen (Seewald et al. 2023).

Das EEG wird für zwei Indikationen bei Patient:innen nach Reanimation herangezogen. Zum einen dient es der Diagnose epileptischer Anfälle, zum anderen der Neuroprognostik bei Patient:innen mit vermuteter hypoxisch-ischämischer Enzephalopathie (HIE). Bei bis zu 35% der Patient:innen nach Reanimation sind im EEG generalisierte periodische Entladungen nachweisbar (Sandroni et al. 2020). Ob diese Veränderungen epileptischer Genese oder Epiphänomen der durch die Hypoxie verursachten Hirnschädigung sind, ist häufig schwer zu differenzieren. In einer randomisiert-kontrollierten Studie konnte gezeigt werden, dass eine pharmakologische Behandlung periodischer EEG-Veränderungen nach Reanimation die funktionelle Prognose nicht verbessert (Ruijter et al. 2022).

Wenn Patient:innen innerhalb von 72 Stunden nach Reanimation das Bewusstsein nicht wiedererlangen, sollen gemäß der S1-Leitlinie „*Hypoxisch-ischämische Enzephalopathie im Erwachsenenalter*“ der Deutschen Gesellschaft für Neurologie Untersuchungen zur Abschätzung der Prognose durchgeführt werden (Leithner et al. 2023). Das EEG ist dabei das am häufigsten verwendete apparative Verfahren zur Einschätzung der weiteren Prognose hinsichtlich des funktionellen Outcomes (Friberg et al. 2015). Vier spezifische EEG-Veränderungen, die ein ungünstiges neurologisches Outcome mit einer Spezifität von 100% bei hoher Interrater-Variabilität voraussagen, sogenannte *highly malignant patterns*, sind

bekannt: Eine supprimierte EEG-Aktivität (Amplitude $< 10 \mu\text{V}$ während der gesamten Ableitungsdauer), eine supprimierte Hintergrundaktivität mit eingelagerten generalisierten periodischen Entladungen sowie ein Burst-Suppressions-Muster mit oder ohne periodische Entladungen (Westhall et al. 2016). Die Interpretation des EEGs nach Reanimation kann durch eine sedierende Medikation erschwert werden und bedarf der Auswertung durch erfahrene Untersuchende (Agarwal et al. 2019, Benarous et al. 2019). Bezüglich des Zeitpunkts der EEG-Untersuchung zur Neuroprognostik wird üblicherweise ein Zeitintervall von < 72 Stunden nach Reanimation empfohlen (Sandroni et al. 2014). Die prognostische Aussagekraft einer späteren EEG-Untersuchung, wie sie häufig dem klinischen Alltag entspricht, war bislang unklar. Die Ergebnisse der EEG-Untersuchung müssen immer im multimodalen Kontext interpretiert werden. Die o.g. Leitlinie empfiehlt die Durchführung und Interpretation einer Kombination von prognostischen Markern, bestehend aus klinischer Untersuchung (Pupillen- und Kornealreflex), Bestimmung der Neuronen-spezifischen Enolase (NSE)-Serumkonzentration, Durchführung von somatosensibel evozierten Potenzialen (SSEPs), EEG sowie Computertomographie oder cMRT mit Bestimmung der *gray-white-matter ratio* (Leithner et al. 2023).

1.8 Epilepsie und Schlaganfall

Beim Schlaganfall kommt es aufgrund vaskulärer Veränderungen zu einer fokalen Schädigung des ZNS. Dabei wird zwischen ischämischen Schlaganfällen, definiert als eine Infarzierung aufgrund einer zerebralen Minderdurchblutung, und hämorrhagischen Schlaganfällen, die Folge einer intrazerebralen Blutung oder einer Subarachnoidalblutung sein können, unterschieden (Sacco et al. 2013).

Zwischen Schlaganfällen und epileptischen Anfällen besteht ein bidirektionaler Zusammenhang.

So sind Schlaganfälle die häufigste Ursache einer Epilepsie bei älteren Patient:innen („*Post-Stroke Epilepsie*“) (Tanaka et al. 2013). Das Risiko, innerhalb der ersten 10 Jahre nach einem Schlaganfall eine Epilepsie zu entwickeln, liegt zwischen 6 und 12%, wobei das Risiko im ersten Jahr am höchsten ist (Kammersgaard et al. 2005, Graham et al. 2013, Lahti et al. 2017).

Andererseits ist bei Patient:innen mit neu aufgetretenen epileptischen Anfällen im höheren Lebensalter das Schlaganfallrisiko um den Faktor 3-4 gegenüber Patient:innen ohne epileptische Anfälle erhöht („*Prä-Stroke Epilepsie*“) (Cleary et al. 2004, Wall et al. 2021). Konzeptionell wird die Prä-Stroke Epilepsie dabei in erster Linie als ein Marker für ein erhöhtes kardiovaskuläres Risiko verstanden (Wall et al. 2021). Allerdings könnten auch Veränderungen im Lebensstil nach Diagnose einer Epilepsie (z.B. durch reduzierte körperliche

Aktivität) sowie metabolische Nebenwirkungen der ASM das Schlaganfall-Risiko erhöhen (Zelano et al. 2017).

Risikofaktoren für eine Post-Stroke Epilepsie umfassen das Auftreten von akut-symptomatischen Anfällen innerhalb der ersten Woche nach dem Akutereignis, eine kortikale Beteiligung, das Vorliegen einer Arteriosklerose, sowie ein Schlaganfall im Versorgungsgebiet der Arteria cerebri media (Galovic et al. 2018). Das Risiko steigt zudem mit dem klinischen Schweregrad eines ischämischen Schlaganfalls (Galovic et al. 2018, Bladin et al. 2000). Auch bei intrazerebralen Blutungen gelten akut-symptomatische Anfälle und eine kortikale Beteiligung als relevante Risikofaktoren für die Entwicklung einer Epilepsie. Zudem sind ein jüngeres Lebensalter und ein größeres Blutungsvolumen mit einem erhöhten Epilepsie-Risiko assoziiert (Haapaniemi et al. 2014). In der Vergangenheit galten auch spezifische EEG-Veränderungen nach Schlaganfall als prädiktiv für die Entwicklung einer Post-Stroke Epilepsie (Bentes et al. 2018). Diese Assoziation konnte in einer multizentrischen Analyse jedoch nicht bestätigt werden (Ferreira-Atuesta et al. 2021).

Nach derzeitigen Leitlinien der *European Stroke Organization* ist auch bei einer Hochrisiko-Konstellation für das Auftreten epileptischer Anfälle nach Schlaganfall keine primärprophylaktische anfallssuppressive Therapie indiziert (Holtkamp et al. 2017). Aus Observationsstudien ergeben sich allerdings Hinweise darauf, dass in bestimmten Konstellationen eine anfallssuppressive Therapie einen günstigen Einfluss auf die Mortalität nach Schlaganfall haben könnte (Sinka et al. 2023, Dörrfuß et al. 2023b, Schubert et al. 2023). Bislang konnte in randomisierten, kontrollierten Studien keine erhöhte Wirksamkeit spezifischer Anfallssuppressiva im Kontext von Post-Stroke Epilepsien gezeigt werden (Gilad et al. 2007, Consoli et al. 2012). Insgesamt gilt die Prognose von Post-Stroke Epilepsien hinsichtlich des Erreichens von Anfallsfreiheit als günstig, wobei Daten zur Therapie mit neueren ASM bislang fehlten (Semah et al. 1998, Stephen et al. 2001).

1.9 Anfallssuppressive Therapie

Eine Indikation zur – formal sekundärprophylaktischen – anfallssuppressiven Therapie besteht, wenn die Diagnosekriterien einer Epilepsie erfüllt sind, also bei einem 10-Jahres Rezidivrisiko eines weiteren unprovzierten Anfalls von > 60% (Fisher et al. 2014, Holtkamp et al. 2023).

Das Risiko, nach akut-symptomatischem Anfall innerhalb der nächsten 10 Jahre einen unprovzierten Anfall zu erleiden, liegt bei ca. 19%, wobei das Risiko bei systemischen Ursachen deutlich niedriger als bei strukturellen Ursachen einzuschätzen ist (Hesdorffer et al. 2009, Herzig-Nichtweiß et al. 2023). Nach einem akut-symptomatischen Anfall wird daher keine langfristige anfallssuppressive Therapie empfohlen (Holtkamp et al. 2023, Holtkamp et

al. 2017). Einen Sonderfall könnte bei akut-symptomatischen Anfällen, die sich als Status epilepticus präsentieren, vorliegen, da hier von einem deutlich höheren Rezidivrisiko auszugehen ist. Dieses überschreitet in bestimmten Konstellationen die oben diskutierte 60%-Schwelle (Hesdorffer et al. 1998, Sinka et al. 2023).

Wenn sich nach einem unprovokierten Anfall im EEG keine ETPs und im cMRT keine epileptogene Läsion zeigen, liegt das 5-Jahres-Rezidivrisiko nach einem einmaligen unprovokierten Anfall bei 30-40% (Kim et al. 2006, Hauser et al. 1998), sodass auch hier keine Indikation für eine anfallssuppressive Therapie besteht.

Das Rezidivrisiko liegt bei 75%, wenn nach einem ersten unprovokierten Anfall im EEG ETPs nachgewiesen werden, bei 65%, wenn sich im MRT eine epileptogene Läsion zeigt, sowie bei 75%, wenn ein zweiter unprovokierter Anfall > 24h nach dem ersten Anfall auftritt (Hesdorffer et al. 2009, Hauser et al. 1998, Bouma et al. 2016). In diesen drei Konstellationen sollte somit eine zunächst dauerhafte anfallssuppressive Therapie begonnen werden (Holtkamp et al. 2023).

Ziel der anfallssuppressiven Therapie ist die Vermeidung weiterer epileptischer Anfälle bei gleichzeitig möglichst geringen Nebenwirkungen und minimalen Beeinträchtigungen im Alltag (Glauser et al. 2006). Ungefähr 30 verschiedene Substanzen stehen hierfür zur Verfügung. Diese werden nach ihrer Entwicklungsgeschichte und ihrem Zulassungsdatum in drei Generationen unterteilt (Löscher et al. 2021).

Die Selektion des geeigneten Anfallssuppressivums basiert auf der Art der Epilepsie, demografischen Faktoren wie Alter und Geschlecht sowie auf Vorerkrankungen und Komedikation.

Nebenwirkungen werden, abhängig vom verwendeten anfallssuppressiven Medikament und von der Art der Erfassung (spontan berichtet vs. durch strukturierte Fragebögen systematisch erfasst), von 12-88% der Patient:innen angegeben (Baker et al. 1997, Beghi et al. 1986). Intolerable Nebenwirkungen führen in ca. 15% der Fälle innerhalb von 6 Monaten zum Absetzen der Medikation (Alsfouk et al. 2020). Für die Lebensqualität der Patient:innen ist die Verträglichkeit der Anfallssuppressiva dabei wichtiger als deren Wirksamkeit (Gilliam et al. 2004). Letztlich bedingen Wirksamkeit und Verträglichkeit eines Anfallssuppressivums die Retentionsrate, also den Anteil an Patient:innen, die nach einem definierten Zeitraum das Medikament noch einnehmen. Die Retentionsrate macht daher einen wichtigen Endpunkt von vergleichenden Therapiestudien aus.

In den größten randomisiert-kontrollierten Studien dieser Art konnte die beste Retentionsrate für Lamotrigin bei fokalen Epilepsien sowie für Valproat bei generalisierten und

unklassifizierten Epilepsien gezeigt werden (Marson et al. 2007a, Marson et al. 2021a, Marson et al. 2007b, Marson et al. 2021b). Aufgrund ausgeprägter teratogener Effekte ist Valproat bei Frauen im gebärfähigen Alter kontraindiziert, sodass hier i.d.R. ebenfalls eine Therapie mit Lamotrigin oder eine Off-Label-Therapie mit Levetiracetam begonnen werden sollte (Holtkamp et al. 2023, Cerulli Irelli et al. 2023).

Die ASM wird mit einer Substanz in Monotherapie begonnen. Bei fehlender Wirksamkeit oder unzureichender Verträglichkeit erfolgt der Wechsel auf eine andere Substanz. Bei fehlender Wirksamkeit des zweiten Anfallssuppressivums erfolgt in einem nächsten Schritt i.d.R. die Umstellung auf eine Kombinationstherapie (Holtkamp et al. 2023). Insgesamt ist die Datenlage an randomisiert-kontrollierten Studien bezüglich Kombinationstherapien unzureichend. Es gibt jedoch Hinweise, dass eine Kombination von Anfallssuppressiva mit verschiedenen Wirkmechanismen in Hinblick auf Wirksamkeit und Verträglichkeit günstig ist (Margolis et al. 2014).

Eine Kombinationstherapie aus mehr als zwei Anfallssuppressiva ist häufig mit einer Zunahme an Nebenwirkungen bei nur eingeschränkter zusätzlicher Wirksamkeit assoziiert und wird daher i.d.R. nicht empfohlen (Poolos et al. 2012, Luciano et al. 2007, Holtkamp et al. 2023).

1.10 Prognose der Epilepsien

Mit dem ersten Anfallssuppressivum werden ca. 50% der Patient:innen anfallsfrei. Mit dem zweiten und dritten anfallssuppressiven Medikament kann bei zusätzlichen 12% bzw. 4% der Patient:innen Anfallsfreiheit erreicht werden. Die Gabe von weiteren Anfallssuppressiva führt nur noch bei jeweils ca. 2% der Patient:innen zu Anfallsfreiheit (Chen et al. 2018).

Die Prognose fokaler und unklassifizierter Epilepsien bezüglich Ansprechens auf eine ASM ist dabei schlechter als die generalisierter Epilepsien (Kwan et al. 2000, Seneviratne et al. 2012), wobei es bislang nur unzureichende Daten zum Ätiologie-spezifischen Ansprechen auf die ASM gab.

Wenn durch Gabe von zwei Anfallssuppressiva in Mono- oder Kombinationstherapie, die sachgemäß und in ausreichender Dosis verabreicht wurden, keine Anfallsfreiheit für mindestens 12 Monate erreicht werden kann, gilt die Epilepsie definitionsgemäß als pharmakoresistent (Kwan et al. 2010). In diesem Fall sollte eine stationäre Behandlung in einem Epilepsie-Zentrum erfolgen, um die Möglichkeit eines epilepsiechirurgischen Eingriffs zu evaluieren. Ca. 64% der pharmakoresistenten Patient:innen werden nach einem resektiven epilepsiechirurgischen Eingriff anfallsfrei (Chen et al. 2018). Die Art der der Epilepsie zu Grunde liegenden Hirnläsion stellt dabei einen der wichtigsten Prädiktoren für postoperative Anfallsfreiheit dar (Englot et al. 2012, Jones et al. 2016, McIntosh et al. 2001, Tonini et al.

2004). So zeigt sich eine gute Prognose bei Patient:innen mit gutartigen Tumoren oder einer Hippocampussklerose (McIntosh et al. 2001, Jones et al. 2016, Tonini et al. 2004). Non-läsionelle Epilepsien sind hingegen mit einer geringeren Rate postoperativer Anfallsfreiheit assoziiert (Englot et al. 2012). Trotz guter Chancen auf Anfallsfreiheit durch einen resektiven epilepsiechirurgischen Eingriff erfolgt nur bei einer Minderheit der pharmakoresistenten Patient:innen eine prächirurgische Abklärung (Steinbrenner et al. 2019).

Bis zu 40% der unter ASM anfallsfreien Patient:innen erleiden ein sporadisches Anfallsrezidiv, das als „*breakthrough seizure*“ bezeichnet wird (Schiller 2009). Hierfür wurde eine Vielzahl möglicher Triggerfaktoren – wie z.B. Schlafentzug, Infekte und diverse Umweltfaktoren – beschrieben (Aldosari et al. 2023, Kumar 2005, Kaddumukasa et al. 2013). Es ist allerdings unklar, ob die Assoziation zwischen vermeintlichen Triggerfaktoren und sporadischem Anfallsrezidiv tatsächlich kausal ist.

Neben dem Erreichen von Anfallsfreiheit ist die Mortalität ein weiterer entscheidender Outcomeparameter hinsichtlich der Prognose von Epilepsien. Diese ist bei Patient:innen mit epileptischen Anfällen im Vergleich zur gesunden Normalbevölkerung um den Faktor 1,6 bis 9,3 erhöht (Olafsson et al. 1998, Loiseau et al. 1999). Hierfür werden unterschiedliche Gründe angeführt: Zum einen kann es anfallsbedingt zu Verletzungen kommen. So erleiden ca. 24% der Patient:innen, die innerhalb eines Jahres epileptische Anfälle haben, eine Kopfverletzung (Buck et al. 1997). Zum zweiten besteht für Patient:innen mit Epilepsie das Risiko, an einem „*Sudden Unexpected Death in Epilepsy (SUDEP)*“ zu versterben. Hierbei handelt es sich um ein plötzliches und unerwartetes Versterben von Patient:innen mit Epilepsie, das nicht auf einen Status epilepticus oder einen anfallsbedingten Unfall bzw. Ertrinken zurückgeführt werden kann (Nashef et al. 2012). Pathophysiologisch wird beim SUDEP von einer akuten, zentral vermittelten kardio-respiratorischen Funktionsstörung, die in der Regel in Folge eines bilateralen oder generalisierten tonisch-klonischen Anfalls auftritt, ausgegangen (Ryvlin et al. 2013). Eine dritte häufige Todesursache ist der bereits oben diskutierte Status epilepticus, dessen Mortalität insgesamt bei ca. 22% liegt (DeLorenzo et al. 1995). Auch das Suizidrisiko ist bei Patient:innen mit Epilepsie im Vergleich zur Normalbevölkerung deutlich erhöht, wobei eine Assoziation zu einer Vielzahl von demografischen und epilepsiebezogenen Faktoren besteht (Giambarberi et al. 2022). Zuletzt wird die Mortalität durch die der epileptischen Anfälle zugrunde liegenden Ursache beeinflusst (Granbichler et al. 2015).

1.11 Absetzen der anfallssuppressiven Medikation

Bei langfristiger Anfallsfreiheit unter anfallssuppressiver Therapie kann ein Absetzen der ASM in Erwägung gezogen werden. Typischerweise wird hierfür ein anfallsfreies Intervall von mindestens zwei Jahren vorausgesetzt (Gloss et al. 2021, Beghi et al. 2013). Ob ein Absetzen

der ASM empfohlen wird, hängt von einer Bewertung des Risikos des Auftretens erneuter Anfälle nach Absetzen ab. Nach Absetzen der ASM treten bei ca. 30-50% der Patient:innen im Verlauf erneut epileptische Anfälle auf (Medical Research Council 1991, Lamberink et al. 2017).

Hierzu wurde eine Vielzahl von Faktoren, die mit dauerhafter Anfallsfreiheit bzw. mit Rezidivanfällen nach Absetzen der ASM assoziiert sind, beschrieben (Contento et al. 2021, Lamberink et al. 2015). Zwölf dieser assoziierten Faktoren werden in einem individualisierten Prädiktionsmodell, dem „*AED withdrawal risk retrieval tool*“, zusammengefasst. Mit diesem kann das 2- und 5-Jahres Rezidivrisiko nach Absetzen berechnet werden (Lamberink et al. 2017). Für den klinischen Alltag steht hierfür ein auf Basis der Ergebnisse der o.g. Arbeit entwickelter Online-Kalkulator zur Verfügung (UMC Utrecht 2017).

Die finale Entscheidung für oder gegen das Absetzen der ASM sollte im Konsens zwischen Ärzt:in und Patient:in getroffen werden. Ein Gespräch hierüber findet jedoch nur in 30-50% der Fälle, in denen ein Absetzen in Frage kommt, statt (Terman et al. 2023a, Henning et al. 2020).

Auch in prognostisch mutmaßlich günstigen Konstellationen führen Patient:innen die ASM oft dauerhaft fort (Terman et al. 2023a). Die Fortführung der ASM kann durch Nebenwirkungen die Lebensqualität der Patient:innen reduzieren und ist zudem mit vermeidbaren Kosten für das Gesundheitssystem verbunden (Joshi et al. 2017, George et al. 2015, Zou et al. 2014, de Kinderen et al. 2014).

Im Falle der Entscheidung zum Absetzen der Medikation gilt die Epilepsie dann als „überwunden“, wenn für 10 Jahre keine Anfälle aufgetreten sind, wovon in den letzten 5 Jahren keine ASM eingenommen wurde (Fisher et al. 2014).

1.12 Fragestellungen

In der Behandlung und Beratung von Patient:innen mit epileptischen Anfällen und Epilepsien haben diagnostische und prognostische Marker einen hohen Stellenwert. Hieraus leiten sich u.a. die Diagnosestellung einer Epilepsie sowie Empfehlungen zum Beginn und zur Beendigung einer anfallssuppressiven Behandlung ab. Die in dieser kumulativen Habilitationsschrift aufgeführten eigenen Arbeiten befassen sich mit klinischen und apparativen Markern in der Epileptologie sowie mit den sich aus ihnen ergebenden klinischen Konsequenzen. Dabei wird ein Fokus auf Grenzfälle in der Diagnosestellung von Anfällen und Epilepsien gelegt. Konkret wurden folgende Fragestellungen adressiert:

1.) Welche klinischen Parameter können herangezogen werden, um Patient:innen mit akut-symptomatischen Anfällen und einer potenziell behandelbaren Ursache frühzeitig zu identifizieren? Welchen Stellenwert hat die zerebrale Bildgebung bei Patient:innen, die

aufgrund epileptischer Anfälle in der Notaufnahme behandelt werden, und wie unterscheidet sich der diagnostische Nutzen der Bildgebung zwischen Patient:innen mit akut-symptomatischen und unprovokierten Anfällen?

2.) Wie ist die Epileptogenität von in der zerebralen Bildgebung detektierten Läsionen der weißen Substanz mutmaßlich vaskulären Ursprungs zu werten? Unterscheiden sich die Häufigkeit des Vorliegens von „*white matter lesions*“ (WML) und deren Ausmaß zwischen Patient:innen mit und ohne epileptischen Anfällen? Welchen Einfluss hat das Vorliegen von WML auf das Rezidivrisiko erneuter epileptischer Anfälle, und ist eine anfallssuppressive Medikation bei Patient:innen mit epileptischen Anfällen und WML – trotz fehlendem Nachweis eines kortikalen epileptogenen Fokus – gerechtfertigt?

3.) Welche Rolle kann das EEG in der Prognoseabschätzung nach Reanimation spielen, wenn dieses ≥ 5 Tage nach Reanimation abgeleitet wird? Welche EEG-Parameter sind mit hoher Spezifität mit der Entwicklung eines schlechten funktionellen Outcomes assoziiert? Welchen Einfluss hat eine Sedierung auf die prognostische Wertigkeit spät durchgeführter EEGs? Wie ist der Beitrag des späten EEGs im Kontext der multimodalen neuroprognostischen Diagnostik zu bewerten?

4.) Wie ist der Einfluss der im Rahmen der apparativen Diagnostik ermittelten Ätiologie von Epilepsien auf die Prognose hinsichtlich Anfallsfreiheit einzuschätzen? Kann die Ätiologie der Epilepsie als Prädiktor für das Erreichen von Anfallsfreiheit herangezogen werden? Und wie unterscheidet sich die medikamentöse Therapie, insbesondere die ASM-Dosierungen, zwischen den verschiedenen Ätiologien fokaler Epilepsien?

5.) Wann wird bei Patient:innen mit Epilepsie und guter Prognose die ASM abgesetzt? Welche Faktoren sind mit dem Beibehalten der ASM trotz eigentlich für einen Absetzversuch günstiger Ausgangslage assoziiert? Wie ist die Prognose bei Patient:innen, die die Medikation absetzen? Wie unterscheiden sich Patient:innen mit Rezidivanfällen nach Absetzen der Medikation von denen ohne Rezidivanfälle?

2. Eigene Arbeiten

2.1 Diagnosestellung von epileptischen Anfällen und Epilepsien

2.1.1 Klinische Marker und Charakteristika akut-symptomatischer Anfälle in der Notaufnahme

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In der Behandlung von Patient:innen mit epileptischen Anfällen in der Notaufnahme ist es von herausgehobener Bedeutung, frühzeitig zu identifizieren, ob es sich bei dem Ereignis um einen akut-symptomatischen oder um einen unprovzierten Anfall gehandelt hat. Dies liegt darin begründet, dass akut-symptomatische Anfälle auf eine zugrundeliegende, potenziell behandelbare Ursache hindeuten (Annegers et al. 1995). Ziel der vorliegenden Studie war daher die Identifizierung von mit akut-symptomatischen Anfällen assoziierten Variablen sowie die Charakterisierung von Patient:innen mit akut-symptomatischen Anfällen.

Hierzu erfolgte eine retrospektive Analyse aller innerhalb eines Jahres aufgrund eines epileptischen Anfalls oder einer Epilepsie in den Notaufnahmen der Charité, Campus Virchow-Klinikum und Campus Mitte, behandelten Patient:innen.

Insgesamt wurden 695 Patient:innen in die Studie eingeschlossen, von denen 24,5% einen akut-symptomatischen Anfall hatten. Drei Variablen waren unabhängig mit dem Vorliegen akut-symptomatischer Anfälle assoziiert: männliches Geschlecht (Odds Ratio (OR): 3,173, 95% Konfidenzintervall (KI): 1,972-5,104), keine vorherige Diagnose einer Epilepsie (OR: 11,235, 95% KI: 7,195-17,537) sowie eine bilaterale oder generalisiert tonisch-klonische Anfallssemiologie (OR: 2,982, 95% KI: 1,172-7,588).

Ein Alkoholzug war mit Abstand die häufigste Ursache für akut-symptomatische Anfälle in der Rettungsstelle (74,1%), hämorrhagische Schlaganfälle waren die zweithäufigste Ätiologie. Bei Patient:innen mit finaler Diagnose eines akut-symptomatischen Anfalls wurde häufiger eine zerebrale Bildgebung veranlasst als bei Patient:innen mit unprovziertem Anfall (82,9% vs. 67,2%, $p < 0,001$). In knapp einem Viertel der durchgeführten zerebralen Bildgebungen bei Patient:innen mit akut-symptomatischem Anfall wurde eine akute Pathologie festgestellt, während dies bei Patient:innen mit unprovziertem Anfall nur bei 4% der Fall war. Bei Patient:innen mit akut-symptomatischem Anfall wurde häufiger eine anfallssuppressive Therapie in der Notaufnahme initiiert als bei Patient:innen mit unprovziertem Anfall (55,9% vs. 30,3%, $p < 0,001$). Es zeigte sich kein Unterschied zwischen Patient:innen mit akut-

symptomatischem und unproviziertem Anfall hinsichtlich der frühen Anfallsrezidivrate in der Notaufnahme (13,5% vs. 11,6%, $p = 0.637$).



Acute symptomatic seizures in the emergency room: predictors and characteristics

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Abstract

Background When treating patients with epileptic seizures in the emergency room (ER), it is of paramount importance to rapidly assess whether the seizure was acute symptomatic or unprovoked as the former points to a potentially life-threatening underlying condition. In this study, we seek to identify predictors and analyze characteristics of acute symptomatic seizures (ASS).

Methods Data from patients presenting with seizures to highly frequented ERs of two sites of a university hospital were analyzed retrospectively. Seizures were classified as acute symptomatic or unprovoked according to definitions of the International League Against Epilepsy. Univariate and multivariate analysis were conducted to identify predictors; furthermore, characteristics of ASS were assessed.

Results Finally, 695 patients were included, 24.5% presented with ASS. Variables independently associated with ASS comprised male sex (OR 3.173, 95% CI 1.972–5.104), no prior diagnosis of epilepsy (OR 11.235, 95% CI 7.195–17.537), and bilateral/generalized tonic–clonic seizure semiology (OR 2.982, 95% CI 1.172–7.588). Alcohol withdrawal was the most common cause of ASS (74.1%), with hemorrhagic stroke being the second most prevalent etiology. Neuroimaging was performed more often in patients with the final diagnosis of ASS than in those with unprovoked seizures (82.9% vs. 67.2%, $p < 0.001$). Patients with ASS were more likely to receive acute antiseizure medication in the ER (55.9% vs. 30.3%, $p < 0.001$).

Conclusions In one quarter of patients presenting to the ER after an epileptic fit, the seizure had an acute symptomatic genesis. The independently associated variables may help to early identify ASS and initiate management of the underlying condition.

Keywords Alcohol withdrawal · Antiseizure medication · Epilepsy · Stroke · Unprovoked seizure

Introduction

Epileptic seizures are among the most common neurological conditions leading to presentation in the emergency room (ER) [1]. With respect to rough etiological groups, epileptic fits are dichotomized into acute symptomatic

seizures (ASS) and unprovoked seizures (US). ASS are defined to occur in close temporal and likely causal relationship to an acute cerebral or systemic impairment of structural, metabolic, toxic, infectious or inflammatory origin [2]. The conceptual reason why ASS and US are differentiated is long-term prognosis regarding seizure recurrence [3]. A patient with an US and risk of at least 60% to develop seizures over the following decade is considered to have epilepsy. This 60% threshold is reached when a second US occurs > 24 h apart from the first US or if EEG and/or MRI findings after the first US indicate a significantly elevated risk of seizure recurrence [4]. In contrast, ASS have a lower long-term recurrence risk which is approximately 20% in the 10 years after the index seizure [3].

When treating a patient after a seizure in the ER, rapidly discerning ASS from US is pivotal as the former may

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indicate the necessity of imminent management of the potentially life-threatening underlying condition. Separating ASS from a first US is also important in a long-term perspective as administration of antiseizure medication (ASM) is handled differently and as the two conditions bear different psychosocial consequences, such as duration of driving ban [5].

In this study, we sought to evaluate predictors for ASS compared to US in patients presenting to the ER with an epileptic fit. As secondary outcome parameter, we aimed to compare the diagnostic findings and the acute pharmacological management of patients with ASS and US.

Methods

Patient sample

In this retrospective analysis, patients who presented to the ERs of two sites of the Charité-Universitätsmedizin Berlin (Campus Virchow-Klinikum and Campus Mitte) from 1st of January 2014 to 31st of December 2014 with the diagnosis of a seizure or epilepsy (ICD-10 codes G40.x and R56.x) were examined. Patients aged 18 years or older with a confirmed diagnosis of an epileptic seizure as the leading cause for presenting in the ER were included in this study. We did not include patients who presented with status epilepticus (G41.X). The rationale behind this decision was to keep the study population more homogenous as status epilepticus differs from self-limiting seizures with respect to the spectrum of causes as well as with respect to clinical management and prognosis [6]. In case of more than one seizure-related visit per patient to the ER in the study period, only the first visit was taken into account. This was done to avoid distortion of our results regarding demographics when including a patient with seizure recurrence more than one time. Data on demographics and seizure characteristics, diagnostic procedures and pharmacological treatment were retrieved from the in-house database. To validate the initially given diagnosis, documentation from the ER and discharge reports were analyzed by two neurologists with expertise in epileptology (LSR and ABK). The study was approved by the local ethics committee (EA1/061/15) and, therefore, has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Due to the retrospective nature of the study, informed consent from individual patients was waived.

Definitions and classifications of variables

ASS were defined according to the International League Against Epilepsy (ILAE) recommendations as a seizure occurring in close temporal relationship with an acute systemic or

central nervous system insult [2]. ASS were categorized into those occurring within 48 h of metabolic-toxic disturbances and those manifesting within 7 days of acute CNS lesions due to structural or infectious/inflammatory pathology. ASS was considered a consequence of alcohol withdrawal if the seizure occurred within 48 h of last alcohol consumption in patients with alcohol addiction; in addition, typical neuropsychiatric and vegetative signs were considered if present. Concomitant etiologies such as dysionias were excluded via blood testing. US were defined as occurring in the absence of the mentioned acute metabolic-toxic disturbances or CNS insults. In accordance with the current ILAE recommendations, seizures due to facilitating factors in patients with established epilepsy such as non-adherence to ASM or sleep deprivation were not considered as acute symptomatic [2]. Based on semiology, seizures were dichotomized into bilateral/generalized tonic-clonic seizures (i.e., focal to bilateral tonic-clonic seizures as well as tonic-clonic seizures with generalized and unknown onset) and focal seizures with preserved or impaired awareness. Patients were classified to have had an unclassified seizure semiology, if seizure description did not allow attribution to a specific semiology.

Statistical analysis

Categorical data were analyzed with Pearson's Chi-Square Test. For continuous data, the median and the interquartile range (IQR) are reported. For group comparison, the Mann-Whitney *U* test was used for continuous nonparametric variables. Logistic regression analysis was performed to calculate odd ratios with 95% confidence intervals (95% CI) for identification of variables being independently associated with ASS (inclusion method: stepwise backward, $p < 0.1$ [p in], $p < 0.05$ [p out], iteration 20, cutoff set 0.26, constant incorporated). In the logistic regression model, relevant clinical data obtainable upon examination in the ER (i.e., patients' sex and age, seizure semiology and absence vs. presence of prior diagnosis of epilepsy) were included as possible confounding variables. *p* values < 0.05 were considered statistically significant. Statistical analysis was performed with SPSS Statistics, version 26, (IBM, Armonk, US-NY).

Results

Study population

During the study period, 1435 adult patients admitted to the ER had been coded with epileptic seizures or epilepsy (ICD-10 codes R 56.8 and G40.x). Of those, 824 admissions were excluded from the analysis. The patient selection is shown in Fig. 1.

Our final analysis included 695 patients, 452 (35%) were female, median age was 47.8 years (IQR 32.0–62.9), 213 patients (30.6%) presented with a first seizure. One hundred seventy patients (24.5%) had an ASS and 525 patients (75.5%) had an US.

Predictors for ASS

Binary logistic regression showed male sex (OR 3.173), no prior diagnosis of epilepsy (OR 11.235), and bilateral/generalized tonic–clonic seizures (OR 2.982) to be independently associated with ASS (see Table 1).

Taking the results from the logistic regression analysis, we developed a scoring system for estimating the probability of acute symptomatic seizure in the ER (Table 2). The positive predictive value of a seizure with bilateral/

generalized tonic–clonic semiology in a male patient without prior diagnosis of epilepsy to be acute symptomatic was 57.1% (95% CI 48.9–64.9).

Causes of ASS and US

ASS were caused by metabolic–toxic disturbances in 138 cases (81.2%), alcohol-withdrawal was most common (126 patients, 74.1% of all ASS), other reasons were withdrawal from or intoxication with different drugs, such as benzodiazepines and gamma-hydroxybutyric acid. Other rare metabolic causes were hyponatremia and hypoglycemia. The remaining 32 ASS (18.8% of all ASS) were due to cerebral insults (intracerebral hemorrhage and ischemic stroke) and other structural etiologies (brain surgery, meningoen- cephalitis, posterior reversible encephalopathy syndrome,

Fig. 1 Patient selection. This figure shows the patient selection according to inclusion and exclusion criteria as well as allocation of patients with regards to acute symptomatic and unprovoked seizures

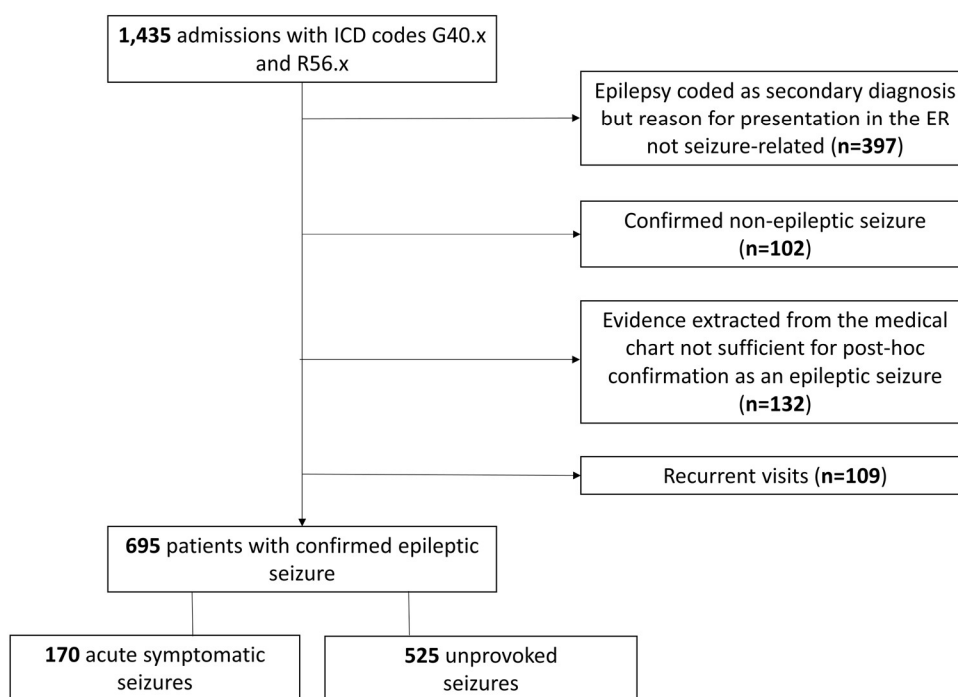


Table 1 Predictors for acute symptomatic seizures

	All epileptic seizures (n = 695)	Acute symptomatic (n = 170 [24.5%])	Unprovoked (n = 525 [75.5%])	Binary logistic regression Exp(B) [95% CI]
Male sex, n (%)	452 (65.0)	140 (82.4)	312 (59.4)	3.173 (1.972–5.104)
Age, years, median [IQR]	47.8 [32–62.9]	48.2 [39.5–58.5]	47.7 [29.5–64.9]	n.s
No prior diagnosis of epilepsy, n (%)	287 (41.3)	139 (81.8)	148 (28.2)	11.235 (7.198–17.537)
Seizure semiology				
Focal (aware/impaired awareness), n (%)	71 (10.2)	6 (3.5)	65 (12.4)	1.000
Bilateral/generalized tonic–clonic, n (%)	532 (76.6)	138 (81.2)	394 (75.0)	2.982 (1.172–7.588)
Unclear, n (%)	92 (13.2)	26 (15.3)	66 (12.6)	2.535 (0.890–7.221)

n number, IQR interquartile range, 95% CI 95% confidence interval, n.s. not significant

Table 2 Scoring system estimating the probability of acute symptomatic seizure in the ER

Total Score	Positive predictive value for acute symptomatic seizure (95% CI)
0	0.0% (0–10.4)
1	2.6% (0.1–6.3)
2	13.3% (9.0–19.0)
3	33.3% (15.5–56.9)
4	47.3% (36.8–57.9)
5	57.1% (48.9–64.9)

Items to score: male sex: 1 point. Generalized/bilateral tonic–clonic seizure semiology: 1 point. No prior diagnosis of epilepsy: 3 points
CI confidence interval

post-hypoxic encephalopathy, and traumatic brain injury). One seizure was due to a high voltage accident. For visualization of details, see Fig. 2a.

Patients with ASS related to alcohol-withdrawal compared to those with ASS due to all other etiologies were more often male (87% vs. 67%; $p < 0.003$), were younger (47 years vs. 62 years, $p < 0.001$) and more often previously had seizures (69% vs. 23%; $p < 0.001$).

Of the 525 patients with US, 13 patients (2.5% of all US) were considered to have had an isolated US, i.e., they had a first US and MRI and EEG showed no relevant pathologies which would indicate an increased risk of seizure recurrence. In 41 patients with first US (7.8% of all US), the diagnostic workup was incomplete, i.e., the patients were

discharged before MRI and/or EEG had been performed, preventing the further allocation of the seizure to an isolated event or to epilepsy. Four hundred and seventy-one patients (89.7%) had US in the context of epilepsy (Fig. 2b), in 377 cases, the diagnosis had been established before presentation to the ER, in 94 cases, the diagnosis was made after the diagnostic workup following the seizure leading to inclusion in this study.

Diagnostic procedures

Neuroimaging was performed in 494 patients (71.1%) during the hospital stay. Three hundred and forty-three patients received a CT, 54 patients an MRI, and 97 patients received both. In 141 patients with the final diagnosis of ASS and in 353 patients with the final diagnosis of US, neuroimaging was performed (82.9% vs. 67.2%, $p < 0.001$). All patients who eventually had ASS underwent neuroimaging within 24 h of presentation to the ER. An acute pathology was seen in 47 out of 494 patients with neuroimaging (9.5%). In patients with ASS, imaging revealed an acute pathology in 33 cases (23.4% of those with imaging) and a remote pathology in 57 cases (40.4%). In 28 of the 33 patients with ASS, the acute pathology was considered the underlying cause for the ASS, while it was the consequence of the epileptic fit such as intracranial hemorrhage in 5 cases (see Fig. 3a).

In patients with a final diagnosis of US, imaging revealed an acute pathology in 14 cases (4.0% of US with neuroimaging). This was significantly less often than in patients who were eventually considered to have had an ASS (23.4%;

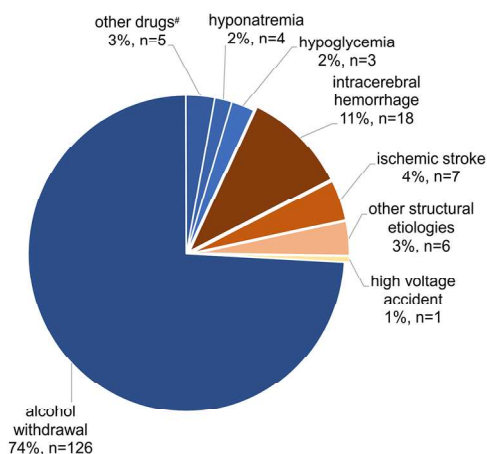
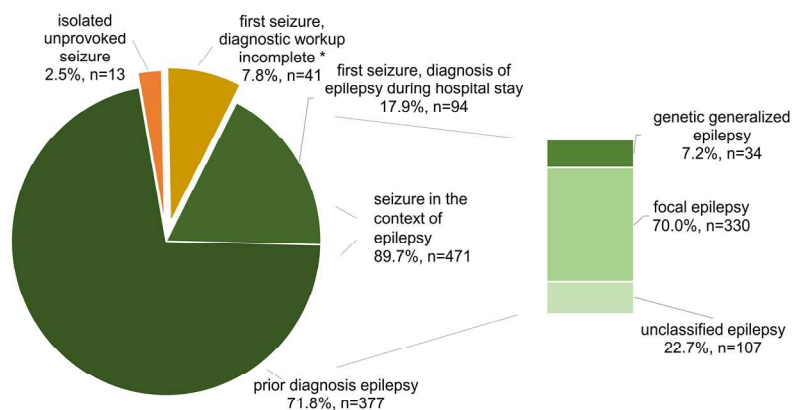
a Etiology of acute symptomatic seizures, n=170**b Allocation of unprovoked seizures, n=525**

Fig. 2 Etiology of acute symptomatic seizures and allocation of unprovoked seizures. **a** Shows the etiologies of ASS. Metabolic–toxic disturbances are shown in blue colors, structural causes are in red tones. **b** Displays the allocation of unprovoked seizures. The bar graph illustrates the classification of established epilepsies. *n* number. [#]Other drugs include intoxication with gamma-hydroxybutyric acid

and withdrawal of benzodiazepines. *This includes 34 patients who presented with a first seizure and seven patients, where it remained unclear, whether the seizure was isolated or recurrent. *PPV* positive predictive value, *NPV* negative predictive value, *CI* confidence interval

$p < 0.001$). In the 8 out of 14 patients with acute pathology, it was considered a consequence of the seizure. In 5 patients, the pathology was considered an incidental finding not related to the seizure (4 patients with subcortical cerebral ischemia, 1 patient with overdrainage of a ventriculo-peritoneal shunt), one patient had an acute progress of the etiology underlying the epilepsy (see Fig. 3b).

Clinical course and therapeutic intervention

A total of 91 patients (13.1%) received acute ASM such as lorazepam and diazepam in the prehospital phase and 254 patients (36.5%) received ASM in the ER (mostly lorazepam and clobazam). Of these, 47 patients received ASM both in the prehospital phase and in the ER.

In the prehospital phase, acute ASM were administered in 29 patients with a final diagnosis of ASS (17.1% of all patients with ASS) and in 62 patients with a final diagnosis of US (11.8% of US; $p = 0.078$).

In the ER, 79 patients (11.4%) had a seizure recurrence. There was no statistically significant difference in early seizure recurrence between patients with ASS and US (13.5% vs. 10.7%; $p = 0.307$). There was also no statistically significant difference in seizure recurrence in the ER between ASS related to alcohol withdrawal and ASS due to other causes (14.2% vs. 11.6%, $p = 0.673$).

In the ER, acute ASM were given to 95 patients with the final diagnosis of ASS (55.9%) and to 159 patients who eventually were considered to have had an US (30.3%, $p < 0.001$).

Figure 4 shows medical treatment in patients with and without seizure recurrence. Of the 616 patients without

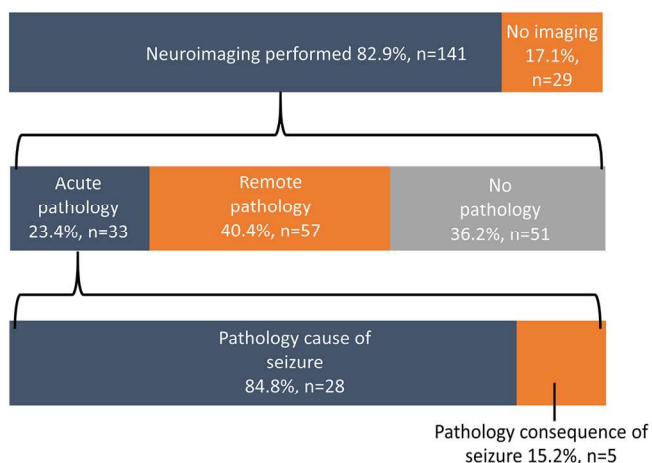
seizure recurrence, 226 (33.6%) received ASM therapy in the prehospital phase and/or the ER. Of the 79 patients with seizure recurrence, 72 (91.2%) received ASM therapy in the ER (seven of these patients also had received ASM therapy in the prehospital phase).

Discussion

In this study, we analyzed ASS as compared to US in the ER with respect to predictors, patient characteristics, diagnostic procedures, and acute treatment. The results of this study are important for everyday clinical management as they can help differentiating ASS from US in the ER, which is essential regarding acute diagnostic workup and decisions on further management of the underlying condition.

One in four patients presenting with an epileptic fit had ASS, all other patients had US. As our main outcome, we identified the variables male sex, no prior diagnosis of epilepsy, and bilateral/generalized tonic-clonic semiology to be independently associated with ASS. The association between male sex and ASS has been described previously [7]. The likely explanation is that most common causes of ASS (alcohol withdrawal, ischemic and hemorrhagic stroke) predominate in male patients [8, 9]. ‘No prior diagnosis of epilepsy’ was the strongest predictor for ASS. Epilepsy is per definition associated with recurrent US. An independent association between prior diagnosis of epilepsy and US, or vice versa no prior diagnosis of epilepsy and ASS is, therefore, plausible. It is noteworthy that the information on prior diagnosis of epilepsy in some cases is not readily available when treating a patient in the ER as the patient

a Neuroimaging in patients with acute symptomatic seizures



b Neuroimaging in patients with unprovoked seizures

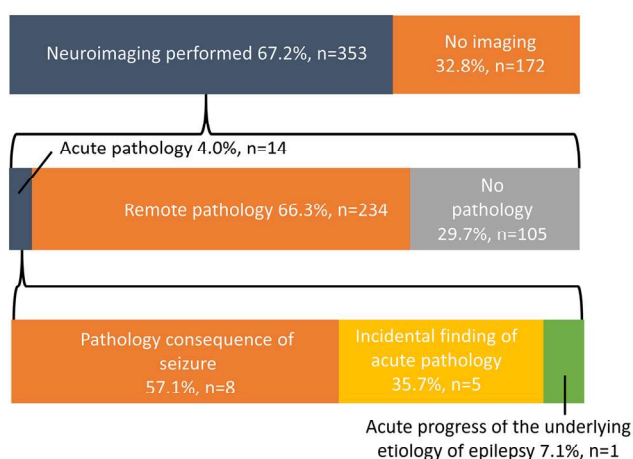


Fig. 3 Neuroimaging in patients with acute symptomatic and unprovoked seizures. **a, b** Show the proportion of patients that received neuroimaging (first row), the findings of the performed neuroimag-

ing (second row) and the causal relationship of acute pathologies with respect to the seizure (third row). *n* number

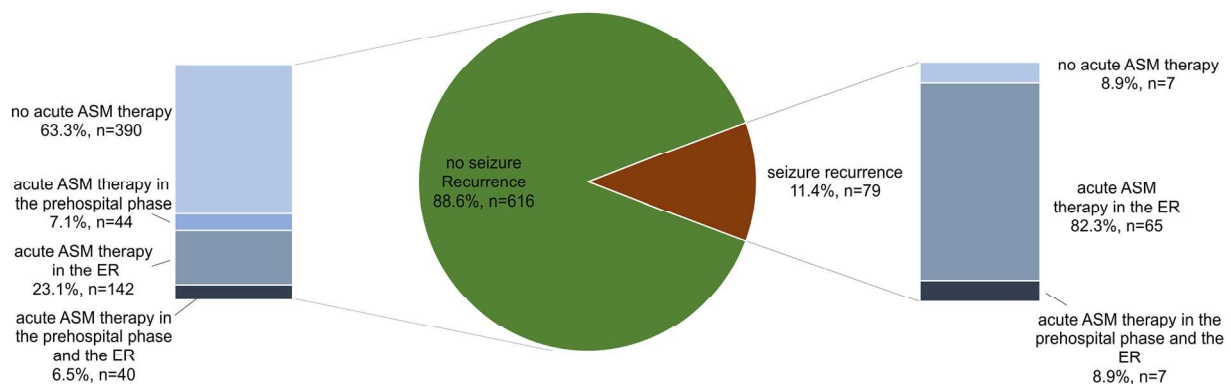


Fig. 4 ASM therapy in patients with and without seizure recurrence. The pie chart illustrates frequency of seizure recurrence. The left bar graph shows ASM therapy in patients without seizure recurrence, the

right bar graph demonstrates ASM therapy in patients with seizure recurrence. *n* number

maybe unable to give this information during postictal desorientation. This stresses the importance of contacting the patients' family, next of kin etc. to attain information on possibly pre-existing epilepsy. The association between ASS and a bilateral/generalized tonic-clonic semiology is more difficult to interpret. It may partly be explained by the high proportion of alcohol withdrawal seizures which are mostly considered to be generalized tonic-clonic [10]. Another possible explanation for the dominance of bilateral/generalized tonic-clonic seizures in the ASS group could be that most patients with unprovoked seizures had a focal epilepsy and thus focal aware and impaired awareness seizures.

The variables identified to be associated with ASS have a moderate diagnostic merit: the positive predictive value of a bilateral/generalized tonic-clonic seizure in a male patient without prior diagnosis of epilepsy to be acute symptomatic is 57%. The simple score that we developed can help identifying patients in whom a thorough search for an acute underlying condition is reasonable. A validation of this score in an external cohort would be desirable.

Approximately 80% of ASS were due to metabolic-toxic disturbances, almost three quarters of all ASS were related to alcohol withdrawal. Around 20% of ASS cases were caused by an acute structural lesion. The dominance of seizures related to alcohol withdrawal in this study is striking. This finding is in accordance with a study on 472 patients in Denver, the rate of ASS due to alcohol withdrawal was 59% [11]. A lower rate of only 14% ASS due to drug withdrawal was seen in an analysis of 692 patients in Rochester County in Minnesota covering the years 1935–1984 [7]. The lowest rate was reported in a study from Hong Kong, where alcohol/drug withdrawal was the cause in only 3.8% of ASS in a total of 155 patients [12]. These low rates of alcohol-withdrawal related seizures may be explained by the overall lesser amount of alcohol consumption in both the United States and especially Asia as compared to Germany [13].

Multicenter studies would be desirable to gain further insight in the proportion of different causes for ASS.

Hemorrhagic and ischemic stroke were the most common structural causes of ASS. The risk of ASS is 4–16% in hemorrhagic stroke patients [14, 15] and 3–6% following ischemic stroke [14, 16]. Most ASS occur within 24 h after the cerebrovascular event [14, 17]. Still, it is likely that a significant proportion of ASS after stroke is not seen in the ER as the patients have already been admitted to a stroke unit when the ASS occurs.

Around 80% of patients with ASS and two thirds of patients with US received timely neuroimaging. The question which patient should receive cerebral imaging and which patient should not is difficult to answer. Roughly 1 in 10 patients who received neuroimaging had an acute pathology, but the diagnostic yield of neuroimaging varied drastically between ASS (20%) and US (4%). In only 2% of patients with US who underwent neuroimaging, an acute pathology was detected that was considered a consequence of the seizure. Even though most injuries caused by epileptic seizures are minor [18], there is evidence that neurological examination is not sufficiently predictive of traumatic brain injuries [19]. This even led to the suggestion that after an epileptic seizure every patient should get a CT scan in the ER [19]. An analysis of data on 381 patients who received neuroimaging after a recurrent (non-index) unprovoked seizure showed pathological findings in 59% of cases. In 3% of cases, neuroimaging led to a treatment change. An increased diagnostic yield of neuroimaging was associated with the clinical parameters acute head trauma, prolonged impaired consciousness, and focal neurological deficits [20]. Taken together, the findings of the aforementioned study as well as the variables that were independently associated with ASS in our study should be considered when deciding whether to request acute neuroimaging or not after an epileptic seizure.

Whether to treat a patient with acute ASM or not is the final relevant question when approaching a patient after an epileptic fit in the ER. In addition, there is no indication for permanent treatment with ASM after an ASS as seizure recurrence rates are overall low [3]. Following a first US, permanent ASM therapy is usually justified when either EEG or MRI examination show signs of an increased risk of further epileptic fits, thus defining epilepsy [21]. In the ER, acute ASM were administered in 56% of the current patients with ASS and in 30% of the patients with US. With more than 10%, the seizure recurrence rate was high in patients with ASS and US. In a study on almost 500 children with a first seizure (about one quarter of which had an ASS), 14% had a recurrence within 24 h [22]. It is important to consider that in our study population approximately 90% of US occurred in the context of epilepsy, which is per definition associated with an inherent risk of seizure recurrence.

More than 90% of the current patients received ASM therapy after seizure recurrence in the ER. Interestingly, also 30% of patients without seizure recurrence were treated with an ASM in the ER. Due to the retrospective nature of the study, no scientifically sound assertions can be made with respect to the effectiveness of treatment with ASM. In a randomized controlled trial, the efficacy of acute antiseizure treatment after ASS due to alcohol withdrawal has been demonstrated; the administration of 2 mg i.v. lorazepam was associated with a significant reduction of seizure recurrence in the first 6 h after the index seizure (3% vs. 24% recurrence rate in the placebo group) [23].

There are limitations to consider. Although our study includes two ERs covering heterogeneous parts of the city, it would be desirable to analyze data from more centers which would increase generalizability of our findings. In addition, the dominance of seizures related to alcohol withdrawal could potentially limit the informative value on ASS of other etiologies. Finally, even though we excluded 102 patients with confirmed non-epileptic seizures and in addition 132 patients, where evidence extracted from the medical charts was not sufficient for post-hoc confirmation of an epileptic seizure, we cannot entirely exclude that single patients in our cohort eventually have had a psychogenic non-epileptic seizure or syncope. In a previous study, a fraction of almost 14% of seizures in the ER was misdiagnosed [24]. However, in the current cohort, diagnosis of epileptic seizures was reassessed by the authors, not only based on information gathered in the ER but, if available, also on findings collected during the subsequent hospital stay.

In summary, we characterized ASS and US in two large ERs. ASS were independently associated with male sex, no prior diagnosis of epilepsy, and bilateral/generalized semiology. Neuroimaging was performed more often in patients with a final diagnosis of ASS than in those after US. The same was true for administration of acute ASM. The results

of this study can help identifying patients with ASS in the ER which is important as ASS bear relevant consequences regarding further diagnostic procedures and treatment. It would be desirable to expand our study to a prospective design in more ERs at different, heterogeneous locations.

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Author contributions Conceptualization: LCR, ABK, JID and MH. Investigation: LCR, ABK. Formal analysis: LCR and JID. Resources: ABK and MH. Visualization: JID. Writing original draft: JID and LCR. Writing—review and editing: ABK and MH. Supervision: ABK and MH. Project Administration—MH. LCR and JID contributed equally to this work and share first authorship. All authors approved the final manuscript.

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Availability of data and materials The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Code availability Not applicable.

Declarations

Conflict of interest LCR, JID, and ABK declared no conflicts of interest with respect to the research, authorship, and/or publication of this article. MH reports personal fees from Arvelle, Bial, Desitin, Eisai, GW Pharma, UCB, and Zogenix, outside the submitted work.

Ethics approval Institutional approval for this observational study was provided by the local Ethics committee (EA1/061/15) of Charité-Universitätsmedizin Berlin.

Consent to participate Not applicable.

Consent for publication Not applicable.

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2.1.2 Epileptogenität von Läsionen der weißen Substanz mutmaßlich vaskulärer Genese

Doerrfuss JI, Hebel JM, Holtkamp M. **Epileptogenicity of white matter lesions in cerebral small vessel disease: a systematic review and meta-analysis**. Journal of Neurology. 2023 Oct; 270(10):4890-4902. doi: 10.1007/s00415-023-11828-6. Epub 2023 Jun 21.

In der zuvor vorgestellten Arbeit (2.1.1) wurden klinische Variablen untersucht, die für die Einschätzung eines Anfalls hinsichtlich seiner unprovokierten oder akut-symptomatischen Genese herangezogen werden können. Ist diese Frage mit ausreichender Sicherheit beantwortet, schließt sich beim Vorliegen unprovokierter Anfälle die Frage an, ob es sich um ein einmaliges Ereignis oder um eine Epilepsie handelt und ob eine ASM indiziert ist. Hierfür werden die Ergebnisse des EEGs sowie einer zerebralen Bildgebung herangezogen (Bouma et al. 2016, Hesdorffer et al. 2009). Bildgebend wird bislang i.d.R. der Nachweis einer strukturellen Beteiligung kortikalen Gewebes gefordert. Bei vielen älteren Patient:innen zeigt sich im MRT zwar keine solche Läsion, allerdings finden sich mehr oder wenig stark ausgeprägte Läsionen der weißen Substanz (WML) mutmaßlich vaskulärer Genese (Hanby et al. 2015, Mao et al. 2016). Die Epileptogenität von Läsionen der weißen Substanz und damit auch deren Behandlungsbedürftigkeit mit ASM ist bislang ungeklärt. In einem systematischen Review mit Meta-Analyse wurde daher die bisherige Datenlage zu drei klinisch relevanten Fragestellungen untersucht und zusammengefasst:

- 1.) Unterscheidet sich das Ausmaß von WML bei Patient:innen mit epileptischen Anfällen im Vergleich zu gleichaltrigen Patient:innen ohne Anfälle?
- 2.) Ist das Vorhandensein von WML bei Patient:innen mit einem ersten epileptischen Anfall oder einer Epilepsie mit einem erhöhten Rezidivrisiko erneuter epileptischer Anfälle assoziiert?
- 3.) Ist eine Therapie mit ASM bei Patient:innen mit erstmaligem epileptischen Anfall bei Vorliegen von WML gerechtfertigt, auch wenn keine kortikalen Läsionen vorliegen?

Hierzu erfolgte ein systematischer Review mit Meta-Analyse nach *PRISMA guidelines*. Insgesamt wurden 2.813 Studien gescreent. Elf Fall-Kontroll-Studien, die 2.983 Teilnehmer:innen umfassten, wurden in die Analyse eingeschlossen.

In sechs der Studien wurde das Vorliegen von WML untersucht. Dabei waren epileptische Anfälle mit einer erhöhten Prävalenz von WML assoziiert (OR: 2,14, 95% KI: 1,38-3,33, $I^2 = 0,27$). Eine noch ausgeprägtere Assoziation zeigte sich in der Analyse von fünf Studien, die das Vorliegen relevanter WML, gemessen durch visuelle Analogskalen, bei Patient:innen mit und ohne epileptische Anfälle verglichen (OR: 3,96, 95% KI: 2,55-6,16, $I^2 = 0,00$). In drei Studien wurde ein volumetrischer Vergleich von WML zwischen Patient:innen mit und ohne Anfälle durchgeführt. In einer Meta-Analyse mit von den Autor:innen der Studien zur Verfügung gestellten Primärdaten zeigte sich keine statistisch signifikante Assoziation zwischen WML-Volumen und Vorliegen von epileptischen Anfällen (OR 1,30, 95% KI 0,91-1,85, $I^2 = 0,00$).

Der Einfluss von WML auf das Rezidivrisiko von epileptischen Anfällen wurde in nur zwei Studien untersucht, die Ergebnisse waren uneindeutig. In beiden Arbeiten wurden Patient:innen mit bereits bestehender Epilepsie eingeschlossen. Es konnten keine Studien identifiziert werden, die die Effektivität einer ASM bei Patient:innen mit WML thematisierten.



Epileptogenicity of white matter lesions in cerebral small vessel disease: a systematic review and meta-analysis

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Abstract

Background The epileptogenic properties of white matter lesions (WML) in cerebral small vessel disease (CSVD) are not yet understood. The aim of our systematic review and meta-analysis was to estimate the association between the extent of WML in CSVD and epilepsy, analyze whether these WML are associated with an increased risk of seizure recurrence, and evaluate if treatment with anti-seizure medication (ASM) is justified in first-seizure patients with WML and no cortical lesions.

Methods Following a pre-registered study protocol (PROSPERO-ID CRD42023390665), we systematically searched PubMed and Embase for relevant literature comparing WML load between patients with epilepsy and controls as well as studies on seizure recurrence risk and ASM therapy in the presence vs. absence of WML. We calculated pooled estimates using a random effects model.

Results Eleven studies comprising 2983 patients were included in our study. Presence of WML (OR 2.14, 95% CI 1.38–3.33) and presence of relevant WML as assessed by visual rating scales (OR 3.96, 95% CI 2.55–6.16) but not WML volume (OR 1.30, 95% CI 0.91–1.85) were significantly associated with seizures. These results stayed robust in sensitivity analyses restricted to studies on patients with late-onset seizures/epilepsy. Only two studies assessed the association between WML and risk of seizure recurrence with conflicting results. Currently, there are no studies on the efficacy of ASM therapy in the presence of WML in CSVD.

Conclusions This meta-analysis suggests an association between presence of WML in CSVD and seizures. More research is needed addressing the association between WML and risk of seizure recurrence and ASM therapy focusing on a population of patients with a first unprovoked seizure.

Keywords Epilepsy · Seizures · Stroke · Leukoencephalopathy

Introduction

Stroke and seizures have a strong reciprocal relationship: Cortical stroke is the most common etiology of late-onset epilepsy [1]. Vice versa, late-onset epilepsy of unknown

etiology is associated with an up to threefold increased risk of subsequent strokes [2]. Usually, only strokes and other pathologies of cortical localization are considered to be epileptogenic. However, in up to 70% of patients with a first unprovoked seizure, a clear epileptogenic lesion cannot be identified [3]. Even after the diagnosis of epilepsy has been made, in approximately 50% of adult patients, the etiology remains unknown [1, 4]. Yet, in a significant proportion of older patients with a first seizure or epilepsy, white matter lesions (WML) are detected [5–7]. In these patients, WML are mainly caused by cerebral small vessel disease (CSVD) [8, 9]. Their epileptogenic properties are not yet understood. However, in patients with a first unprovoked seizure, it is of utmost clinical importance to know if WML increase the risk of further seizures significantly and thus contribute to fulfill the definition criteria of epilepsy [10]. This would have implications with respect to starting anti-seizure

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medication (ASM) and concerning the duration of a driving ban. The potential epileptogenic properties of WML are of particular importance in first-seizure patients where the EEG shows no epileptiform discharges. The latter would already indicate epilepsy and in most cases the need for ASM.

There are hypotheses that WML may cause seizures by disruption of subcortical networks, blood–brain barrier dysfunction, impaired cerebral perfusion, and inflammation [11, 12]. Moreover, WML could be a surrogate marker for smaller cortical infarcts that are not detected even by 3 Tesla MRI [13, 14].

To determine whether WML of presumed vascular origin should be considered epileptogenic or not, three questions must be addressed:

- (1) In patients with a first unprovoked seizure or epilepsy, do the amount and localization of WML of presumed vascular origin differ in comparison to people who never had a seizure?
- (2) In patients with a first unprovoked seizure or epilepsy, is the presence of WML of presumed vascular origin associated with an increased risk of recurrent seizures as compared to patients without WML?
- (3) For patients with a first unprovoked seizure and WML of presumed vascular origin with no cortical structural lesions in MRI, does treatment with ASM reduce the risk of seizure recurrence compared to patients with no pharmacological treatment?

This systematic review and meta-analysis aim to provide an overview of the current evidence regarding these very questions.

Methods

This systematic review and meta-analysis follow the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [15]. The review protocol was registered in the PROSPERO database for systematic reviews prior to the commencement of the literature search (registration number CRD42023390665).

Search strategy

We systematically searched the Embase and MedLine databases using OVID on February 3, 2023. The full search strategy can be accessed in the supplemental material (Table E1, online only). The literature search included studies published from January 2003 to February 2023, and was restricted to studies in English language. Editorials, case reports, comments, and review articles were not included in this systematic review and meta-analysis. As several research questions

were epidemiological, we considered observational studies as eligible. To answer our research questions, all studies needed a control group consisting of patients without seizures/epilepsy (research question 1), without WML (research question 2), or without pharmacological treatment (research question 3).

Duplicates in the search results were removed through a combination of automated and manual methods using End-Note. Two authors (JID and JMH) independently screened titles and abstracts. The same authors then assessed the full-texts of potentially eligible studies to decide on inclusion. Discrepancies in the assessment of eligibility were resolved by consensus between the authors.

Data extraction and synthesis

In a next step, we extracted data on study characteristics, patient population, exposure, and outcome using a pre-specified template. The following data were extracted: author, year of publication, study design, sample size, size and properties of case groups and control groups, mean age, sex, quantification method of WML, imaging modality, outcome assessment, and outcomes (presence of WML, lesion load and volume with mean and standard deviation, seizure recurrence rate, effect estimates and 95% confidence intervals (CI) where applicable).

Assessment of risk of bias

Risk of bias for each study was assessed independently by two of the authors (JID and JMH) using the case–control subscale of the Newcastle–Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses [16]. This score ranges from 0 to 9 with a score of ≥ 7 indicating a study of high methodical quality. The NOS comprises the domains ‘selection’, ‘comparability’ and ‘outcome’. In the domain ‘comparability’, a maximum of two points can be awarded. One point is given if the study controls for the most important risk factor as selected by the raters. Another point is awarded if the study controls for any additional factor. We considered the cardiovascular risk profile to be the most important factor to control for. Discrepancies in the assessment of bias were resolved through consensus. The authors then assessed the overall quality of evidence for each research question using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) scale. The GRADE scale is a 4-point rating scale, ranging from ‘*very low*’ (the true effect is probably markedly different from the estimated effect) to ‘*high*’ (the authors have a lot of confidence that the true effect is similar to the estimated effect). Observational studies are primarily given a certainty rating of ‘*low*’ with several factors being able to reduce or increase the certainty of evidence [17].

Missing data

To obtain relevant missing data, we contacted the corresponding authors of six studies through email. Authors of three studies sent additional data.

Statistical analysis

In our meta-analysis, we calculated summary Odds Ratio (OR) and 95% Confidence Intervals (CI) for the association of seizures or epilepsy and WML as measured by different WML quantification methods.

For the presence of any WML and the presence of relevant WML (Fazekas scale score > 1 or ARWMC scale score > 2), we extracted frequencies in the epilepsy/seizure groups and the control groups from each study and then performed a random effects meta-analysis for binary outcomes.

For the association between WML volume and epilepsy, we extracted effect estimates from studies if they were provided. If these were not given in the studies, we requested original data from the corresponding authors and calculated adjusted effects estimates for each study with z-scores of WML volume (adjustment for age and sex; inclusion method: enter, $p < 0.05$ [p in], $p < 0.1$ [p out], iteration 20, and constant included). We then pooled the log-transformed OR and 95% CIs using a random effects model.

To assess heterogeneity, Cochran Q-statistics were calculated and quantified using the I^2 values. We considered an I^2 value > 50% as significant heterogeneity. We assessed publication bias by visual exploration of Funnel plots and Egger's test. All statistics were performed using SPSS Version 28 (IBM, Chicago, USA).

Results

Literature search and study characteristics

A total of 2813 records were screened of which 11 studies were finally included in this systematic review. Figure 1 shows the PRISMA flow chart.

The included studies were published between 2006 and 2022. Ten studies reported WML load of patients with first unprovoked seizure and/or epilepsy as compared to control groups (research question 1) [5–7, 18–25]. Two studies compared risk of seizure recurrence in patients with and without WML (research question 2) [18, 21]. We could not identify any study on treatment with ASM in patients with CSVD-related WML (research question 3). The characteristics of all included studies including imaging modality, properties of the control groups, and WML quantification method are summarized in Table 1. The studies included in this systematic review comprised

a total of 2983 patients; 862 cases and 2121 controls. According to our quality assessment, three studies were of high methodological quality (Table 1, and for more detail: Table E2, online only).

Research question 1: In patients with a first unprovoked seizure or epilepsy, do the amount and localization of WML of presumed vascular origin differ in comparison to people who never had a seizure?

Studies assessing WML load in cases and controls reported either (a) presence of any WML and/or (b) WML load as assessed by a visual rating scale and/or (c) WML volume. One study reported a not further specified degree of white matter changes and was therefore not included in any of the following meta-analyses [24]. A detailed description of the properties of the epilepsy groups as well as individual results regarding lesion load for each study can be found in the supplementary material (Table E3, online only).

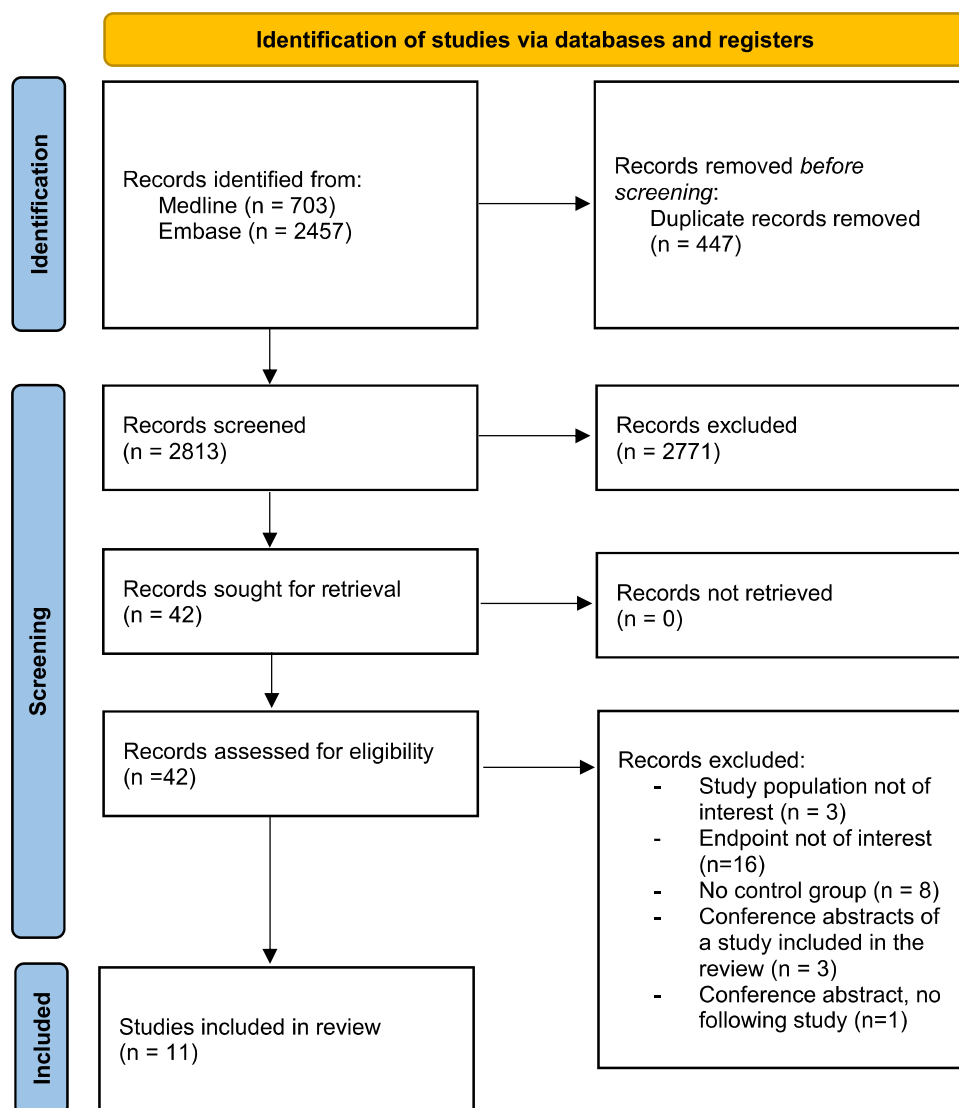
Meta-analysis on presence of WML

Six studies reported presence of WML in 600 cases and 329 controls [5, 6, 18, 20, 23, 25]. Of these studies, four covered only patients with epilepsy [5, 18, 23, 25], one study included only patients with respective first seizures [6], and one study investigated patients with either a first seizure or epilepsy [20]. None of the four studies focusing on patients with epilepsy stated whether patients had new-onset epilepsy or already established epilepsy. One study had two control groups: patients with a transient ischemic attack or lacunar infarction and one control group with healthy controls. Only the second control group was used for the current meta-analysis to facilitate comparability [25].

Patients with a first unprovoked seizure or epilepsy had WML more frequently than the control group (OR 2.14, 95% CI 1.38–3.33, $I^2 = 0.27$, Fig. 2a). This association was more pronounced in a sensitivity analysis including only studies on late-onset seizures in patients aged ≥ 60 years (OR 2.74, 95% CI 1.72–4.34, $I^2 = 0.00$) [6, 20, 25]. The results stayed robust in a sensitivity analysis excluding the single study that only included patients with respective first seizures and in which the control group did not consist of healthy controls (OR 2.05, 95% CI 1.22–3.46, $I^2 = 0.41$) [6].

Visual analysis of the funnel plot for the primary analysis as well as Egger's test ($p = 0.11$) showed no significant asymmetry and was therefore not indicative of a relevant publication bias (Fig. 3a). According to the GRADE certainty ratings, we rate the certainty of evidence as 'low'.

Fig. 1 PRISMA Flow chart of inclusion of studies



Meta-analysis on relevant WML load as measured by visual rating scales

A total of five studies reported the extent of WML as measured by visual rating scales [5, 6, 19, 20, 25]. These studies comprised 500 cases and 299 controls. Two studies included only patients with epilepsy [5, 25], one study investigated only patients with first seizures [6], and two studies included patients with both first seizures and epilepsy [19, 20].

For quantification of WML, all studies used variants of the Fazekas and Wahlund scales, although the application of these scales differed [26, 27]. We considered a score of > 1 on the Fazekas scale (scale range 0–3) and a score of > 2 Wahlund scale (scale range 0–30) as ‘relevant’ WML load. Its presence was associated with seizure(s) (OR 3.96, 95% CI 2.55–6.16, $I^2=0.00$ Fig. 2b). A sensitivity analysis excluding the single study that was not on late-onset seizures/epilepsy and used the Wahlund scale instead of the

Fazekas scale [5] showed similar results (OR 3.93, 95% CI 2.47–6.23, $I^2=0.00$). The results also remained largely unchanged in a sensitivity analysis restricted to studies using a control group of healthy participants (OR 3.89, 95% CI 3.89, 95% CI 1.65–9.15, $I^2=0.00$) [5, 20, 25].

Again, visual inspection of the funnel plot and Egger’s Test ($p=0.77$) were not evident of a relevant publication bias (Fig. 3b).

For the association of a relevant WML load as measured by visual rating scales and seizure(s), we award a GRADE certainty rating of ‘low’.

Meta-analysis on WML volume

Three studies (77 patients, 1403 controls) assessed WML volume in patients with and without epilepsy [7, 22, 23]. None of these studies assessed patients with first seizures or new-onset epilepsy. One study was a retrospective

Table 1 Study characteristics

Author	Year	Study design		Number of participants of cases	Number of controls	Mean age cases (years)	Mean age controls (years)	Properties of control group	Imaging modality	WML quantification method	NOS
		Retrospective case-control	Prospective case-control								
Abraira	2019	✓		100	41/26 ^a	70.9	73.2/68.0	-Control group I: patients with transient ischemic attack or lacunar infarction and no cortical infarcts -Control group II: healthy controls	✓	Fazekas scale ranging from 0–3, including deep WML and periventricular WML	5
De Reuck	2007	✓		242	205	nr	nr	Patients with acute lacunar stroke	✓	Degree of white matter changes, not further specified	3
Hanby	2015		✓	31	15	67.6	65.1	Healthy controls	✓	WML volume	6
Jansen	2008		✓	49	16	43	40	Healthy controls	✓	WML volume	5
Johnson	2019	✓		1,526/ 1,404 ^b	1,429/ 1,372 ^b	78.3	77.0	Participants of a community-based study on atherosclerosis risk without seizures	✓	WML volume WML grade score (0–9)	8
Mao	2016	✓		240	23	42	36	Healthy controls	✓	ARWMC scale ranging from 0–30	8
Maxwell	2013	✓		210	105	72.7	72.4	Healthy controls	✓	Fazekas scale ranging from 0–3, not including periventricular WML	4
Stösser	2019	✓		236	118	82 (median)	79 (median)	Patients with transient ischemic attack	✓	Fazekas scale for periventricular and deep lesions and global (modified) score, each ranging from 0–3 ^c ARWMC scale ranging from 0–3 for each region	5
Tartara	2022	✓		162	87	nr	nr	Patients without leukoariosis	✓	Fazekas scale ranging from 0–3, not further defined	6

Table 1 (continued)

Author	Year	Study design		Number of participants	Number of cases	Number of controls	Mean age cases (years)	Mean age controls (years)	Properties of control group	Imaging modality		WML quantification method	NOS
		Retrospective case-control	Prospective case-control							MRI	CT		
Turon	2021	✓	✓	54	27	27	74.2	72.1	Patients with CSVD (subcortical microbleeds, Fazekas score ≥ 1 or ≥ 1 lacunar infarct)	✓		(a) Fazekas scale for deep WML, dichotomized as Fazekas < 2 vs. Fazekas ≥ 2 and Fazekas scale for periventricular WML (b) 4-point CSVD burden score including WML, lacunar infarcts, microbleeds, and enlarged perivascular spaces	5
Uslu	2021	✓	✓	135	94	41	30.5	33.1	Healthy controls	✓		“global” ARWMC scale, defined as score of the region with the most severe WML ranging from 0–3	7

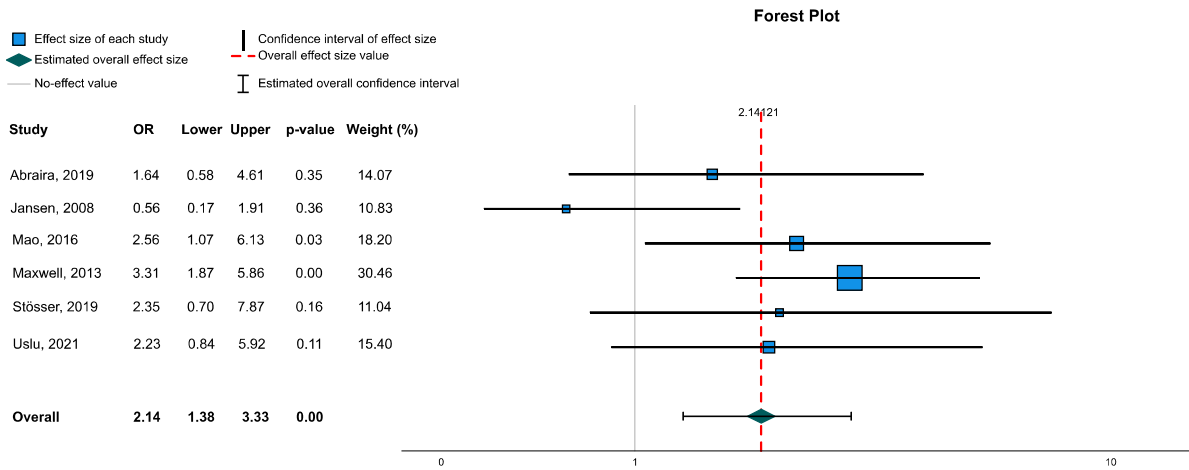
The NOS scale ranges from 0 to 9 with a higher score indicating a superior quality. A score of ≥ 7 indicates a study of high methodological quality *nr* not reported, *na* not applicable, *ARWMC* age-related white matter changes, *WML* white matter lesions, *NOS* Newcastle–Ottawa Scale, *CSVD* cerebral small vessel disease, *CT* computed tomography, *MRI* magnetic resonance imaging

^aTwo control groups, the control group “healthy individuals” was included in the meta-analysis

^bTwo overlapping study populations, the second study population for which a white matter hyperintensity volume was provided was included in the meta-analysis

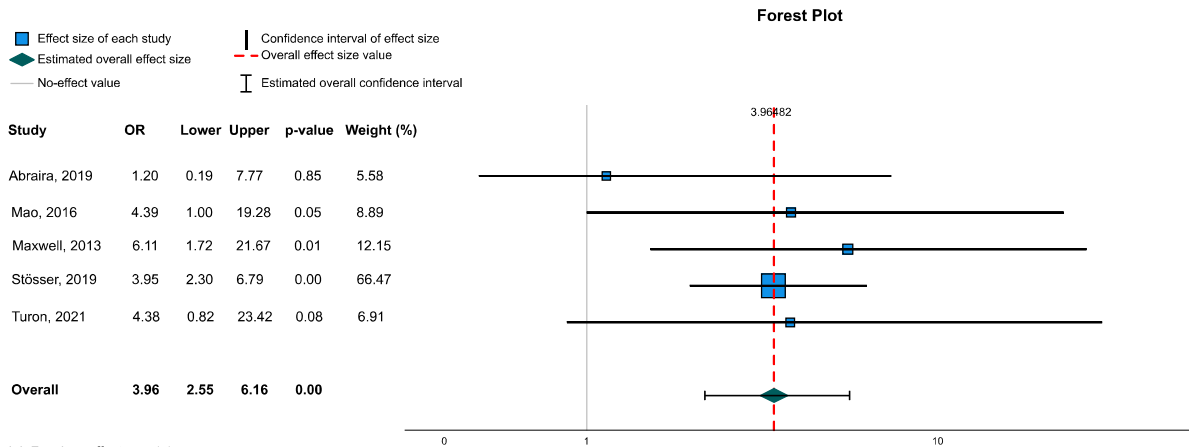
^cThe global score was used in the meta-analysis

a



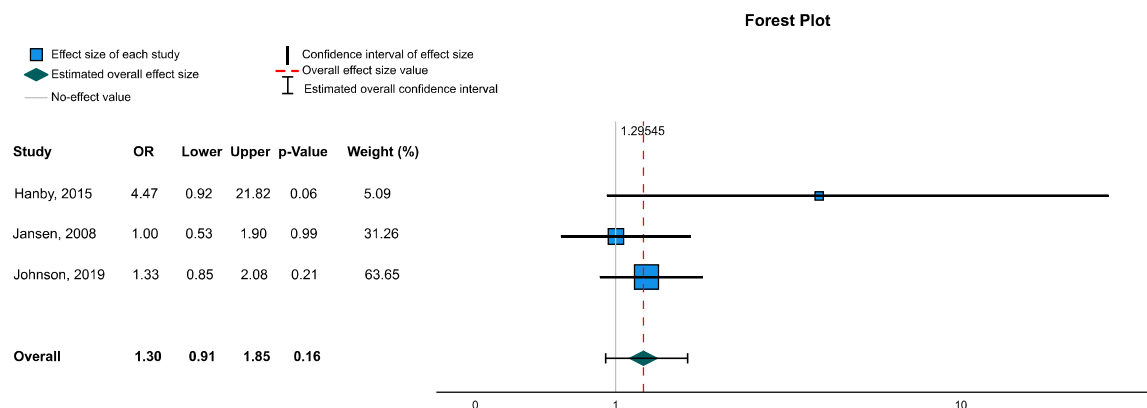
Model: Random-effects model
 Heterogeneity: Tau-squared = 0.08, H-squared = 1.37, I-squared = 0.27
 Homogeneity: Q = 7.12, df = 5, p-value = 0.21
 Axis is shown using log scale

b



Model: Random-effects model
 Heterogeneity: Tau-squared = 0.00, H-squared = 1.00, I-squared = 0.00
 Homogeneity: Q = 2.05, df = 4, p-value = 0.73
 Axis is shown using log scale

c



Model: Random-effects model
 Heterogeneity: Tau-squared = 0.00, H-squared = 1.00, I-squared = 0.00
 Homogeneity: Q = 2.97, df = 2, p-value = 0.23
 Axis is shown using log scale

Fig. 2 Meta-analysis on the association between epilepsy and **a** presence of WML, **b** relevant WML as assessed by visual rating scales, and **c** WML volume

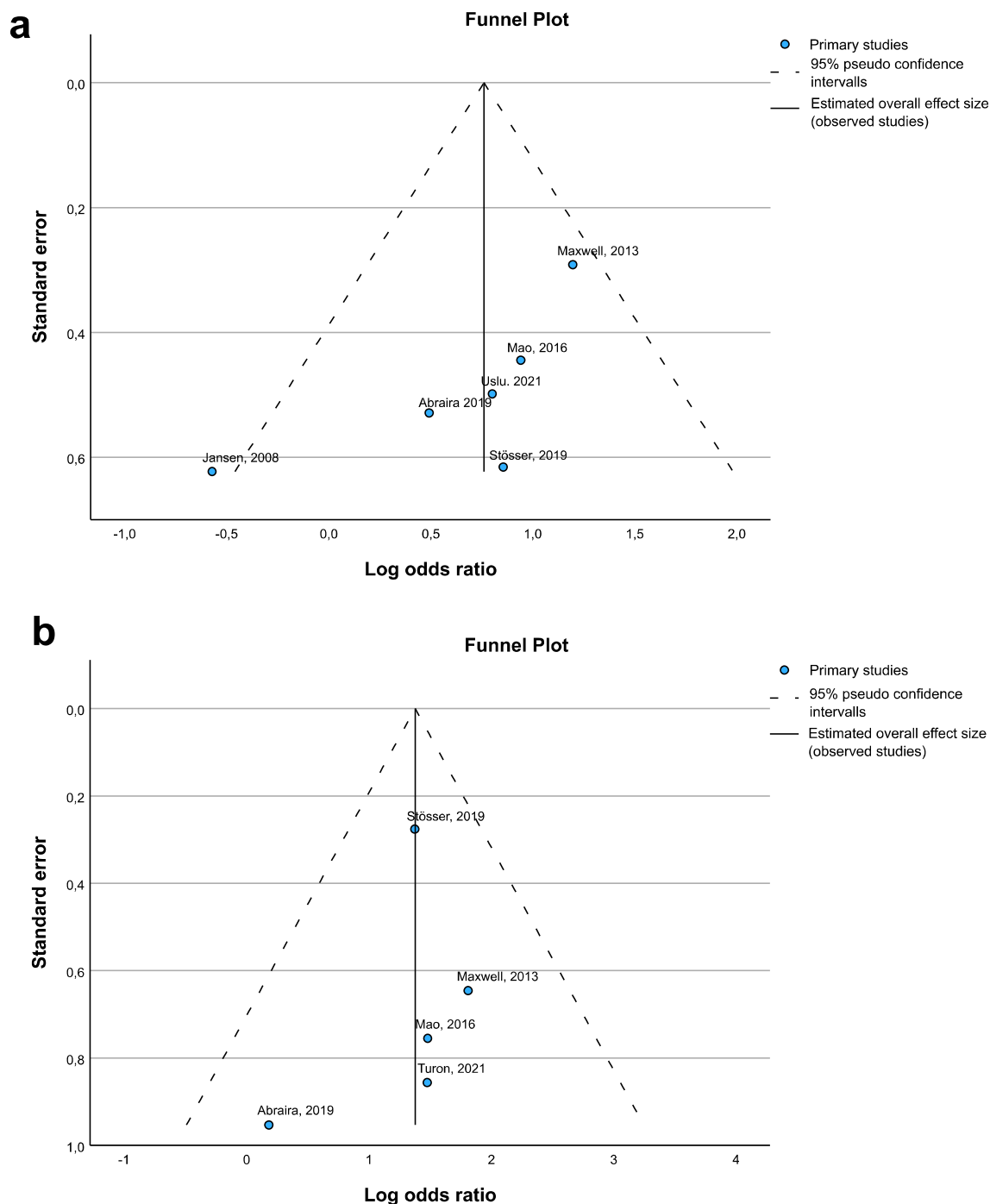


Fig. 3 Funnel plots. This figure shows funnel plots for the association between epilepsy and **a** presence of WML, and **b** relevant WML as assessed by visual rating scales. Due to the small number of stud-

ies on WML volume ($n=3$), we did not calculate funnel plots for the association between epilepsy and WML volume

case–control study, which analyzed the association of the degree and volume of WML earlier in life, as measured in the Arteriosclerosis Risk in Communities (ARIC) study, with epilepsy that was diagnosed later in life [22].

Mean WML volume in the three studies ranged from 160 to 21,800 mm³ in the epilepsy group and 203 to 17,500 mm³

in the control group. All WML volumes were confirmed (and in one study corrected) by the corresponding authors. The numbers given here are the corrected values.

Due to extensive heterogeneity of WML volume between different studies, a meta-analysis of mean differences was not deemed appropriate. We instead analyzed whether

WML volume was independently associated with presence of epilepsy. For this analysis, we used the reported adjusted OR from one study [22], and with original data provided by the authors, calculated OR for z-scores of WML volume adjusting for age and sex for the two other studies [7, 23]. The following meta-analysis showed no association between WML volume and presence of epilepsy (OR 1.30, 95% CI 0.91–1.85, $I^2=0.00$, Fig. 2c). In a sensitivity analysis excluding the one study in which MRI was performed before onset of epilepsy and in which the controls were not necessarily healthy, the results remained without a statistically significant difference (OR 1.76, 95% CI 0.43–7.28, $I^2=0.66$) [22]. The same was true for another sensitivity analysis excluding the one study that was not on late-onset epilepsy (OR 1.90, 95% CI 0.64–5.62 $I^2=0.52$) [23]. Because of the small number of studies, we did not test for funnel plot asymmetry.

Overall, with a GRADE certainty rating of ‘very low’ due to inconsistency of results, there was no association between WML volume and epilepsy.

Research question 2: In patients with a first unprovoked seizure or epilepsy, is the presence of WML of presumed vascular origin associated with an increased risk of recurrent seizures as compared to patients without WML?

We identified two studies analyzing the association between risk of seizure recurrence and WML [18, 21]. These studies included a total of 256 patients with epilepsy of whom 113 had and 143 did not have WML. The characteristics of these studies are summarized in Table 1.

The first study [21] focused on patients with late-onset epilepsy of unknown or structural etiology. Presence of WML was independently associated with an elevated risk of seizure recurrence (RR 1.76, 95% CI 1.01–3.06). The study showed no association between severity of WML and seizure frequency.

The main focus of the second study [18] was to compare lesion load between patients with epilepsy (age ≥ 18 years, exclusion of patients with cardiovascular risk factors) and a control group; therefore, this study is also part of the meta-analysis on presence of WML. In the epilepsy group, presence of WML was not associated with seizure frequency ($p=0.444$). However, the assessment of seizure frequency in this study was not further specified, and seizure frequencies in the case and control groups were not reported. Thus, it was impossible to conduct a meta-analysis of these two studies. Additional information on these two studies can be accessed in the supplemental material (Table E4, online only).

Overall, there is little and conflicting evidence on the association between WML and seizure frequency. We rate the GRADE certainty of this association as ‘very low’ due to inconsistency of the results.

Research question 3: For patients with a first unprovoked seizure and WML of presumed vascular origin with no cortical structural lesions in MRI, does treatment with ASM reduce the risk of seizure recurrence compared to patients with no pharmacological treatment?

In our systematic review, no studies on the treatment of patients with WML of presumed vascular origin and first unprovoked seizure without cortical structural lesions could be identified.

Discussion

This is the first systematic review and meta-analysis on the association of WML of presumed vascular origin with seizures or epilepsy. Gathering data from 11 studies comprising almost 3000 participants, we analyzed the current evidence on the association of WML with the presence of seizures, rate of seizure recurrence, and necessity of ASM treatment.

Association between WML and presence of epilepsy and seizures

There was a statistically significant association between (a) seizure or epilepsy and presence of WML, (b) seizure or epilepsy and presence of relevant WML as measured by a visual rating scale, but no association between (c) WML volume and epilepsy.

Given the current evidence, it is difficult to determine, whether this discrepancy is due to methodological or pathophysiological reasons. It is important to mention that there are significant differences in the design of the three studies on WML volume and epilepsy [7, 22, 23]. The only study to show a statistically significant difference in WML volume load was on patients with late-onset epilepsy > 50 years [7]. One study had a much younger population (mean age in epilepsy group: 43 years) [23]. The third study did not assess lesion load at onset of epilepsy. Instead, the authors analyzed MRIs that were performed before the occurrence of the respective first seizures, with the time from MRI to first seizure not being reported [22]. After excluding this study from the meta-analysis, the results regarding association between WML volume and epilepsy remained without statistically significant difference. The differences in mean WML volume between these three studies are striking. To our understanding, this could only partly be explained by differences

in methods of WML segmentation. Therefore, we confirmed the WML volumes with the corresponding authors of all three studies to ensure the plausibility of the data. This led to the correction of WML volumes in one study. Still, in the epilepsy group, a 16-fold difference in mean WML volume between the study with the highest and the lowest WML volume remained [7, 22]. Reassuringly, all reported WML volumes are within the range of what has been described previously [28, 29]. Therefore, it might be reasonable to assume that in fact, significant WML as detected by a visual rating scale are more relevant with respect to epilepsy than WML volumes. The Fazekas scale as applied by most authors in the studies included in this meta-analysis focuses on deep WML located > 13 mm from the ventricular surface [27, 30]. In contrast, a WML volumetry takes into account WML in the entire brain including periventricular and juxtacortical WML. It is generally accepted that deep WML differ from WML in other locations like periventricular and juxtacortical regarding histopathology and clinical relevance: Deep and confluent white matter alterations are more likely of ischemic origin and are more often associated with clinical symptoms than periventricular and juxtacortical WML [8, 31, 32]. This distinction is better represented by visual scores than by a global quantitative measurement. Results of one study in which presence of deep and periventricular WML was analyzed separately are in line with this notion: Deep WML were more common in the epilepsy group, while periventricular WML were more common in the control group [19]. In a study comparing first-seizure patients to patients with transient ischemic attacks, both periventricular and deep WML were more present in the seizure group [6]. The same study also showed a statistically significant higher prevalence of juxtacortical lesions in the first-seizure group as compared to the control group (80.5% vs 22%, $p < 0.001$). Finally, in a study that was considered for eligibility in the systematic review but was excluded due to lack of a control group, in patients with epilepsy, WML mainly affected the temporal lobe [13].

Importantly, there is also heterogeneity in the studies on presence of (relevant) WML as assessed by visual rating scales. This is mainly represented in (a) patient populations and (b) differences in visual WML scoring. Regarding patient populations of these studies, four included patients with late-onset seizures [6, 19, 20, 25] while two had no age restrictions [5, 18], and one study did not report the age of its participants [24]. There were also significant differences within comorbidities of the patient populations, especially with regard to cardiovascular risk factors [18, 19]. Another challenge in comparing studies were differences in WML scoring: The most widely used scale for WML was proposed by Fazekas et al. [27] more than 30 years ago. In this scale, both periventricular and deep WML are scored separately on a 4-point rating scale ranging from 0 to 3. To

assess CSVD, usually only deep WML are considered [27]. The so-called age-related white matter changes (ARWMC) or Wahlund scale is an updated version of the Fazekas scale. Again, WML are scored on a 4-point rating scale with slight alterations in scoring. More importantly, in this scale, five different brain regions are scored for each hemisphere separately. Thus, a maximum of 30 points theoretically can be given [26].

Even though most studies included in this meta-analysis refer to the paper introducing the Wahlund scale, they in fact mostly provide a “global” or “deep” WML score ranging from 0 to 3, which is more in line with the Fazekas scale in its original form. Out of the seven studies using a visual rating scale, none applied the exact same scoring method. A standardization of WML rating scales to be used in clinical studies would be highly desirable.

So far, this review has interpreted the assumed association between WML and seizures as unidirectional in the sense that WML might cause seizures. However, also the inverse relationship is worthy of discussion. This point is of particular importance, as none of the studies included in this meta-analysis that focused on epilepsy (as opposed to first-seizure patients), stated that it was on new-onset epilepsy patients. Therefore, we do not have certainty on the lesion load at the onset of epilepsy. Thus, given the current data, we cannot exclude that a significant proportion of WML developed after the diagnosis of epilepsy. From a pathophysiological perspective, it seems unlikely that seizures could directly cause WML [33]. Yet, it is possible that epilepsy indirectly causes WML through ASM therapy. Interestingly, in one study included in this review, WML load was highest in patients receiving enzyme-inducing ASM as compared to patients with non-enzyme-inducing ASM and controls without epilepsy [5]. This was interpreted to be caused by negative effects of enzyme-inducing ASM on cardiovascular risk factors [34].

To answer our research questions, only studies with an appropriate control group were eligible for inclusion. It is, however, important to mention that there was heterogeneity in the properties of the control groups in the studies included in this review. We therefore performed sensitivity analyses, including only studies where the control group consisted of healthy participants. Reassuringly, our results stayed robust for all outcome parameters.

Association between WML and risk of seizure recurrence

We identified two studies on seizure recurrence risk in patients with epilepsy with conflicting results. One study focused on patients with late-onset epilepsy of unknown or structural etiology. Here, presence of WML was independently associated with an elevated risk of seizure recurrence

[21]. The other study did not show any statistically significant difference in seizure frequency between patients with and without WML [18]. It is noteworthy, that this study has extensive exclusion criteria: In essence, patients with cardiovascular risk factors, such as hypertension and diabetes mellitus, were not eligible for inclusion [18]. To us, excluding these patients seems counter-intuitive, especially when considering the presumed pathomechanisms behind the suspected epileptogenic properties of WML, namely the hypothesis of WML being a surrogate parameter of cortical microinfarcts [13, 14]. Moreover, it has been demonstrated that cardiovascular risk factors are higher in late-onset epilepsy patients than in controls [35]. It is therefore plausible that this study did underestimate the effect of WML on seizure recurrence.

Assessing the influence of WML on the risk of seizure recurrence is an important milestone in evaluating their epileptogenicity. Both studies identified in this review were on patients with established diagnoses of epilepsy. As these patients are usually treated with ASM, a more desirable study population would be patients with first seizures not yet treated. Only this population would allow assessing the influence of WML on the rate of seizure recurrence without the risk of bias by ASM.

ASM treatment of patients with WML in the absence of cortical lesions

Ultimately, all aspects discussed above lead to the final, clinically most relevant question, whether ASM treatment is justified or even necessary in patients with a first seizure at the presence of WML, even if there are no cortical lesions in the MRI and the EEG is without epileptiform discharges. Our systematic review did not show any prospective studies on ASM treatment in patients with WML with regard to seizure outcome.

Strengths, limitations, and scope of this review

The strength of this review lies in its rigorous adherence to the PRISMA guidelines and its meta-analysis using original patient data where possible.

There are limitations to consider. We have already addressed the significant heterogeneity between studies on WML lesion load. Through several sensitivity analyses, we aimed to diminish its effects, but even so, the certainty of evidence remains impaired. This is especially relevant for the fact that all studies included in this review and meta-analysis were observational studies. Thus, the overall quality of evidence included in this review has to be considered as low. In our opinion, a major limitation in the design of most included studies was the lack of adjustment for cardiovascular risk factors (see Table E2, online only).

Initially, we had set out to compare WML load in first-seizure patients and epilepsy patients separately. However, only one study was identified focusing on first-seizure patients [6]. In two studies, a small number of patients with a single seizure were also part of the respective “epilepsy group”, and neither of them performed a separate analysis [20, 24]. A sensitivity analysis without the study only on first-seizure patients did not significantly alter the results of our meta-analysis.

This review explicitly focuses on WML of presumed vascular origin. It is important to mention that CSVD is more than WML. Other signs of CSVD include lacunar infarcts, enlarged perivascular spaces, micro-bleeds, and brain atrophy [8]. These signs were assessed as secondary outcomes by some studies included in this review [6, 7, 19, 20, 22, 25]. To summarize, it was mainly shown that epilepsy was associated with reduced cortical volume and hippocampal or temporal atrophy [6, 7, 22, 25]. This seems plausible from a pathophysiological viewpoint. Also, CSVD in general (including lacunar infarcts, perivascular spaces, and micro-bleeds along with WML) was more prevalent in patients with epilepsy than in controls [19, 20]. The topic of this review on WML of presumed vascular origin also implicates that we did not look into microstructural alterations of white matter as detected in diffusion tensor imaging studies, which were reviewed elsewhere [36].

Conclusions

Our findings suggest that WML are more frequent in patients with epilepsy than in controls. It seems reasonable to assume that WML of presumed vascular origin contribute to epileptogenesis in patients with late-onset epilepsy. This is especially true for deep WML. As of now, there has not been shown a clear association between WML volume and epilepsy. Currently, evidence is insufficient to answer the questions whether WML are associated with an increased risk of seizure recurrence, and thus, if patients with a first seizure and WML should receive ASM, even in the absence of cortical lesions. In our opinion, these two aspects should be addressed in further studies, ideally focusing on a first-seizure patient population, with an emphasis on alterations of the deep white matter.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s00415-023-11828-6>.

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Author contributions JID: conceptualization (equal), resources, data curation, investigation (equal), formal analysis (lead), visualization, writing—original draft preparation. JMH: investigation (equal), formal analysis (supporting), writing—review and editing. MH: conceptualization (equal), resources, supervision, writing—review and editing.

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Data availability Data are available on request from the corresponding author.

Declarations

Conflicts of interest JID and JMH declare no conflicts of interest with respect to the research, authorship, and/or publication of this article. MH reports personal fees from Arvelle, Bial, Desitin, Eisai, Jazz Pharma, and UCB within the last 3 years, outside the submitted work.

Ethical approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

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2.2 Prognostische Einschätzung epileptischer Anfälle sowie spezifischer EEG-Veränderungen

2.2.1 Prognostische Wertigkeit von späten EEG-Untersuchungen bei Patient:innen nach Reanimation

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In den beiden Vorarbeiten (2.1.1 und 2.1.2) wurde die Relevanz einer zerebralen Bildgebung in der Diagnostik von epileptischen Anfällen herausgearbeitet. Neben dem MRT bildet das EEG die zweite Säule der apparativen Diagnostik in der Epileptologie (Bouma et al. 2016). Das EEG ist nicht nur für die Beurteilung des Rezidivrisikos bei epileptischen Anfällen wichtig, sondern spielt auch eine entscheidende Rolle bei der Prognoseeinschätzung nach kardiopulmonaler Reanimation. Die prognostische Aussagekraft gilt bei Ableitung des EEGs innerhalb der ersten Tage nach Reanimation als am größten (Sandroni et al. 2014, Taccone et al. 2017). Im klinischen Alltag ist ein frühes EEG aber nicht immer umsetzbar. In dieser Observationsstudie wurde daher die diagnostische Wertigkeit eines „späten“ EEGs – fünf bis 14 Tage nach Reanimation – untersucht.

In der Studie wurden EEG-Daten von Patient:innen, die nach Reanimation auf den Intensivstationen der Charité Universitätsmedizin Berlin behandelt wurden, ausgewertet. Das funktionelle Outcome wurde mittels Cerebral Performance Category (CPC) zum Zeitpunkt der Entlassung bestimmt. Primärer Endpunkt war ein ungünstiges Outcome, das als CPC-Wert von 4 oder 5 (Koma bzw. apallisches Syndrom oder Hirntod) definiert wurde.

Insgesamt wurde bei 187 Patient:innen nach Reanimation ein „spätes“ EEG durchgeführt (Median: 8 Tage nach Reanimation, Quartilen: 7;10). Bei 127 dieser Patient:innen wurde innerhalb der letzten 24 Stunden vor EEG-Ableitung keine sedierende Medikation verabreicht. In dieser Gruppe von Patient:innen wurde bei Vorliegen einer durchgehend unterdrückten EEG-Hintergrundaktivität mit einer Amplitude $< 10 \mu\text{V}$ ein ungünstiges Outcome mit einer Sensitivität von 31% (95% KI 20-45) und einer Spezifität von 99% (95% KI 91-100) vorhergesagt. Eine Patientin mit supprimierter EEG-Hintergrundaktivität hatte ein günstiges Outcome. Bei Vorliegen von generalisierten periodischen Entladungen (GPDs) vor dem Hintergrund einer supprimierten EEG-Hintergrundaktivität betrug die Sensitivität für die Vorhersage eines ungünstigen Outcomes 15% (95% KI 7-27) und die Spezifität lag bei 100% (95% KI 94-100). GPDs bei nicht-supprimierter EEG-Hintergrundaktivität hatten eine Sensitivität von 42% (95% KI 29-46) und eine Spezifität von 92% (95% KI 82-97).



Prognostic value of ‘late’ electroencephalography recordings in patients with cardiopulmonary resuscitation after cardiac arrest

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Abstract

Background Electroencephalography (EEG) significantly contributes to the neuroprognostication after resuscitation from cardiac arrest. Recent studies suggest that the prognostic value of EEG is highest for continuous recording within the first days after cardiac arrest. Early continuous EEG, however, is not available in all hospitals. In this observational study, we sought to evaluate the predictive value of a ‘late’ EEG recording 5–14 days after cardiac arrest without sedatives.

Methods We retrospectively analyzed EEG data in consecutive adult patients treated at the medical intensive care units (ICU) of the Charité—Universitätsmedizin Berlin. Outcome was assessed as cerebral performance category (CPC) at discharge from ICU, with an unfavorable outcome being defined as CPC 4 and 5.

Results In 187 patients, a ‘late’ EEG recording was performed. Of these patients, 127 were without continuous administration of sedative agents for at least 24 h before the EEG recording. In this patient group, a continuously suppressed background activity < 10 μ V predicted an unfavorable outcome with a sensitivity of 31% (95% confidence interval (CI) 20–45) and a specificity of 99% (95% CI 91–100). In patients with suppressed background activity and generalized periodic discharges, sensitivity was 15% (95% CI 7–27) and specificity was 100% (95% CI 94–100). GPDs on unsuppressed background activity were associated with a sensitivity of 42% (95% CI 29–46) and a specificity of 92% (95% CI 82–97).

Conclusions A ‘late’ EEG performed 5 to 14 days after resuscitation from cardiac arrest can aid in prognosticating functional outcome. A suppressed EEG background activity in this time period indicates poor outcome.

Keywords EEG · Predictive value of tests · Resuscitation · Outcome · Targeted temperature management

Introduction

Predicting neurological outcome after cardiopulmonary resuscitation (CPR) following cardiac arrest (CA) is important for determining further treatment choices and decisions regarding withdrawal of life-sustaining therapy. Diagnostic workup after CA to assess prognosis consists of clinical examination, short-latency somatosensory evoked potentials

(SSEPs), measurement of neuron-specific enolase (NSE), brain imaging and electroencephalography (EEG). This outcome prediction is especially important in patients who remain comatose after resuscitation from CA [1].

Several EEG parameters are associated with a poor prognosis after CA [2]. Recent studies have suggested that ‘early’ continuous EEG can detect poor outcome with higher sensitivity than ‘late’ EEG [3, 4]. In early EEG measurements, the sensitivity for the prediction of unfavorable outcome decreased after > 12 h following resuscitation from CA while the specificity remained robust [4]. However, EEG measurements are not broadly available at all times. EEG activity underlies a natural evolution following CA and could also be altered due to effects of sedative medication [5, 6]. This has become of particular importance since the routine implementation of targeted temperature management (TTM). According to current guidelines, almost all survivors after CA not responding to painful stimuli should receive

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TTM in a range of 32–36 °C for at least 24 h, which requires administration of sedatives [1].

Current guidelines provide different recommendations regarding the timing of EEG recordings for the assessment of prognosis after CA: an advisory statement from the European Resuscitation Council from 2015 recommends measuring EEG 72 h after recovery of spontaneous circulation (ROSC) [7]. In contrast, the task force for Belgian recommendations suggests measuring EEG ‘as soon as possible’ [8].

In this study, we seek to determine the clinical significance of a ‘late’ EEG recording between days 5 and 14 after resuscitation from CA in comatose patients. We hypothesize that the evaluation of such a ‘late’ EEG can aide in predicting functional outcome and that the predictive value of ‘late’ EEG recordings is higher in patients not under continuous sedative medication.

Methods

Data source and patients

We analyzed data from consecutive adult patients (aged 18 or above) admitted to the medical intensive care units (ICU) of the Charité—Universitätsmedizin Berlin (at Campus Virchow-Klinikum) after successful resuscitation from CA between June 1st 2009 and May 31st 2013. At that time, EEG recordings performed between days 5 and 14 after successful resuscitation from CA were part of clinical routine. Late EEG recordings were requested by ICU physicians only in patients still comatose. Institutional approval for this retrospective, observational study was provided by the local Ethics committee (EA2/115/13).

Clinical data were derived from a large prospective database described previously [9]. These data comprised age at CA, sex, location of CPR (out-of-hospital vs. in-hospital), initial cardiac rhythm (shockable vs. non-shockable), time to ROSC (tROSC), NSE at day 3 after CA, SSEP data (24 h to 4 days post CA), EEG data (5 to 14 days post CA), and CPC score at discharge. CPC scores were determined at the time of ICU discharge and prospectively documented in the database. Electroencephalography and SSEP data were assessed following strict criteria by three of the authors (JD, AK, MT) and, in uncertain cases, reassessed by two other authors (MH, CL).

Primary and secondary outcomes

Our primary study outcome parameter was cerebral performance category (CPC) at discharge from the ICU. We dichotomized CPC, defining a CPC score of 1–3 as favorable outcome and a CPC of 4 and 5 as unfavorable neurological

outcome. This was done to avoid falsely allocating patients with prolonged recovery to the unfavorable outcome group. To improve comparability to other studies, we performed a supplementary analysis where a CPC score of 3 (severe cerebral disability) at discharge was considered an unfavorable outcome.

Definition of parameters

EEG

5 to 14 days after CA, a ‘late’ EEG with video-monitoring was performed for 20 min using a digital 21-channel recording system (Nihon Kohden, Japan) with the international 10–20 system for electrode placement and reviewed with standard montages. EEG data were analyzed for four predefined features that were previously described to be associated with unfavorable outcome after CPR [10]:

- (1) *Suppressed background activity without discharges* was defined as amplitude < 10 μ V, during the entire recording, resulting in non-assessable frequency, without disruption by focal or generalized discharges.
- (2) *Generalized periodic discharges (GPDs) on suppressed background activity* was defined as amplitude of background activity < 10 μ V during the entire recording which was interrupted by GPDs defined according to the American Clinical Neurophysiology Society’s (ACNS) Standardized Critical Care EEG Terminology. GPDs are characterized by periodically recurring monomorphic discharges with waveforms of a duration < 0.5 s regardless of number of phases or waveforms lasting \geq 0.5 s with a maximum of three phases [11]. An example of GPDs on suppressed background activity is given in Fig. 1.
- (3) *GPDs on unsuppressed background activity* was defined as amplitude of background activity \geq 10 μ V which was interrupted by GPDs.
- (4) *Burst-suppression pattern (BSP)* was defined in accordance to the ACNS standardized critical care EEG terminology as generalized periodic, recurring high-voltage discharges occurring with more than three phases and a duration of \geq 0.5 s against a suppressed background activity [11].

SSEPs Median nerve somatosensory evoked potentials (SSEPs) were recorded using Nihon Kohden Neuropack four mini system (Nihon Kohden, Japan). Stimulation intensity was adjusted to produce a peripheral response (thumb twitch). For each recording > 500 SSEPs were performed and averaged. The highest amplitude of a reproducible cortical potential (> 4.5 ms after the N13 peak) was measured (peak to peak or baseline to peak). N20 was only deter-

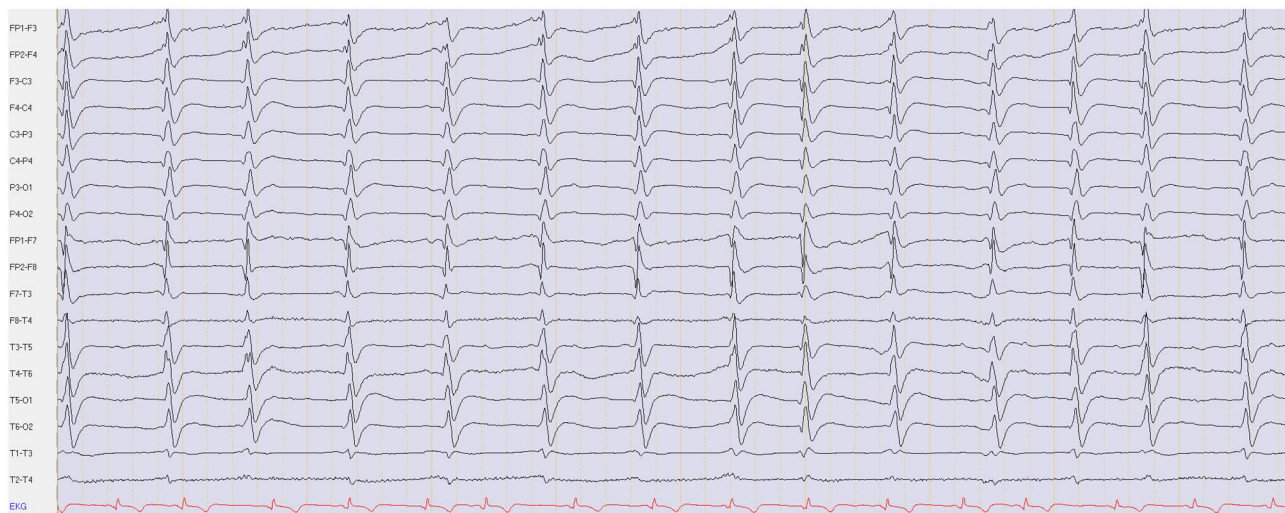


Fig. 1 Example of GPDs on suppressed background activity

mined as bilaterally absent, if cortical noise level was below $0.25 \mu\text{V}$ and there were no reproducible cortical potentials but reproducible spinal and peripheral potentials. SSEPs were recorded 24 h to 4 days after resuscitation from CA.

NSE

Serum concentration of NSE was determined at day 3 after CA. A threshold of $90 \mu\text{g/l}$ was applied for calculation of sensitivities and specificities [12].

Standardized care at the intensive care units

All patients were treated with TTM following a strict in-house protocol along the lines of the International Liaison Committee on Resuscitation recommendations [13]. The target temperature of $33 \text{ }^\circ\text{C}$ was maintained for 24 h followed by a controlled re-warming rate of $0.25 \text{ }^\circ\text{C}$ per hour. Fever had to be avoided for further 72 h. In all patients, a computer controlled surface cooling device (Arctic Sun™ Temperature Management System, C.R.BARD, Colorado, USA) was used. A combination of intravenous midazolam and fentanyl or isoflurane (volatile) and remifentanyl was used for analgesedation.

Withdrawal of life-sustaining therapy

Withdrawal of life-sustaining therapy was always based on careful consideration of multimodal neurological prognostication and a considerable observation period. In 2011, an internal protocol for prognostication was established [14] and modified according to new evidence over time. The protocol is largely in line with the 2014 guidelines of the European Society of Intensive Care Medicine [7]

and emphasizes multimodal prognostication and an observation period of at least 7 days in most cases. Patients' advanced directives and preferences communicated by relatives were taken into account. In a relevant subset of patients, withdrawal of life-sustaining therapy was not performed despite poor prognostic findings. These patients were discharged in coma or unresponsive wakefulness syndrome. We followed these patients in long-term and found no case of an unexpected late recovery, indicating a low probability of a self-fulfilling prophecy for our prognostication algorithm [15].

Statistical analysis

Categorical variables were analyzed with Pearson's χ^2 or Fischer's test. Continuous data were checked for normal distribution using Kolmogorov–Smirnov test and were then presented as mean \pm standard deviation or median and interquartile range (IQR) where appropriate; Mann–Whitney U test was used for continuous variables.

Sensitivity and specificity were calculated with 2×2 contingency tables and are presented with 95% confidence intervals (CI). For the identification of independent predictors for unfavorable outcome at ICU discharge, a binary logistic regression analysis (inclusion method: stepwise backward, $p < 0.1$ [p in], $p < 0.05$ [p out], iteration 20, cutoff set 0.26 and constant was included) was used with clinically relevant covariates to estimate odds ratios (OR) with 95% CI. Parameters with quasi-complete separation were excluded from the logistic regression analysis.

Statistical analyses were performed with SPSS version 25 (IBM, Chicago, IL, USA).

Results

Patient population

During the 4-year study period, 320 patients were treated with TTM after out-of-hospital or in-hospital CA and successful resuscitation. One hundred and thirty-three patients were excluded from the analysis because they were discharged or had died before the EEG was performed, because no EEG was recorded in the time window from day 5–14 after CA or because EEG recordings could not be retrieved (Fig. 2).

Our final analysis included 187 patients, mean age was 62 ± 16 years, 28% female, 71% with out-of-hospital CPR. Median CPC at discharge was 2 (interquartile range (IQR) 1–5), 41% of patients had an unfavorable outcome at discharge, and mortality rate was 27%. Median time point of EEG recording was 8 days after CA (IQR 7–10), and median ICU length of stay was 21 days (IQR 13–33).

Comparing included and excluded patients, we found no significant differences concerning sex, age, and location of CPR. However, the initial presence of non-shockable rhythm, time to ROSC, mean NSE, CPC, and mortality showed significant group-differences (Table-e1, online only).

Of all 187 included patients, 127 were without continuous administration of sedative agents for at least 24 h before the EEG recording. In 60 patients, the EEG recording was performed under or within 24 h of continuous administration of sedatives. There were no statistically significant differences between both groups with regards to sex, age, proportion of

out-of-hospital CPR and initial shockable rhythm, NSE at day 3, and clinical outcome (Table e-2, online only).

Outcome prediction in patients without continuous administration of sedatives for > 24 h before EEG measurements

In the 127 patients without continuous administration of sedatives, 55 patients (43%) had an unfavorable outcome.

Seventeen patients with unfavorable outcome (31%) had a continuously suppressed background activity with no discharges. A suppressed background activity with no discharges predicted unfavorable outcome with a sensitivity of 31% (95% confidence interval [CI] 20–45) and a specificity of 99% (95% CI 91–100). GPDs on unsuppressed background activity were associated with a sensitivity of 42% (95% CI 29–56) and a specificity of 92% (95% CI 82–97) for the prediction of unfavorable outcome.

One patient with suppressed background activity without discharges and six patients with GPDs on unsuppressed background had a favorable outcome. Two of the patients with GPDs on unsuppressed background and favorable outcome had received a bolus of sedatives in the 24 h preceding the EEG recordings. The patient with suppressed background activity without discharges and favorable outcome was a 67 old female who was resuscitated from CA following pulmonary artery embolism. Sedation with midazolam and fentanyl was discontinued 4.5 days before the EEG recording and no bolus of sedative medication was given in the 48 h preceding the EEG recording. We provide a more detailed description of this case in the supplementary material.

No false positives were present in the eight patients who showed both GPDs and suppressed background activity (GPDs on suppressed background; sensitivity for the prediction of unfavorable outcome 15% (95% CI 7–27); specificity 100% (95% CI 94–100). The prognostic parameters are summarized in Table 1; the analyses for an unfavorable outcome being defined as CPC 3–5 are provided in the supplementary material (Table e3, online only).

The presence of suppressed background activity without discharges (OR 36.9, 95% CI 3.3–414.3) and of GPDs on unsuppressed background (OR 57.3, 95% CI 8.4–390.8) both independently predicted unfavorable outcome after CA, see Table 2 (for CPC 3–5 as unfavorable outcome see Table e4, online only).

In the patient group without continuous administration of sedatives for at least 24 h before the EEG measurement, 24 patients (19%) had NSE values $> 90 \mu\text{g/l}$ 3 days after resuscitation from CA. The sensitivity for the prediction of an unfavorable outcome in patients with $\text{NSE} > 90 \mu\text{g/l}$ was 42% (95% CI 29–56) and specificity was 98% (95%

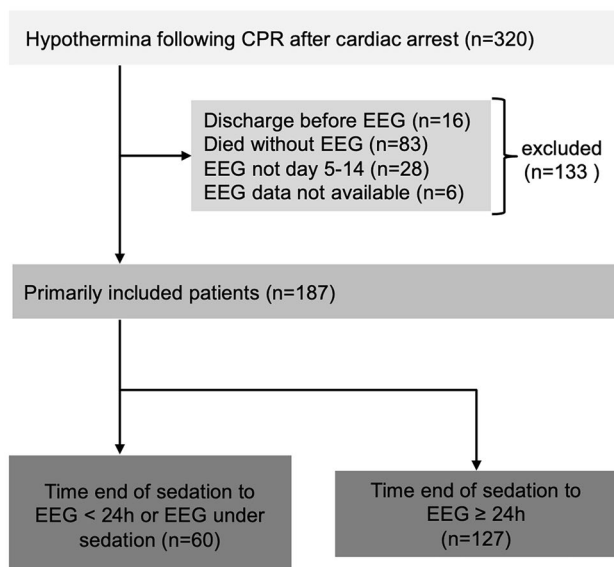


Fig. 2 Patient recruitment

Table 1 Predictive values for unfavorable outcome (CPC 4 and 5)

	Fre- quency (n) (n = 127)	Sensitivity (95% CI)	Specificity (95% CI)	True positive	False positive	True negative	False negative
<i>Patients without continuous sedative-administration for at least 24 h</i>							
EEG parameters							
Suppressed background without discharges	14% (18)	31% (20–45)	99% (91–100)	17	1	71	38
GPDs on suppressed background	6% (8)	15% (7–27)	100% (94–100)	8	0	72	47
GPDs on unsuppressed background	23% (29)	42% (29–56)	92% (82–97)	23	6	66	32
Other parameters							
NSE > 90 µg/l	19% (24)	42% (29–56)	98% (91–100)	23	1	71	32
Bilateral absent SSEPs	14% (18)	33% (21–47)	100% (94–100)	18	0	72	37
<i>Patients with continuous sedative-administration stopped less than 24 h before or with EEG during continuous sedation</i>							
EEG parameters							
Suppressed background without discharges	8% (5)	23% (9–46)	100% (89–100)	5	0	38	17
GPDs on suppressed background	5% (3)	14% (4–36)	100% (89–100)	3	0	38	19
GPDs on unsuppressed background	20% (12)	27% (12–50)	84% (68–93)	6	6	32	16
Other parameters							
NSE > 90 µg/l	15% (9)	32% (15–55)	95% (81–99)	7	2	36	15
Bilateral absent SSEPs	7% (4)	18% (6–41)	100% (89–100)	4	0	38	18

CPC cerebral performance category at intensive care unit discharge, CI confidence interval, GPDs generalized periodic discharges, NSE neuron-specific enolase, SSEPs short-latency somatosensory evoked potentials

CI 91–100). One patient with NSE > 90 µg/l had a favorable outcome at discharge (CPC 1).

In the same patient group, SSEPs were bilateral absent in 18 patients (14%). In no patient with favorable outcome, SSEPs were bilateral absent, resulting in a sensitivity for this outcome parameter of 33% (95% CI 21–47) and a specificity of 100% (95% CI 94–100).

Late EEG correctly predicted unfavorable outcome in 23 patients in whom SSEPs were not bilaterally absent and NSE was ≤ 90 µg/l (4 patients with GPDs on unsuppressed background, 7 patients with suppressed background without discharges and 12 patients with GPDs on unsuppressed background). SSEPs were able to correctly predict unfavorable outcome in one patient with normal EEG and NSE ≤ 90 µg/l. In all patients with unfavorable outcome and NSE > 90 µg/l, either SSEPs or EEG parameters were also predictive of unfavorable outcome. In five patients with CPC > 3, no prognostic parameter was predictive of this unfavorable outcome.

Outcome prediction in patients with continuous sedative-administration stopped < 24 h before or with EEG during continuous sedation

Of the 60 patients with EEG recording within 24 h after administration of sedatives or with EEG recording during continuous sedation, 22 patients (37%) had an unfavorable outcome. In this patient group, the sensitivity for the prediction of unfavorable outcome was lower for the EEG parameters ‘suppressed background without discharges’ and ‘GPDs on unsuppressed background’ parameters as compared to the group of patients with EEG without continuous administration of sedatives. The diagnostic accuracy of the EEG parameter ‘GPDs on suppressed background’ was not different between the two groups. Specificities of all outcome predictors were comparable between both patient groups (see Table 1). The analysis of predictors for CPC-based outcome is shown in Table 2.

Table 2 Predictors for CPC-based outcome (CPC 1–3 vs 4 and 5)

	CPC-based outcome		Univariate analyses	Binary logistic regression, Exp(B) [95% CI]
	Favorable (CPC 1–3) <i>n</i> = 72	Unfavorable (CPC 4 and 5) <i>n</i> = 55		
<i>Patients without continuous sedative-administration for at least 24 h</i>				
Demographics and basic information:				
Female sex, <i>n</i> (%)	17 (24)	19 (35)	<i>p</i> = 0.233 ^a	Not included
Age [years], median (IQR)	63 (52–73)	70 (61–75)	<i>p</i> = 0.052 ^b	Not significant
Out-of-hospital CPR, <i>n</i> (%)	47 (69)	37 (77)	<i>p</i> = 0.403	Not included
Initial rhythm: not shockable, <i>n</i> (%)	18 (32)	30 (67)	<i>p</i> = 0.001^a	5.9 [1.3–26.5]
TROSC [min], median (IQR)	12 (7.5–20)	18 (10–28)	<i>p</i> = 0.055 ^b	Not significant
NSE day 3				
[μg/l], median (IQR)	20 (15–27)	68 (33–130)	<i>p</i> < 0.001^b	Not included
NSE > 90 μg/l, <i>n</i> (%)	1 (1)	23 (42)	<i>p</i> < 0.001^a	56.3 [4.5–704.7]
Electrophysiology:				
EEG				
Suppressed background without discharges, <i>n</i> (%)	1 (1)	17 (31)	<i>p</i> < 0.001^a	36.9 [3.3–414.3]
GPDs on suppressed background, <i>n</i> (%)	0 (0)	8 (15)	<i>p</i> < 0.001^a	Not included [†]
GPDs on unsuppressed background, <i>n</i> (%)	6 (8)	23 (42)	<i>p</i> < 0.001^a	57.3 [8.4–390.8]
SSEP				
SSEPs bilateral absent, <i>n</i> (%)	0 (0)	18 (33)	<i>p</i> < 0.001^c	Not included [†]
	<i>n</i> = 38	<i>n</i> = 22		
<i>Patients with continuous sedative-administration stopped less than 24 h before or with EEG during continuous sedation</i>				
Demographics and basic information:				
Female sex, <i>n</i> (%)	11 (29)	6 (27)	<i>p</i> = 1.000 ^a	Not included
Age [years], median (IQR)	61 (51–70)	61 (55–73)	<i>p</i> = 0.634 ^b	Not significant
Out-of-hospital CPR, <i>n</i> (%)	25 (66)	15 (75)	<i>p</i> = 0.559 ^a	Not included
Initial rhythm: not shockable, <i>n</i> (%)	10 (31)	9 (53)	<i>p</i> = 0.218 ^a	Not significant
TROSC [min], median (IQR)	12 (10–20)	19 (12–24)	<i>p</i> = 0.118 ^b	Not significant
NSE day 3				
[μg/l], median (IQR)	21 (13–28)	44 (26–111)	<i>p</i> < 0.001^b	Not included
NSE > 90 μg/l, <i>n</i> (%)	2 (5)	7 (32)	<i>p</i> = 0.009^a	6.6 [1.1–39.1]
Electrophysiology:				
EEG				
Suppressed background without discharges, <i>n</i> (%)	0 (0)	5 (23)	<i>p</i> = 0.005^a	Not included [†]
GPDs on suppressed background, <i>n</i> (%)	0 (0)	3 (14)	<i>p</i> = 0.045^a	Not included [†]
GPD on unsuppressed background, <i>n</i> (%)	6 (16)	6 (27)	<i>p</i> = 0.327 ^a	Not significant
SSEP				
SSEPs bilateral absent, <i>n</i> (%)	0 (0)	4 (18)	<i>p</i> = 0.015^a	Not included [†]

The *p*-values and odds-ratios of statistically significant parameters are written in bold

CPC cerebral performance category at intensive care unit discharge, IQR interquartile range, tROSC time to resuscitate spontaneous circulation, NSE neuron-specific enolase, CPR cardiopulmonary resuscitation

^aFisher's exact (two-sided)

^bMann–Whitney *U* test (two-sided)

^cPearson's χ^2 test (two-sided). Exp(B) odds ratio; CI confidence interval

[†]The variables were not included to avoid quasi-complete separation in the model

Only three patients had a burst-suppression-pattern at the time of EEG recording. Therefore, we omitted this EEG pattern from our statistical analysis.

Outcome prediction with unfavorable outcome defined as CPC 3–5

When an unfavorable outcome was more broadly defined as CPC 3–5, five patients shifted to the unfavorable outcome group (four patients without continuous administration of sedatives for at least 24 h before the EEG measurement, one patient with sedative administration). With this alternative definition, 59 patients (46%) without continuous sedative-administration had an unfavorable outcome. In this patient group, suppressed background without discharges predicted unfavorable outcome with a sensitivity of 29% (95% CI 18–42) and a specificity of 99% (95% CI 91–100). GPDs on suppressed background had a sensitivity of 14% (95% CI 6–26) and a specificity of 100% (95% CI 93–100). The sensitivity for GPDs on unsuppressed background was 41% (95% CI 28–54) and the specificity was 93% (95% CI 83–97).

All results with this alternative outcome definition including predictive values for all parameters and analysis of predictors of CPC-based outcome are listed in the supplementary material (Tables e3 and e4).

Discussion

In this study, a suppressed background activity without discharges in a ‘late’ EEG recording 5–14 days after CPR following CA had a specificity of 99% for the prediction of unfavorable outcome in patients without continuous administration of sedative medication for at least 24 h prior to the EEG recording. When both GPDs and a suppressed background activity (GPDs on suppressed background) were present, there were no false-positives, although the number of patients in this group was small ($n=9$), resulting in a broader confidence interval. The predictive values of these EEG parameters were comparable to bilateral absent SSEPs 24 h to 4 days post CA or to a NSE $> 90 \mu\text{g/l}$ 3 days after CA.

With a specificity of 92% and a false-positive rate of 8%, the predictive value of GPDs on unsuppressed background activity does not seem suitable as a parameter for the detection of an unfavorable outcome after CPR.

The sensitivities of the EEG parameters ‘suppressed background activity without discharges’ and ‘GPDs on unsuppressed background activity’ were lower in patients in whom continuous administration of sedatives was stopped less than 24 h before the EEG recording while GPDs on unsuppressed background did not seem to be affected by sedative medication. While the sensitivities of most outcome predictors were reduced in patients under influence of

sedative medication, the specificity of these outcome predictors remained mostly similar.

EEG plays an important role in prognostication after CA, and its importance has not declined since the introduction of TTM into clinical routine [10, 16, 17]. The diagnostic yield of EEG recordings in patients with TTM is time-dependent [4–6]. Focusing on a ‘late’ EEG recording, presumably associated with a lower load of sedative drugs, our study extends prior reports on time specificity of EEG patterns to 5–14 days after CA.

One patient with suppressed EEG background activity without discharges, who was not sedated during or 24 h before the EEG measurement, had a favorable functional outcome at discharge. This result is surprising as in other studies no patient with EEG background activity $< 10 \mu\text{V}$ had a favorable functional outcome [3, 18]. In these studies, EEG was performed within 24 h after cardiac arrest. While low voltage EEG $< 20 \mu\text{V}$ is present in up to 10% of the general population and is often considered a normal variant, suppressed EEG background activity ($< 10 \mu\text{V}$) is regarded as a malignant EEG feature unequivocally associated with unfavorable outcome [19, 20]. We provide a more detailed description of the patient in the supplementary material. Summing up, the clinical course of the patient provides no clear explanation for the suppressed background activity. However, we cannot entirely exclude that the patient was administered a bolus of sedatives in the hours prior to EEG recording which was not documented in the electronic chart.

Suppressed background activity without discharges and the presence of GPDs on unsuppressed background both independently predicted unfavorable outcome. The presence of one of these parameters correctly predicted unfavorable outcome in 11 patients in whom SSEPs and NSE were uninformative of unfavorable outcome. The pathophysiology underlying GPDs is not yet fully understood. GPDs are considered to be a consequence of loss of inhibitory interneurons, which are in particular vulnerable to hypoxia [21, 22]. The predictive value of GPDs in patients with hypoxic ischemic brain damage has been described previously in a group of 119 patients after CA in whom the EEG was performed within the first 14 days (mean 3.8 days) after the event [23]. In that study, a similar rate of GPDs after CA was detected.

In comparison to other studies in which an EEG was performed early after CA, there was a somewhat higher rate of suppressed background activity with GPDs [10, 17] and suppressed background activity without discharges [17] in our patients with unfavorable outcome. In contrast to studies with EEG examinations performed early after CA [10, 17], burst suppression patterns were only rarely detected in our study ($n=3$). Our findings could hint towards an increased relevance of GPDs and a suppressed background activity in late EEG recordings, when these EEG patterns are not

modified by sedative drugs which are required during TTM. This hypothesis corresponds with our finding of a diminished sensitivity for both EEG parameters in patients under sedative medication. These results are also in line with a recently published study focusing on EEG reactivity, the significance of this parameter for the prediction of unfavorable outcome after CA was reduced in patients under sedative medication [24]. The reduced sensitivity of EEG parameters in patients under sedative medication could also be explained alternatively: patients with reduced brain activity could be in less ‘need’ of sedative medication while patients with more brain activity could require more sedative medication. Thus, sedation would not be the cause of a reduced sensitivity for the detection of unfavorable outcome but it would be a sign of a certain amount of brain activity which might be associated with unfavorable outcome but might be high enough to prevent suppressed background activity.

BSPs, especially those with ‘identical bursts’, recorded in the first 72 h after CA are an important predictor for unfavorable outcome [6]. However, it was demonstrated that these BSPs evolve into less specific EEG patterns early after CA [25], which may explain their low frequency in our patient population.

There are limitations to consider. First, a comparison of the results of an ‘early’ vs. a ‘late’ EEG recording would have been desirable. Second, we only have data on outcome at ICU discharge and no data on long-term outcome. To avoid assigning patients with prolonged recovery falsely to the ‘unfavorable outcome group’, we considered a CPC of 3 to be a favorable outcome. There were no relevant changes to our results when the assignment of a CPC of 3 was changed to the unfavorable outcome group. Third, although we accounted for sedative drugs, we did not assess intake of classical antiseizure medication, which about 9% of ICU patients receive [26] and which could also have influenced EEG findings [27]. Fourth, we cannot exclude that in patients in whom sedatives had been withdrawn ≥ 24 h before the EEG recording, there was still some effect of these lipophilic substances after prolonged release and redistribution from fatty tissue. What is more, in 28 subjects (22%) in the patient group without continuous administration of sedatives, a bolus administration of either benzodiazepines or propofol was documented, which could also have influenced EEG results. Fifth, assessing outcome late after CA in a clinical study bears the risk of selection bias. At 5 days after CA, a considerable proportion of patients with severe hypoxic encephalopathy have already died. Likewise, it is possible that patients with mild hypoxic encephalopathy already have been discharged from the ICU at this time point. Therefore, we cannot rule out that our study includes a relatively low proportion of patients with either severe or very mild hypoxic encephalopathy. Thus, our patient selection most likely differs from those of studies

on early EEG after CA. This could be an explanation for the relatively high proportion of patients with suppressed EEG background activity. Lastly, a major possible confounding factor in most studies assessing prognostication after CA is that of self-fulfilling prophecy as the results of the EEG examinations were known to the caregivers and, therefore, are likely to have influenced decisions regarding continuation or withdrawal of further therapy [28].

In summary, suppressed background activity without discharges and suppressed background activity with GPDs in a ‘late’ EEG recording 5–14 days after resuscitation from CA predict unfavorable outcome in patients not under continuous administration of sedatives. A relevant minority of patients with GPDs on unsuppressed background activity may regain consciousness within the next days.

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Declarations

Conflict of interest JID, ABK, and MT declared no conflicts of interest with respect to the research, authorship, and/or publication of this article; MH reports personal fees from Arvelle, Bial, Desitin, Eisai, GW Pharma, UCB, and Zogenix, outside the submitted work; CL reports institutional fees from Bard Medical, Pfizer, and Zoll, personal fees from Edwards Lifesciences, outside the submitted work; CS reports personal fees from BD Bard, Braincool, Pfizer, Xenios, and Sedana Medical, outside the submitted work.

Ethical approval Institutional approval for this observational study was provided by the local Ethics committee (EA2/115/13) of Charité—Universitätsmedizin Berlin.

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2.2.2 Ätiologie-spezifische Wirksamkeit einer anfallssuppressiven Therapie bei Patient:innen mit fokaler Epilepsie

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In den vorangehend vorgestellten Arbeiten (2.1.1, 2.1.2 und 2.2.1) wurde die apparative Diagnostik mittels Bildgebung und EEG sowie deren Einfluss auf die Diagnostik von Epilepsien und zur Prognoseabschätzung behandelt. Insbesondere die bildgebende Diagnostik hat neben dem Ziel der Diagnosestellung von Epilepsien auch die Einordnung hinsichtlich der vorliegenden Ätiologie zur Aufgabe. Welche Assoziationen zwischen Ätiologie einer Epilepsie und deren Prognose bestehen, ist Gegenstand der nächsten Arbeit.

Es herrscht breiter Konsens darüber, dass die Ätiologie einen der wichtigsten Prädiktoren für postoperative Anfallsfreiheit nach epilepsiechirurgischem Eingriff darstellt (Englot et al. 2012, Jones et al. 2016, McIntosh et al. 2001). Für das Ansprechen auf ASM war dieser Zusammenhang bislang nicht ausreichend belegt. Ziel der Studie war daher zu untersuchen, ob bei fokalen Epilepsien das Outcome hinsichtlich Anfallsfreiheit unter ASM mit der zu Grunde liegenden Ätiologie assoziiert ist. Darüber hinaus wurde untersucht, ob sich die ASM-Last im Hinblick auf die Ursachen der Epilepsien unterscheidet.

Es erfolgte eine retrospektive Auswertung der Ambulanzbesuche aller Patient:innen mit fokaler Epilepsie, die an den drei Standorten der Epilepsie-Sprechstunde der Charité Universitätsmedizin Berlin behandelt wurden. Dabei wurde für jede/n Patient:in die angenommene Ätiologie der Epilepsie bestimmt, und es wurde die ASM-Last (individuelle ASM-Dosis / definierte Standard-Tagesdosis) berechnet. Primärer Endpunkt war das Vorhandensein von Anfallsfreiheit für mindestens 12 Monate.

Insgesamt konnten 591 Patient:innen in die Studie eingeschlossen werden. Davon waren 47,7% der Patient:innen bei der letzten Visite anfallsfrei. Patient:innen mit Epilepsie nach ischämischen Schlaganfall hatten dabei die höchste Rate an Anfallsfreiheit (71,2%, 95% KI 57,9-82,2). Die schlechteste Prognose zeigte sich für Patient:innen mit Epilepsie aufgrund einer Hippocampussklerose (28,2% anfallsfrei, 95% KI 15,6-44,9) und aufgrund einer kortikalen Malformation (16,7% anfallsfrei, 95% KI 2,1-48,4). In der multivariaten Analyse zeigte sich eine unabhängige Assoziation zwischen der Ätiologie ischämischer Schlaganfall und einer höheren Wahrscheinlichkeit für das Erreichen von Anfallsfreiheit (OR: 2,093, 95%-KI 1,039-4,216). Im Kruskal-Wallis Test zeigte sich ein statistisch signifikanter Unterschied in der ASM-Last zwischen den einzelnen Ätiologien ($\chi^2[8] = 31,032$, $p < 0,001$). Dabei hatten Patient:innen mit einer Epilepsie nach ischämischen Schlaganfall die niedrigste ASM-Last.

Etiology-specific response to antiseizure medication in focal epilepsy

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Abstract

Objective: In focal epilepsy, data on the etiology-specific response to antiseizure medication (ASM) are surprisingly sparse. In this study, we sought to reappraise whether seizure outcome of pharmacological treatment is linked to the underlying etiology. Furthermore, we assessed ASM load with respect to the cause of epilepsy.

Methods: Data were retrospectively obtained from the electronic database of the three sites of an academic adult epilepsy outpatient clinic. For each patient, presumed cause of epilepsy was categorized into one of nine etiological groups. Individual drug loads were calculated according to the 2020 World Health Organization Center for Drug Statistics Methodology ATC/DDD Index. Univariate and multivariate analyses were conducted to explore the association between different etiologies and outcome regarding 12-month seizure freedom as well as ASM load.

Results: A total of 591 patients with focal epilepsy were included in the final analysis. Ischemic stroke was the etiology with the highest rate of 12-month terminal seizure freedom (71.2%, 95% confidence interval [CI] = 57.9–82.2) and, considering all etiological groups, was an independent predictor of seizure freedom (odds ratio = 2.093, 95% CI = 1.039–4.216). The lowest rates of seizure freedom were observed in patients with hippocampal sclerosis (28.2%, 95% CI = 15.0–44.9) and malformation of cortical development (16.7%, 95% CI = 2.1–48.4). In patients with ischemic stroke, median ASM load (1.0, interquartile range [IQR] = .5–1.8) was significantly lower compared to that in patients with hippocampal sclerosis (median = 1.8, IQR = 1.2–3.0, $p = .008$) and brain tumors (median = 1.7, IQR = .7–3.2, $p = .049$).

Significance: Response to treatment with ASM is highly etiology-specific and best in patients with epilepsy due to ischemic stroke. Interestingly, this most favorable treatment outcome can be achieved by the lowest ASM load considering all etiological groups. In focal epilepsy, etiology should be taken into account when counseling patients about their expected seizure outcome with pharmacological treatment and when tailoring initial ASM doses.

KEYWORDS

drug load, hippocampal sclerosis, prognosis, seizure freedom, stroke

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1 | INTRODUCTION

Estimating seizure outcome in epilepsy is of high importance with regard to counseling patients on overall prognosis and tailoring treatment decisions. Approximately 60%–70% of people with epilepsy (PwE) achieve seizure freedom with antiseizure medication (ASM); in mono- or polytherapy, treatment success in focal epilepsy (57%–62% seizure-free)^{1,2} is generally lower as compared to genetic generalized epilepsy (68%–85%).^{1,3,4} Beyond seizure control, equipollent therapeutic goals for PwE comprise minimal adverse effects of ASM and overall low interference of ASM with the patient's lifestyle,⁵ both of which may be achieved by a preferably low drug load.

It is well-established scientific consensus that etiology of intractable focal epilepsy is the major predictor for seizure outcome after resective epilepsy surgery.^{6–8} Curiously, there is only very limited evidence on the significance of etiology for pharmacological treatment success in focal epilepsy.

Twenty years ago, two studies assessed the etiology-specific response to ASM in patients with focal epilepsy, showing unfavorable findings in epilepsy caused by hippocampal sclerosis, whereas epilepsy due to stroke had the highest seizure freedom rates.^{2,9} Stroke was not separated into ischemic and hemorrhagic forms. Furthermore, it remained unresolved whether the superior ASM treatment response in epilepsy of certain etiologies comes at the cost of intensified medical therapy, possibly associated with a higher burden of adverse effects. In the past 2 decades, a multitude of new ASMs have been approved,¹⁰ and magnetic resonance imaging (MRI) techniques have improved significantly, allowing for better detection of smaller pathologies underlying focal epilepsy.¹¹ Both issues may impact the overall and the etiology-specific pharmacological treatment response in focal epilepsy.

In this study, we aimed to reappraise the response to ASM in patients with focal epilepsy caused by different etiologies. To this end, we assessed 12-month terminal seizure freedom and load of ASM in nine etiological groups.

2 | MATERIALS AND METHODS

2.1 | Data source and patients

Data were obtained from the electronic database of the three sites of the adult epilepsy outpatient clinic of the Department of Neurology at Charité–Universitätsmedizin Berlin. The study was approved by the local ethics committee (EA4/022/20). Due to the retrospective design of this study, informed consent from individual patients was waived.

We included patients with a diagnosis of focal epilepsy according to the 2017 International League Against Epilepsy

Key Points

- In patients with focal epilepsy, response to treatment with antiseizure medication is highly etiology-specific
- Focal epilepsy due to ischemic stroke has the best outcome, resulting in 12-month terminal seizure freedom in >70% of patients
- Superior prognosis of postischemic stroke epilepsy is achieved by the lowest antiseizure medication load considering all other etiologies
- Etiology of focal epilepsy should be taken into account when counseling patients about the expected response to antiseizure medication

classification.¹² We only considered patients with ≥ 2 visits in the outpatient clinic, which had to be ≥ 12 months apart. The vast majority of patients had undergone head MRI following a standardized epilepsy protocol; in some cases, the etiology relied on head computed tomography findings only, for example, in patients with middle cerebral artery infarction and suitable seizure semiology. All patients who were allocated to "unknown etiology" had undergone head MRI. Exclusion criteria were insufficient documentation of clinical data in the database, previous resective epilepsy surgery, and concurrent neurostimulation (Figure 1). Our analysis comprised all visits to the outpatient clinic from January 2010 to March 2020. In Germany, academic epilepsy outpatient clinics, at least the one at the Charité, serve for the broad population of patients with epilepsy and do not focus on difficult-to-treat cases.

Parameters retrieved from the database were sex, age at last visit, duration of epilepsy, presumed etiology of epilepsy, 12-month terminal seizure freedom, number of all ASMs taken so far (including current medication), and number of ASMs including dosage at the last visit to the outpatient clinic.

Etiology of epilepsy was allocated to one of the following common groups: cerebrovascular malformation, hippocampal sclerosis, malformation of cortical development, brain tumor, hemorrhagic stroke, ischemic stroke, traumatic brain injury, other etiologies, and unknown etiology. Due to the undetermined role of microvascular leukoencephalopathy in the etiology of epilepsy, this MRI finding was subsumed into "unknown etiology."

2.2 | Primary and secondary outcomes

The primary outcome parameter was seizure freedom for ≥ 12 months as assessed at the last documented visit

in our outpatient clinics. Secondary outcome parameter was individual ASM load at the last documented visit. For each patient, the drug load was calculated according to the 2020 World Health Organization Center for Drug Statistics Methodology ATC/DDD Index using the formula "individual ASM dosage per day divided by defined daily dose (DDD)." In patients taking more than one ASM, the sum of all ratios was calculated and used for analysis. For example, a patient on 1500 mg levetiracetam per day (DDD of levetiracetam = 1500 mg) would have an ASM load of 1. A patient on 1500 mg levetiracetam and 150 mg lacosamide per day (DDD of lacosamide = 300 mg) would have an ASM load of 1.5.

2.3 | Statistical analysis

Data were checked for normal distribution using the Kolmogorov–Smirnov test. Categorical variables were analyzed with chi-squared tests. Accordingly, continuous data were analyzed with Mann–Whitney *U*-tests. The significance level was set at $p < .05$. Confidence intervals (CIs) for frequencies were calculated using the Clopper–Pearson method.

We conducted unadjusted and adjusted multiple logistic regression analyses to assess the association between etiology of epilepsy and seizure freedom. Etiology of epilepsy was entered as a categorical variable with unknown etiology used as reference. The model was adjusted for age, sex, duration of epilepsy, and number of ASMs taken so far, including current medication (inclusion method: enter, $p < .05$ [p in], $p < .1$ [p out], iteration 20, cutoff set at .26 and constant included).

To compare the ASM load of different etiologies of epilepsy at the last visit and the number of substances used in the patient's history, we performed Kruskal–Wallis tests and post hoc analyses with pairwise comparisons using Dunn procedure with a Bonferroni correction for multiple comparisons.

Statistical analyses were performed with SPSS Version 25 (IBM).

3 | RESULTS

3.1 | Study population

In our database, we identified 1318 patients with focal epilepsy. Of these, 727 patients were not eligible for inclusion. The patient selection is shown in Figure 1.

Our final analysis included 591 patients; 49.2% were female, median age at last visit was 52 years (interquartile range [IQR] = 37–67), and median duration of epilepsy was 14 years (IQR = 6–27). Median time between first and

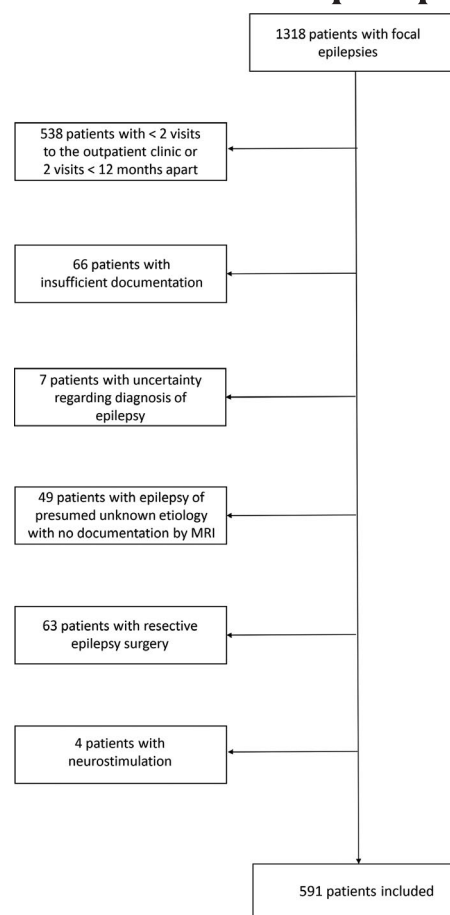


FIGURE 1 This flowchart illustrates patient selection and reasons patients were not eligible for inclusion

last documented visit was 5.2 years (IQR = 2.7–9.9). At the last visit, 47.7% (95% CI = 43.6%–51.8%) of patients were seizure-free for at least the previous 12 months; 323 of all patients were treated in monotherapy (54.7%), 240 in polytherapy (40.6%), and 28 patients (4.7%) were off ASM. The most commonly prescribed ASMs were lamotrigine (41.7% of patients with ASM), levetiracetam (41.2%), lacosamide (9.9%), and carbamazepine and oxcarbazepine (each 8.2%).

3.2 | Characteristics of patients with seizure freedom

In univariate analyses, seizure-free patients significantly more often had epilepsy caused by ischemic stroke than patients who were not seizure-free (14.9% vs. 5.5%, $p < .001$); they were less likely to have hippocampal sclerosis (3.9% vs. 9.1%, $p = .012$) and malformation of cortical development (.7% vs. 3.2%, $p = .030$). Seizure-free patients were older and had a shorter duration of epilepsy than patients who had seizures in the 12-month period prior to the last outpatient visit. Seizure freedom was also associated with a significantly lower ASM load and a lower number

of ASMs prescribed in the patient's history (Table 1). There was no statistically significant difference in duration of follow-up between patients who were seizure-free and those who were not (median 5.7 vs. 4.7 years, $p = .275$).

3.3 | Etiology-specific seizure freedom rates

Seizure freedom rates for different etiologies are shown in Table 2 and Figure 2. Ischemic stroke was the underlying etiology with the highest rate of seizure freedom (71.2%, 95% CI = 57.9–82.2). Hippocampal sclerosis and malformation of cortical development were the etiologies with the lowest seizure freedom rates (28.2% [95% CI = 15.0–44.9] and 16.7% [95% CI = 2.1–48.4], respectively).

When entered as a categorical variable into logistic regression analysis considering causes of epilepsy, with unknown etiology as a reference and adjustment for age, sex, duration of epilepsy, and total number of ASMs taken since diagnosis of epilepsy, ischemic stroke was independently associated with a higher odds of seizure freedom (odds ratio = 2.093, 95% CI = 1.039–4.216; Table 2).

Patients with ischemic stroke, compared to those with all other etiologies (including unknown), were significantly older, had a shorter duration of epilepsy, were more often seizure-free, and had a lower ASM load at the last visit (Table 3). Patients with hippocampal sclerosis had

a longer duration of epilepsy, a higher ASM load, and a higher number of ASMs prescribed since diagnosis of epilepsy as compared to patients with other causes of focal epilepsy (Table 4).

3.4 | Etiology-specific drug loads

Loads of ASM for different etiologies of epilepsy are given in Table 5. Kruskal–Wallis test showed a significant difference between epilepsy etiologies ($\chi^2[8] = 31.032$, $p < .001$). Post hoc analysis with pairwise comparisons using Dunn procedure with a Bonferroni correction for multiple comparisons demonstrated a significantly lower drug load in patients with ischemic stroke as compared to those with hippocampal sclerosis (adjusted $p = .008$) and brain tumor (adjusted $p = .049$) as well as a significantly higher load in patients with hippocampal sclerosis compared to those with unknown etiology (adjusted $p = .029$). Figure 2 summarizes and contrasts the seizure freedom rates and ASM loads for the specific etiological groups.

The total number of ASMs prescribed since diagnosis of epilepsy also significantly differed with respect to the underlying etiology ($\chi^2[8] = 26.268$, $p = .001$). In post hoc analyses, pairwise comparisons showed that in patients with ischemic stroke as compared to those with hippocampal sclerosis, the number of previous and current ASMs was significantly lower ($p = .030$).

TABLE 1 Clinical variables associated with seizure freedom

Variable	Seizure-free, $n = 282$	Not seizure-free, $n = 309$	Statistical analysis
Female sex, n (%)	135 (47.9)	156 (50.5)	$p = .526^a$
Age, years, median (IQR)	55 (39–70)	48 (35–62)	$p = .001^{b,c}$
Duration of epilepsy, years, median (IQR)	11 (5–24)	17 (7–31.5)	$p = .001^{b,c}$
All ASMs since diagnosis of epilepsy, n , median (IQR)	2 (1–3)	3 (2–5)	$p < .001^{b,c}$
ASM load at last visit, median (IQR)	.8 (.4–1.3)	1.8 (1.0–3.0)	$p < .001^{b,c}$
Seizure etiology, n (%)			
Cerebrovascular malformation	17 (6.0)	16 (5.5)	$p = .784^a$
Hippocampal sclerosis	11 (3.9)	28 (9.1)	$p = .012^{a,c}$
Malformation of cortical development	2 (.7)	10 (3.2)	$p = .030^{a,c}$
Brain tumor	26 (9.2)	41 (13.3)	$p = .121^a$
Hemorrhagic stroke	14 (5.0)	15 (4.5)	$p = .804^a$
Ischemic stroke	42 (14.9)	17 (5.5)	$p < .001^{a,c}$
Traumatic brain injury	27 (9.6)	28 (9.1)	$p = .830^a$
Other etiologies	4 (1.4)	7 (2.3)	$p = .447^a$
Unknown etiology	139 (49.3)	147 (47.6)	$p = .676^a$

Abbreviations: ASM, antiseizure medication; IQR, interquartile range.

^aPearson chi-squared test.

^bMann–Whitney U -test,

^cStatistically significant.

TABLE 2 Etiology-specific seizure freedom rates

Etiology	Seizure freedom rate, n/N (%)	Logistic regression, adjusted OR (95% CI) ^a
Unknown etiology	139/286 (48.6%, 95% CI = 42.7–54.6)	1 (reference)
Cerebrovascular malformation	17/33 (51.5%, 95% CI = 33.5–69.2)	.944 (.466–2.120)
Hippocampal sclerosis	11/39 (28.2%, 95% CI = 15.0–44.9)	.561 (.248–1.269)
Malformation of cortical development	2/12 (16.7%, 95% CI = 2.1–48.4)	.400 (.075–2.141)
Brain tumor	26/67 (38.8%, 95% CI = 27.1–51.5)	.827 (.446–1.535)
Hemorrhagic stroke	14/29 (48.3%, 95% CI = 29.4–67.5)	1.069 (.451–2.535)
Ischemic stroke	42/59 (71.2%, 95% CI = 57.9–82.2)	2.093 (1.039–4.216)
Traumatic brain injury	27/55 (49.1%, 95% CI = 35.4–62.9)	.866 (.464–1.617)
Other	4/11 (36.4%, 95% CI = 10.9–69.2)	.976 (.223–4.266)

Abbreviations: CI, confidence interval; OR, odds ratio.

^aAdjusted for age, sex, duration of epilepsy, and number of all ASMs taken since diagnosis of epilepsy.

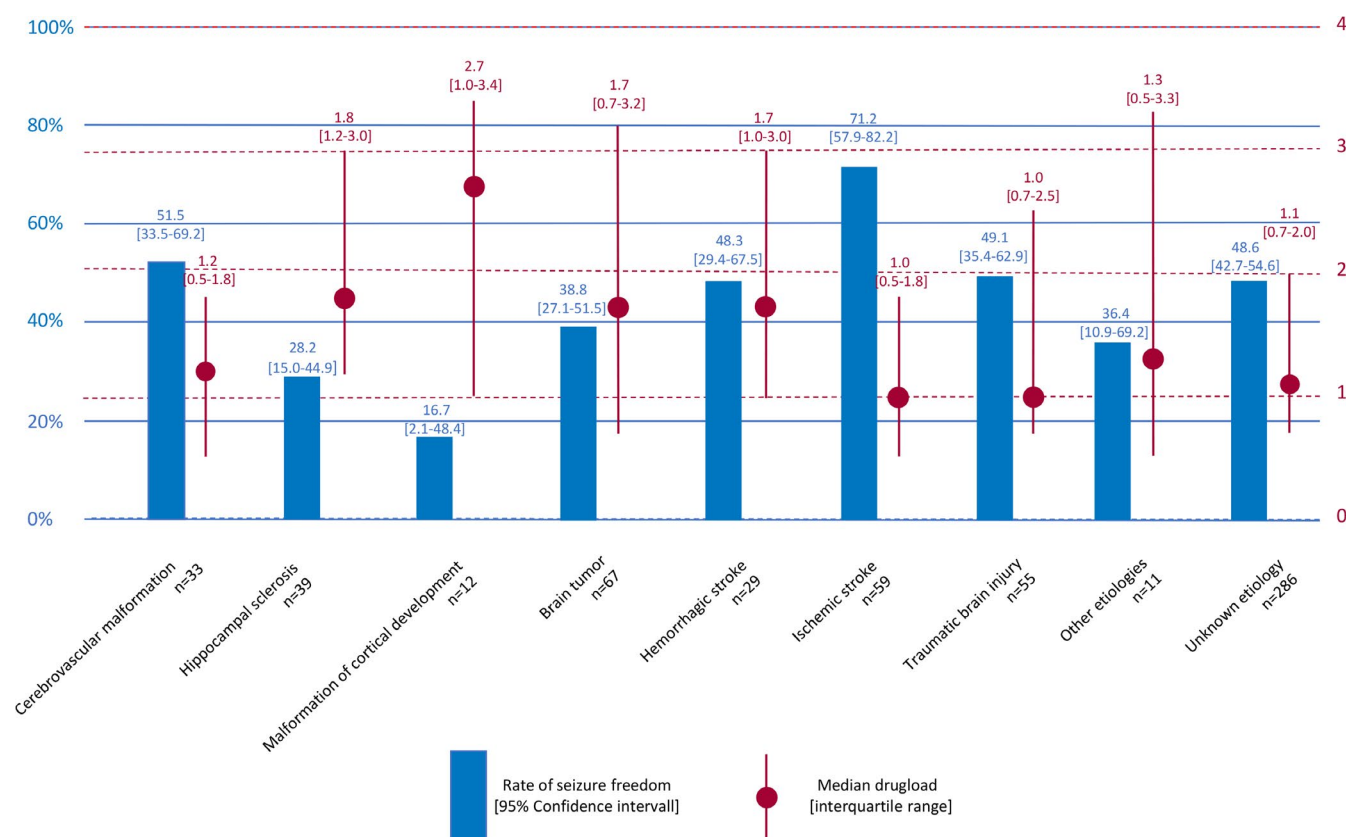


FIGURE 2 Comparison of seizure-freedom rates and drug loads for different epilepsy etiologies. Rate of seizure freedom for each etiology of epilepsy is represented by the blue bars (left y-axis). Median load of antiseizure medication for each etiology is represented by the purple dots (right y-axis), with the vertical lines indicating interquartile ranges. Load of antiseizure medication was calculated according to the 2020 World Health Organization Center for Drug Statistics Methodology ATC/DDD Index using the formula "individual antiseizure medication dosage per day divided by defined daily dose"

4 | DISCUSSION

In this study, we demonstrated that the response to ASM in focal epilepsy is highly etiology-specific. Almost three in

four patients with epilepsy caused by ischemic stroke were seizure-free for at least the previous 12 months, which is superior to all other etiologies assessed. In contrast, hippocampal sclerosis (28%) and malformation of cortical development (17%) had a significantly lower rate of seizure

TABLE 3 Clinical variables associated with epilepsy caused by ischemic stroke

Variable	Patients with epilepsy caused by ischemic stroke, <i>n</i> = 59	Patients with epilepsy of other etiology, <i>n</i> = 532	Statistical analysis
Female sex, <i>n</i> (%)	24 (40.7)	264 (50.2)	<i>p</i> = .166 ^a
Age, years, median (IQR)	73 (60–77)	50 (37–64)	<i>p</i> < .001 ^{b,c}
Duration of epilepsy, years, median (IQR)	9 (5–17)	15 (6–29)	<i>p</i> = .009 ^{b,c}
All ASMs since diagnosis of epilepsy, <i>n</i> , median (IQR)	2 (1–3)	2 (1–4)	<i>p</i> = .069 ^b
Seizure-free at last visit, <i>n</i> (%)	40 (71.2)	240 (45.1)	<i>p</i> < .001 ^{a,c}
ASM load at last visit, median (IQR)	1 (.5–1.8)	1.3 (.7–2.4)	<i>p</i> = .019 ^{b,c}

Abbreviations: ASM, antiseizure medication; IQR, interquartile range.

^aPearson chi-squared test.

^bMann–Whitney *U*-test.

^cStatistically significant.

TABLE 4 Clinical variables associated with epilepsy caused by hippocampal sclerosis

Variable	Patients with epilepsy caused by hippocampal sclerosis, <i>n</i> = 39	Patients with epilepsy of other etiology, <i>n</i> = 552	Statistical analysis
Female sex, <i>n</i> (%)	23 (59.7)	268 (48.6)	<i>p</i> = .208 ^a
Age, years, median (IQR)	53 (41–69)	52 (37–67)	<i>p</i> < .579 ^b
Duration of epilepsy, years, median (IQR)	35 (12–48)	13 (6–26)	<i>p</i> < .001 ^{b,c}
All ASMs since diagnosis of epilepsy, <i>n</i> , median (IQR)	3 (2–6)	2 (1–4)	<i>p</i> = .003 ^{b,c}
Seizure-free at last visit, <i>n</i> (%)	11 (28.2)	271 (49.1)	<i>p</i> = .012 ^{a,c}
ASM load at last visit, median (IQR)	1.8 (1.2–3.0)	1.2 (.7–2.2)	<i>p</i> = .002 ^{b,c}

Abbreviations: ASM, antiseizure medication; IQR, interquartile range.

^aPearson chi-squared test.

^bMann–Whitney *U*-test.

^cStatistically significant.

freedom. Ischemic stroke also was independently associated with increased odds of 12-month seizure freedom as compared to the other etiological groups when adjusted for age, sex, duration of epilepsy, and number of ASMs taken so far. As secondary outcome, we also report ASM load to be etiology-specific in focal epilepsy. Interestingly, patients with epilepsy caused by ischemic stroke had the lowest drug load, which obviously was sufficient to result in the highest seizure freedom rate. Furthermore, in patients with post-ischemic stroke epilepsy, the number of previously and currently administered ASMs was significantly lower compared to that in patients with hippocampal sclerosis.

Counseling on the expected probability of seizure freedom with ASM treatment is paramount to meet the information needs of patients with epilepsy and to tailor drug doses. Nonetheless, the scarcity of data on the impact of underlying etiology is striking. More than 20 years ago, two studies assessed the etiology-specific response to ASM in focal epilepsy.^{2,9} Since then, multiple new ASMs have been approved,¹⁰ which may impact the response to treatment. In our study, 56.4% of patients on ASM received

such novel compounds, confirming the necessity to reappraise the precedent data. In one study from 1998 on seizure outcome in focal epilepsy, the highest rate of seizure freedom (54%) was observed in patients with stroke; the lowest rate (11%) was seen in patients with hippocampal sclerosis.⁹ In another study from 2001, 67% of patients with stroke were seizure-free, and seizure freedom was reported in 42% of patients with hippocampal sclerosis.² The surprisingly high seizure freedom rate in hippocampal sclerosis in the latter study may be explained by >70% of patients having newly diagnosed epilepsy and thus likely a small number of previously failed ASMs. In the current study, 28% of 39 patients with hippocampal sclerosis were seizure-free, which is still a considerably high rate. The group of 11 seizure-free patients so far have taken significantly fewer ASMs (median = 2 vs. 4, *p* = .001), which also hints at less severe forms of epilepsy; the 28 patients with drug resistance and hippocampal sclerosis either were ineligible candidates for resective surgery or had rejected the operation.

A more recent analysis of the etiology-specific treatment response was done in a post hoc analysis of the

TABLE 5 Comparison of ASM load according to etiology of epilepsy

Etiology	ASM load at last visit, median (IQR)	All ASMs since diagnosis of epilepsy, <i>n</i> , median (IQR)	Statistical analysis	Statistical analysis
Cerebrovascular malformation, <i>n</i> = 33	1.2 (.5–1.8)	2 (1–3)	$\chi^2[8] = 31.032, p < .001^{a,b}$	$\chi^2[8] = 28.989, p < .001^{a,c}$
Hippocampal sclerosis, <i>n</i> = 39	1.83 (1.2–3.0)	3 (2–6)		
Malformation of cortical development, <i>n</i> = 12	2.7 (1–3.4)	4 (2.5–6.5)		
Brain tumor, <i>n</i> = 67	1.67 (.67–3.2)	3 (2–5)		
Hemorrhagic stroke, <i>n</i> = 29	1.7 (1.0–3.0)	2 (2–4)		
Ischemic stroke, <i>n</i> = 59	1 (.5–1.8)	2 (1–3)		
Traumatic brain injury scar, <i>n</i> = 55	1 (.7–2.5)	2 (1–3)		
Other, <i>n</i> = 15	1.3 (.5–3.3)	4 (2–6)		
Unknown etiology, <i>n</i> = 286	1.1 (.67–2.0)	2 (1–4)		

Abbreviations: ASM, antiseizure medication; IQR, interquartile range.

^aKruskal–Wallis test.^bSignificant differences in ASM load between ischemic stroke and brain tumor (Bonferroni adjusted $p = .049$), ischemic stroke and hippocampal sclerosis (adjusted $p = .008$), and hippocampal sclerosis and unknown etiology (adjusted $p = .029$).^cSignificant differences in number of all ASMs since diagnosis of epilepsy between ischemic stroke and hippocampal sclerosis (adjusted $p = .030$).

Euro-Esli study on patients all of whom were treated with eslicarbazepine acetate in mono- or polytherapy. In that study, patients with epilepsy due to stroke compared to all other causes of focal epilepsy had a significantly higher 50% responder rate; that is, >50% fewer seizures with eslicarbazepine acetate than before.¹³ However, there is no reason to assume that specific ASMs are more or less efficacious in focal epilepsy of different etiologies.

The three aforementioned studies did not differentiate strokes of ischemic versus hemorrhagic origin.^{2,9,13} In our study, the response to treatment trended to be better in epilepsy caused by ischemic (71%) compared to hemorrhagic stroke (48%), and only ischemic stroke differed significantly from other etiologies. It is believed that the epileptogenic pathomechanisms between epilepsy caused by ischemic stroke and intracerebral hemorrhage differ. Pathogenesis of post-ischemic stroke epilepsy includes changes in regional cerebral blood flow, alteration of the blood–brain barrier, and remodeling of neuronal networks,¹⁴ whereas epileptogenesis after intracerebral hemorrhage is mediated additionally by effects of hemosiderin disposition and mechanical effects due to hematoma expansion.¹⁵ What is more, hemorrhagic stroke is a stronger risk factor for the development of epilepsy than ischemic stroke. In a large study on more than 750 000 stroke patients, 14.7% of patients with hemorrhagic stroke and 8.3% of patients with ischemic stroke developed epilepsy within 8 years after the index event.¹⁶ Our results encourage differentiating between ischemic and hemorrhagic stroke when estimating the prognosis of epilepsies and the response to ASM.

To our knowledge, this study is the first to compare ASM loads between different etiologies of focal epilepsy. Patients with post-ischemic stroke epilepsy had the lowest ASM load, in particular if compared to those with brain tumor and hippocampal sclerosis. This finding is of high clinical relevance, as it unequivocally shows that the favorable response to ASM treatment in epilepsy due to ischemic stroke does not come at the cost of the need for higher ASM dosages. Even more, the dosages administered in ischemic stroke were even lower than in other etiologies, which generally decreases the probability of adverse effects, improves adherence to ASM intake, and likely increases quality of life.¹⁷ The favorable response of poststroke epilepsy to ASM has been demonstrated in a small series with 35 patients, two thirds of whom had had ischemic strokes, as 16 patients (46%) became seizure-free with the first ASM.¹⁸ In the present study, epilepsy due to ischemic stroke so far has been treated with a median of only two ASMs, which is significantly less than in epilepsy caused by hippocampal sclerosis. Thus, etiology-specific seizure freedom rates inversely correspond to the number of ASMs administered so far. The association between the number of previously failed ASMs and

the probability of seizure freedom has been demonstrated previously; the fewer ASMs have failed so far, the higher the chance of seizure freedom with the next compound, and vice versa.¹⁹ This general observation has now been confirmed with respect to specific etiologies.

There are limitations to this study. First, although we report results from three sites of the epilepsy outpatient clinic of the Charité–Universitätsmedizin Berlin covering vast parts of the city with heterogenic patient populations, our methodological approach still has to be considered monocentric. Second, data were assessed in a specialized epilepsy outpatient clinic, which bears the risk of bias due to treatment of rather challenging cases and thus lower rates of seizure freedom. However, this bias would be true for all etiologies and would not impact the relative differences in response to ASM between the underlying causes of epilepsy. Furthermore, almost every second patient was seizure-free, which is what can be expected in the overall group of patients with focal epilepsy. Third, due to the retrospective nature of the study, differences in follow-up time between different seizure etiologies could not be ruled out. Pairwise comparisons revealed that there was a significant difference in duration of follow-up between patients with specific etiologies. For example, follow-up time was shorter in patients with brain tumor as compared to unknown etiology and hippocampal sclerosis. The analysis of follow-up time between different etiologies is summarized in the supplementary material (Table S1, online only). The cause of the difference in follow-up time is unclear, as we have no reliable information on the reason patients discontinue treatment at our outpatient clinic. One major cause could be mortality. As our study design required at least two visits to the outpatient clinic that had to be at least 12 months apart, it is plausible that the impact of mortality on the outcome of our study due to a reduced observation period is limited. Reassuringly, there was no statistically significant difference in duration of follow-up between patients who were seizure-free and those who were not. The validity of our data is also limited by differences in group sizes. Although the overall number of patients in our study was large, we had only few patients with, for example, malformation of cortical development. Finally, a potential source of bias could lie in incomplete data collection; for example, we could not differentiate affected vascular territories in ischemic stroke or primary versus secondary brain tumors.

5 | Conclusions

Our study demonstrates that in focal epilepsy, both the response to pharmacological treatment regarding rate of seizure freedom and ASM load are highly etiology-specific. Ischemic stroke was the etiology with the most favorable

prognosis, whereas hippocampal sclerosis and malformation of cortical development were those with the worst. Patients with ischemic stroke underlying epilepsy obviously need a rather low ASM load to achieve a high probability of seizure freedom. Etiology should be considered when informing patients about their prognosis and when tailoring the doses of ASM. Further data on the etiology-specific response to pharmacological treatment of epilepsy are warranted to substantiate our findings. They may be extracted from existing large trials such as SANAD, which provide detailed information on previous or current neurological disorders likely corresponding to the underlying etiology.^{20,21}

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CONFLICT OF INTEREST

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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2.2.3 Nicht-Absetzen der anfallssuppressiven Medikation bei anfallsfreien Patient:innen mit Epilepsie

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Wie in der Vorarbeit (2.2.2) gezeigt wurde, waren ca. 50% der Patient:innen mit fokaler Epilepsie unter anfallssuppressiver Therapie anfallsfrei. Bei anfallsfreien Patient:innen stellt sich die Frage, ob und wie mit der ASM fortzufahren ist. In Fällen, in denen das Rezidivrisiko im Falle eines Absetzens der Medikation als ausreichend niedrig eingeschätzt wird, sollte ein Absetzversuch in Erwägung gezogen werden (Holtkamp et al. 2023, Gloss et al. 2021, Beghi et al. 2013). Trotz einer mutmaßlich günstigen Nutzen-Risiko Konstellation behalten eine Vielzahl von Patient:innen ihre ASM dauerhaft bei, was mit negativen Auswirkungen für die Patient:innen (Nebenwirkungen der Medikation, Einschränkungen hinsichtlich der Ausübung bestimmter Berufe und des Führens von Kraftfahrzeugen bestimmter Fahrzeugklassen) und die Öffentlichkeit (Kosten im Gesundheitssystem) assoziiert sein kann (Jacoby et al. 2009, Möller et al. 2023).

In der hier vorgestellten Arbeit sollten die dahinterstehenden Entscheidungsprozesse näher beleuchtet werden. Es erfolgte eine retrospektive Auswertung der Visiten anfallsfreier Patient:innen in den Epilepsie-Ambulanzen der Charité Universitätsmedizin Berlin. Eingeschlossen wurden Patient:innen, die unter anfallssuppressiver Therapie für mindestens 24 Monate anfallsfrei waren. Für jede/n Patient:in wurde die „Indexvisite“ analysiert. Dies war die letzte Visite im letzten anfallsfreien Intervall von mindestens 24 Monaten, in der noch eine anfallssuppressive Therapie verabreicht wurde. Primärer Endpunkt war die Entscheidung gegen die Durchführung eines Absetzversuchs oder einer signifikanten Reduktion der ASM um $\geq 25\%$ der zuvor eingenommenen Dosis.

Insgesamt wurden 338 Patient:innen mit einer medianen anfallsfreien Zeit von 5 Jahren (Quartilen: 3;10) in die Studie eingeschlossen. Bei 81,7% der Patient:innen erfolgte kein Absetzversuch und keine signifikante Dosisreduktion. Fokal zu bilaterale oder generalisierte tonisch-klonische Anfälle (OR: 2,33, 95% KI: 1,08-5,06), vorangegangene sporadische Anfallsrezidive (OR: 3,32, 95% KI: 1,10-10,04) und gescheiterte Absetzversuche (OR: 4,67, 95% KI: 1,03-21,11) sowie eine höhere Dosierung der ASM (OR: 6,10, 95% KI: 2,09-17,78) waren mit einem Nicht-Absetzen assoziiert.

Absetzversuche waren nicht unabhängig mit der Dauer der Anfallsfreiheit assoziiert. Sie wurden zu jedem Zeitpunkt der Anfallsfreiheit unternommen, waren aber häufiger nach einem

Zeitraum von > 10 Jahren im Vergleich zu einem anfallsfreien Zeitraum von ≤ 10 Jahren ($p = 0,026$). Bei 54,1% der Indexvisiten wurde eine Erörterung eines Absetzversuchs dokumentiert.

Von 62 der Patient:innen, bei denen ein Absetz- oder Reduktionsversuch unternommen wurde, lagen Follow-Up-Daten vor (medianer Beobachtungszeitraum 20 Monate, Quartilen 9;35). Alle Patient:innen hatten die Entscheidung zum Absetzen bzw. zur Reduktion der Medikation umgesetzt. 62,9% der Patient:innen blieben auch nach Absetzen bzw. Reduktion der Dosis der ASM anfallsfrei.

ORIGINAL ARTICLE

Non-discontinuation of antiseizure medication in seizure-free epilepsy patients

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Abstract

Background and purpose: In patients with epilepsy and sustained seizure freedom, guidelines recommend considering discontinuation of antiseizure medication (ASM) based on shared decision-making. This study aims to identify factors associated with non-discontinuation of ASM in seizure-free patients.

Methods: Retrospective data from three sites of an academic outpatient clinic were analyzed. Adult patients with epilepsy who have been seizure-free for ≥ 24 months on ASM monotherapy were included. The primary end-point was non-discontinuation of ASM, defined as no discontinuation or no dose reduction of $\geq 25\%$ at the last outpatient clinic visit in the ultimate seizure-free interval. Secondary end-points included frequency of discussion on discontinuation attempts between patients and physicians, adherence to ASM discontinuation decisions, and post-discontinuation seizure outcomes.

Results: Out of 338 included patients, 81.7% did not discontinue ASM and did not reduce its dose, 11.5% discontinued ASM and 6.8% had a significant dose reduction. Factors independently associated with non-discontinuation of ASM were history of focal to bilateral or generalized tonic-clonic seizures (odds ratio [OR] 2.33, 95% confidence interval [CI] 1.08–5.06), history of breakthrough seizures (OR 3.32, 95% CI 1.10–10.04), history of failed attempts to discontinue or reduce the ASM dose (OR 4.67, 95% CI 1.03–21.11) and higher ASM load at the index visit (OR 6.10, 95% CI 2.09–17.78). Discontinuation attempts were made during the entire period of seizure freedom and were most commonly undertaken ≥ 10 years after the last seizure.

Conclusions: This study provides insights into factors associated with the shared decision-making process regarding ASM discontinuation in seizure-free patients and highlights the importance of considering individual patient characteristics and seizure history.

KEYWORDS

drugs, epilepsy, pharmacotherapy, prognosis, seizure

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INTRODUCTION

In people with epilepsy, antiseizure medication (ASM) is the main pillar of treatment. Approximately 60%–85% of patients achieve sustained seizure freedom [1, 2]. When patients have become seizure-free for some time, the question arises whether ASM may be discontinued. Typically, physicians recommend discontinuing ASM or reducing its dose significantly only when they estimate the risk for seizure recurrence to be low [3, 4]. Several factors have been described to be associated with seizure remission after ASM discontinuation [5–7].

As duration since last seizure is one of the strongest predictors for remaining seizure-free, ASM discontinuation is usually recommended if the patient has been without seizures for a minimum of 2 years [3, 4]. However, a significant proportion of patients remain on ASM long beyond that time [8]. As long-term ASM therapy may be associated with significant adverse effects [9, 10], which reduce quality of life [11, 12] and impose financial burdens on the health-care system [13], it is important to identify factors associated with lack of discontinuation or significant dose reduction of ASM.

Previous studies on seizure-free patients have shown that ASM discontinuation is discussed in only 30%–50% of outpatient visits [8, 14]. In a recent study on a heterogeneous patient population with focus on the first decade of seizure freedom including children, adolescents and adults treated in monotherapy and polytherapy, the decision to attempt ASM discontinuation was independently associated with four variables: longer duration of seizure freedom, treatment with an older generation ASM, self-limiting epilepsy syndrome and lower estimated risk of seizure recurrence as calculated with the antiepileptic drug withdrawal risk retrieval tool [6, 8].

Nevertheless, there are gaps in the evidence regarding ASM discontinuation practices in outpatient epilepsy clinics. It remains unstudied how previous unsuccessful discontinuation attempts and breakthrough seizures influence ASM discontinuation decisions. Furthermore, open questions persist regarding timing of ASM discontinuation, particularly concerning discontinuation after more than 10 years of seizure freedom. It is possible that the probability of discontinuing ASM or reducing the dose is lower after a long time of seizure freedom as either the patients have made a final decision regarding continuation of ASM therapy or the physicians have given up on suggesting ASM discontinuation.

In the light of these considerations, this study aims to examine factors associated with non-discontinuation (i.e., lack of either discontinuation or dose reduction of at least 25%) of ASM monotherapy in seizure-free patients.

METHODS

Data source and participants

Data from the three sites of the epilepsy outpatient clinic of the Department of Neurology at Charité—Universitätsmedizin Berlin in Germany were retrospectively analyzed. Approval for the study was

granted by the local ethics committee (EA2/181/20). The study conforms with the World Medical Association Declaration of Helsinki. Since this study was retrospective, the requirement for individual patient informed consent was waived.

All adult patients with a diagnosis of epilepsy according to the International League Against Epilepsy [15], who had been seizure-free for at least 24 months on ASM monotherapy, were included. Patients who were pregnant in the respective seizure-free interval, patients in whom resective epilepsy surgery had been performed, patients with ASM polytherapy, patients in whom the seizure-free interval had occurred before treatment in our outpatient clinics as well as patients with insufficient documentation were excluded.

All visits to the outpatient clinics from January 2010 until 30 September 2022 were potentially eligible for inclusion.

For each patient fulfilling the inclusion criteria, retrieval and analysis of data refer to the index visit. The index visit was defined as the last visit to the epilepsy outpatient clinic in the ultimate seizure-free interval of >24 months in which the patient was still taking one ASM. If a patient had more than one seizure-free interval, the ultimate interval was analyzed. This was done to prevent any potential distortion of our findings pertaining to demographic factors. Figure 1 shows examples of the application of our definition of index visits in different illustrative patients.

Primary and secondary end-points

The primary end-point of our study was non-discontinuation of ASM (i.e., not discontinuing ASM or not reducing the dose by at least 25%) at the index visit. Our study goal was to identify factors that are associated with the primary end-point and to analyze rate of non-discontinuation of ASM according to duration of seizure freedom.

Secondary end-points were (i) whether the topic of reducing or discontinuing ASM was actually addressed by the treating physician at the index visit (irrespective of the final decision), (ii) whether a shared decision by physician and patient to reduce or discontinue ASM was followed by the patient and (iii) to what extent patients remained seizure-free after discontinuation of ASM.

Data extraction

The data were retrieved from the patients' electronic medical records examining the following demographic and clinical parameters: sex, duration of epilepsy before remission, duration of seizure freedom, epilepsy type, number of all ASMs taken so far (including current ASM), number of previous seizures (1–9 seizures vs. ≥ 10 seizures), family history of epilepsy, history of febrile seizures, history of status epilepticus, history of breakthrough seizures (defined as seizure recurrence after 12 months of seizure freedom without reduction of ASM dose in the prior 3 months) and history of failed attempts to reduce or discontinue ASM.

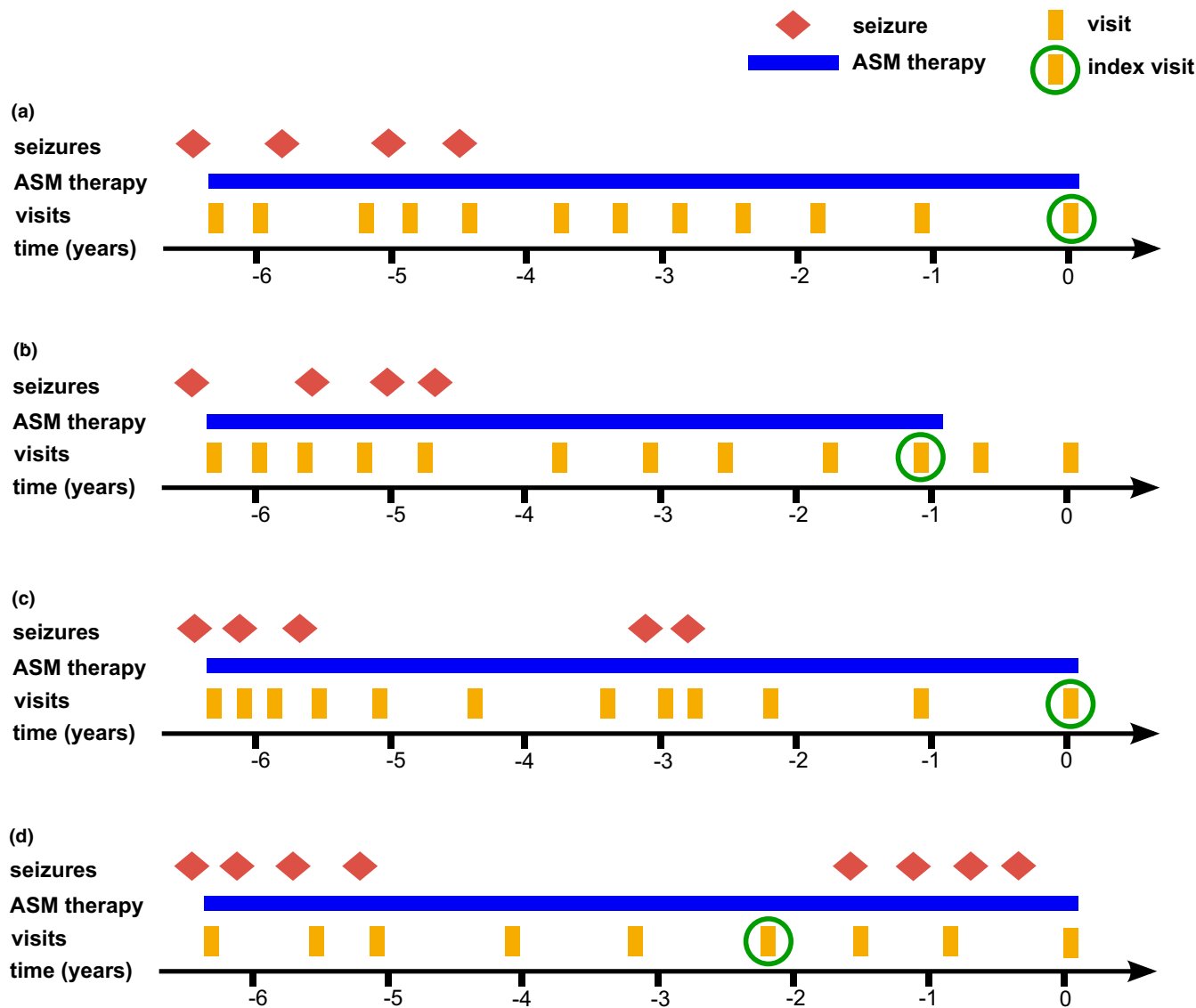


FIGURE 1 Definition of index visits. ASM, antiseizure medication. This figure shows examples of index visits in different exemplary patients. (a) This patient has been seizure-free for approximately 4 years and has not yet discontinued ASM therapy. The index visit is the last visit in the seizure-free interval. (b) This patient has discontinued ASM therapy after a seizure-free interval of approximately 4 years. The index visit is the last visit in the seizure-free interval where the patient still received ASM. (c) This patient has two seizure-free intervals >24 months. Only the last visit in the last seizure-free interval is considered the index visit. (d) This patient had a seizure-free interval of approximately 3.5 years but now again has seizures. The last visit in the seizure-free interval is considered the index visit.

In addition, the following data specific to the index visit were retrieved: age at index visit, duration of epilepsy and duration of seizure freedom at the time of the index visit, Liverpool Adverse Effects Profile score [16], decision of physicians regarding discontinuation or dose reduction of ASM as well as specific ASM drug and dose. Individual ASM drug loads (i.e., a normalized ASM dose for each patient) were calculated according to the 2020 World Health Organization Center for Drug Statistics Methodology ATC/DDD Index with the formula “individual daily ASM dosage divided by defined daily dose (DDD)”. ASMs were also categorized based on their approval dates. Carbamazepine, ethosuximide, phenobarbital, phenytoin, primidone and valproic acid were defined as first-generation ASMs.

In patients in whom the index visit was not the same as the last visit to the outpatient clinic (i.e., cases where ASM had been discontinued, and patients in whom seizures had re-occurred after the index interval; for case examples, see Figure 1b,d), data on seizure outcome since the index visit and adherence to the decision to continue or discontinue ASM therapy were also retrieved.

Taking together all available data, 2- and 5-year seizure recurrence risk after possible ASM discontinuation was calculated according to the antiepileptic drug withdrawal risk retrieval tool (<http://epilepsypredictiontools.info/aedwithdrawal>) [6]. The recurrence risks were calculated using a Microsoft Excel script provided by its authors.

Statistical analysis

Categorical variables were expressed as frequencies and were analyzed with Pearson's chi-squared tests. Due to a non-normal distribution as checked in the Kolmogorov–Smirnov test, continuous variables were expressed as median and interquartile range (IQR) and were analyzed using Mann–Whitney *U* tests. Confidence intervals (CIs) of frequencies were calculated using the exact Clopper–Pearson method. A significance level of $p < 0.05$ was considered statistically significant.

Adjusted multiple logistic regression analysis (inclusion method: enter) was conducted to calculate the odds ratio (OR) with 95% CI in order to identify variables independently associated with consensus to not discontinue or reduce ASM. Age, sex and variables with p values < 0.25 in univariate analysis were included in our logistic regression analysis. The calculated 2-year and 5-year recurrence risks were not included in our model to avoid multicollinearity as the calculation of these risks encompassed several parameters already included in the logistic regression analysis. All statistical analyses were performed using SPSS Statistics, version 28.

RESULTS

Study population

In all, 566 patients with a seizure-free interval of ≥ 24 months were identified. After applying the exclusion criteria, 338 patients were eligible for inclusion in the study. [Figure 2](#) shows the patient selection.

Median age at index visit was 51 years (IQR 36–68); 52.1% were female. Median duration of epilepsy was 17 years (IQR 8–34) and median duration of seizure-free interval before the index visit was 5 years (IQR 3–10).

Primary outcomes

In 81.7% of epilepsy patients ($n = 276$), ASM was not discontinued and there was no ASM dose reduction. Accordingly, only in 11.5% ($n = 39$) was ASM discontinued, and the ASM dose was significantly reduced in 6.8% ($n = 23$). [Table 1](#) contrasts different variables in patients in whom ASM was not discontinued. Non-discontinuation rates for individual ASMs are listed in [Table S1](#) (supplementary material).

In the logistic regression analysis, non-discontinuation of ASM was independently associated with (i) history of focal to bilateral or generalized tonic-clonic seizures (OR 2.33, 95% CI 1.08–5.06), (ii) history of breakthrough seizures (OR 3.32, 95% CI 1.10–10.04), (iii) history of a failed attempt to discontinue or reduce dose of ASM (OR 4.67, 95% CI 1.03–21.11) and (iv) higher ASM load at the index visit (OR 6.10, 95% CI 2.09–17.78) ([Table 1](#)).

When entered as a continuous variable, there was no statistically significant association between the decision not to discontinue or

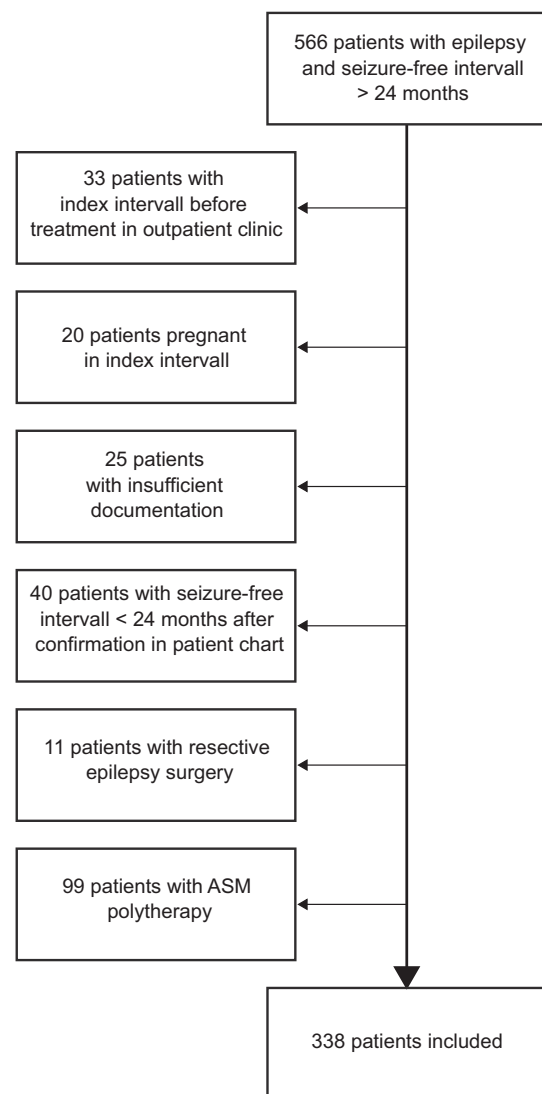


FIGURE 2 Flow diagram showing the selection of patients for this study.

not to reduce the dose of ASM and duration of seizure freedom. [Figure 3](#) shows discontinuation rates in relation to duration of seizure freedom; a seizure-free period of ≤ 10 years was associated with non-discontinuation of ASM ($p = 0.026$).

Secondary outcomes

A discussion between physicians and patients regarding discontinuation or dose reduction of ASM was documented in 54.1% ($n = 183$) of index visits.

In 117 out of 276 patients (42.3%) where ASM was not discontinued, documentation was sufficient to evaluate whether this decision was mainly driven by the patient or by the epileptologist. Physicians advised to remain on ASM therapy in 38 cases (32.4%) and patients wished to stay on current ASM in 79 cases (67.5%).

Out of the 62 patients who discontinued or reduced the ASM dose, 35 patients (56.5%) had a follow-up visit to the outpatient clinic

TABLE 1 Clinical variables associated with non-discontinuation of ASM therapy.

	Non-discontinuation of ASM (n = 276)	Discontinuation or significant dose reduction of ASM (n = 62)	Univariate analysis	Binary logistic regression, exp(B) (95% CI)
Female sex, n (%)	140 (50.7%)	36 (58.1%)	$p=0.296^a$	0.76 (0.41–1.42)
Age, years, median (IQR)	51 (37–68)	51 (33–71)	$p=0.804^b$	1.01 (0.99–1.02)
Duration of seizure freedom, years, median (IQR)	5 (3–10)	6 (3–12)	$p=0.203^b$	1.00 (0.96–1.04)
Duration of epilepsy until remission, years, median (IQR)	9.5 (1–24)	6 (1–16)	$p=0.149^b$	1.01 (0.98–1.03)
Generalized tonic-clonic or focal to bilateral tonic-clonic seizures, n (%)	244 (90.0%)	47 (75.8%)	$p=0.002^a$	2.33 (1.08–5.06)
Epilepsy type, n (%)			$p=0.484^a$	Not included ^c
Focal	194 (70.3%)	46 (74.2%)		
Generalized	62 (22.5%)	10 (16.1%)		
Unclassified	20 (7.2%)	6 (9.7%)		
Structural epilepsy, n (%)	94 (34.2%)	19 (30.6%)	$p=0.594^a$	Not included ^c
History of status epilepticus, n (%)	20/230 ^d (8.5%)	3/50 ^d (5.7%)	$p=0.529^a$	Not included ^c
First-generation ASM, n (%)	63 (22.8%)	20 (32.3%)	$p=0.119^a$	0.78 (0.36–1.67)
History of breakthrough seizure, n (%)	57 (20.7%)	4 (6.5%)	$p=0.009^a$	3.32 (1.10–10.04)
History of failed attempt to reduce dose or discontinue ASM, n (%)	36 (13.0%)	2 (3.2%)	$p=0.027^a$	4.67 (1.03–21.11)
Intellectual disability, n (%)	15 (5.4%)	4 (6.5%)	$p=0.753^a$	Not included ^c
LAEP score, median (IQR)	33 (26–41)	32 (27–40)	$p=0.546^b$	Not included ^c
Number of all ASM since diagnosis of epilepsy, median (IQR)	2 (1–3)	1 (1–3)	$p=0.088^b$	1.02 (0.79–1.32)
ASM load at index visit, median (IQR)	0.67 (0.5–1)	0.37 (0.33–0.67)	$p<0.001^b$	6.10 (2.09–17.78)
Calculated 2-year recurrence risk, %, median (IQR)	57 (41–70)	50 (37–64)	$p=0.058^b$	Not included ^e
Calculated 5-year recurrence risk, %, median (IQR)	70 (52–81)	62 (47–77)	$p=0.060^b$	Not included ^e

Abbreviations: ASM, antiseizure medication; CI, confidence interval; IQR, interquartile range; LAEP, Liverpool Adverse Effects Profile; n, number.

^aPearson's chi-squared test.

^bMann-Whitney *U* test.

^cAge and sex as well as variables with *p* values <0.25 in univariate analysis were included in our binary logistic regression model; inclusion method: enter.

^dAvailable data on status epilepticus in 280/338 patients.

^eThese variables were excluded from the binary logistic regression model to avoid multicollinearity.

(case example (b) in [Figure 1](#)). The median time from the intended discontinuation/dose reduction to last follow-up visit was 20 months (IQR 9–35). All patients had followed the decision to discontinue or reduce the dose of ASM. At the last follow-up visit, 62.9% ($n=22$) of these patients were still seizure-free. In patients with seizure recurrence, median time from discontinuation to recurrent seizure was 8 months (IQR 3–18).

Patients who were seizure-free at the last visit had a significantly lower calculated 2-year and 5-year seizure recurrence risk than patients where seizures re-occurred (53% [40%–68%], $p=0.017$ vs. 62% [47%–78%] and 66% [50%–80%] vs. 75% [58%–89%], $p=0.017$).

DISCUSSION

In this study, almost 82% of patients who had been seizure-free for at least 2 years remained on their ASM in unchanged dose at the

last visit to the outpatient clinic. Non-discontinuation of ASM was independently associated with history of focal to bilateral or generalized tonic-clonic seizures as well as history of previously failed discontinuation or dose reduction attempts, breakthrough seizures and higher ASM drug load.

In contrast to a recent study on a more heterogeneous patient population (including children, adolescents and patients with ASM polytherapy) [8], non-discontinuation of ASM per se was not associated with shorter duration of seizure freedom, although there was an association between non-discontinuation of ASM and duration of seizure freedom ≤ 10 years. Differences in the findings from our study may be explained through different patient populations, as the aforementioned study included children. In children, the time dependence of successful ASM discontinuation with respect to longer duration of seizure freedom is much better established [17]. Furthermore, the mentioned study reports results of a duration of seizure freedom of up to 10 years, whilst our results go beyond 20 years of seizure freedom. We had hypothesized that the rate of

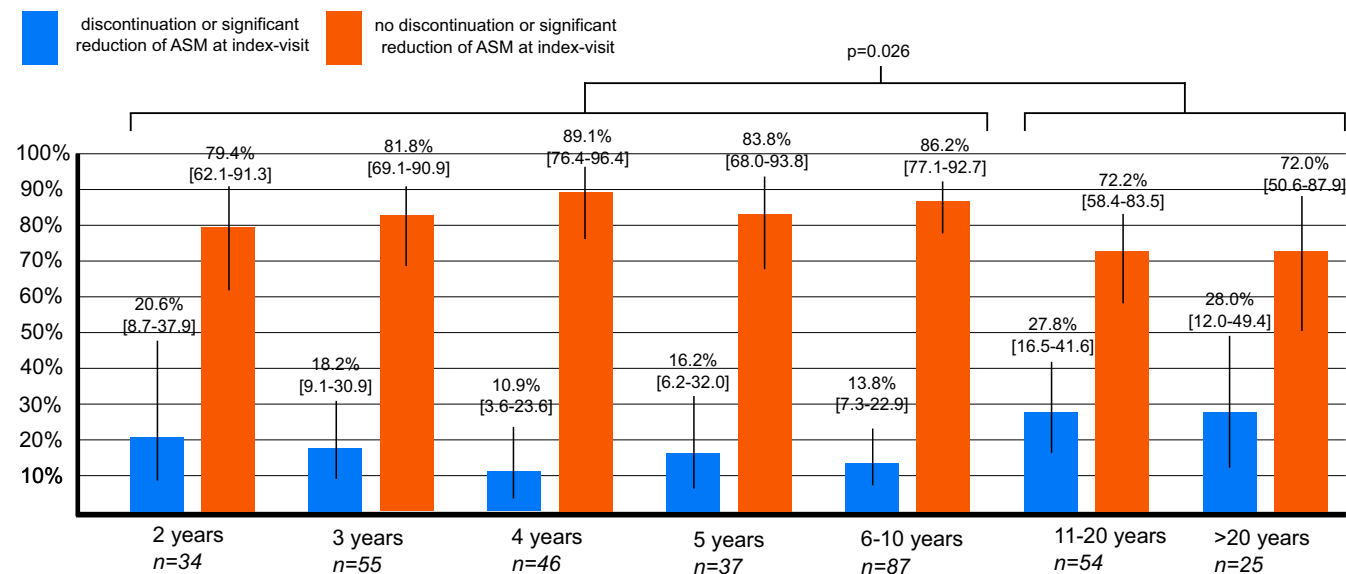


FIGURE 3 Rate of discontinuation and continuation of ASM therapy according to duration of seizure freedom. This figure shows the rate of patients who continued ASM (red bar) and who discontinued ASM or significantly reduced the dose of ASM (blue bar). Vertical lines represent 95% confidence intervals. ASM, antiseizure medication, n, number.

non-discontinuation of ASM would be high initially, decrease with sustained seizure freedom, and then increase again over time, forming a U-shaped curve. The rationale behind this idea was that, at the beginning of seizure freedom, the risk of discontinuation would be perceived as too high. Later, it would be considered safer to discontinue medication, but there may be a certain point beyond which the decision not to discontinue would become final and irreversible—a point of no return, so to speak. However, our data did not confirm this hypothesis. On the contrary, after being seizure-free for 10 or 20 years, ASM was discontinued at even higher rates than after shorter periods of seizure freedom. This finding is important as it suggests that discussing ASM discontinuation with seizure-free patients is always worthwhile.

Our study is the first to show that history of breakthrough seizures and failed discontinuation or reduction attempts are independently associated with non-discontinuation of ASM. These findings are worthy of further investigation. To our knowledge, there have been no previous reports exploring whether a failed reduction attempt or history of breakthrough seizures is indeed associated with a lower likelihood of remaining seizure-free after ASM discontinuation [7]. Regarding our final predictor of ASM non-discontinuation, ASM load at the index visit, the overall low ASM load stands out. This might be interpreted as an expression of the benign course in our patient cohort. Previously published data from our outpatient clinics on patients with focal epilepsies, including those on polytherapy, also demonstrate similarly low values [18].

It is important to recognize that the decision to continue or discontinue ASM is not solely based on rational factors but also depends on the feelings and attitudes of both patients and physicians. As is known from randomized studies, the 1- and 2-year risk of recurrence in patients who discontinue their medication is twice as high as in patients who remain on ASM [19, 20]. Understandably,

not every patient and not every physician is willing to take such a risk, especially as seizure relapse may be more burdensome for the patient than continuing low-dose ASM [20, 21]. Furthermore, there might be several lifestyle-associated factors that can hinder discontinuation, such as dependence on the permission to drive motorized vehicles. Therefore, remaining on ASM despite being seizure-free is a completely acceptable decision. It is crucial, however, that this decision is the result of a shared decision-making process, necessitating a discussion of the pros and cons with the patient. Such a discussion was documented in approximately half of the index visits, confirming the findings of previous studies [8, 14]. Still, our results showing that ASM might be discontinued even after decades of seizure freedom under ASM suggest that there is still much room to improve. Importantly, it is possible that our study, as well as previous studies, underestimate the rate of discussion regarding ASM discontinuation as this item relies on the physician's documentation. However, retrospective assessment is the only way of measuring the rate of discussion regarding ASM therapy as participation in any prospective study on this matter would come with an inherent bias [22]. The significance of a shared decision-making process is highlighted by our secondary finding that all patients who eventually made the decision to discontinue ASM or reduce its dose followed through with it.

Of all patients with a follow-up visit after ASM discontinuation, approximately 63% of patients were still seizure-free during a median follow-up time of 20 months. These patients had a significantly lower calculated 2-year and 5-year seizure recurrence risk according to the antiepileptic drug withdrawal risk retrieval tool [6]. It is reassuring that there was an association between the calculated risk of seizure recurrence and the actual recurrence rate in our study. The antiepileptic drug withdrawal risk retrieval tool has now been validated in three external cohorts and, although there was a trend towards overestimating the risk of recurrence, it has proven to be

reliable [5, 23, 24]. It is important to mention that the prediction tool was not routinely used in counseling our patients, and a relevant number of index visits (19.5%) included in this study occurred prior to the publication of the tool.

LIMITATIONS

Acknowledging the limitations associated with our retrospective study design is crucial. Therefore, a deliberate emphasis was placed on conducting analysis on objectively verifiable variables. Consequently, the reasoning contributing to continuing or discontinuing ASM, as an example, was not examined. In our opinion, a prospective study is necessary to address these aspects adequately. Still, as in every retrospective study, potential source of bias lies in incomplete data documentation.

In our study, only a very small number of patients had electroencephalogram (EEG) examinations at the index visit, as in our outpatient clinics EEGs are not performed routinely at each visit. Therefore, EEG findings were not included in our analysis. Also, whilst it was possible to conduct an investigation regarding a possible association between non-discontinuation of ASM and type of epilepsy (focal vs. generalized, as well as structural vs. non-structural), the patient sample size was too small to do so for individual epilepsy syndromes. Finally, even though this study covers three different outpatient clinics in Berlin with heterogeneous patient populations, the generalizability of our findings should be interpreted with caution.

CONCLUSION

To summarize, our paper conveys two important findings. First, non-discontinuation of ASM in long-term seizure freedom is associated with history of focal to bilateral or generalized tonic-clonic seizures, breakthrough seizures and failed attempt to reduce dose of or discontinue ASM as well as higher current ASM load. As the latter three variables are not part of established scores to estimate seizure relapse risk after discontinuation, further studies are in place to investigate if these factors are in fact associated with an increased recurrence risk. In addition, our study expands previous knowledge on the time dependence of seizure duration to the intervals beyond one decade of seizure freedom. These patients had the highest rate of seizure discontinuation attempts. Thus, there does not seem to be a 'point of no return' after which ASM will not be discontinued. Our results should encourage physicians to engage in discussions regarding the discontinuation of ASM, even after an extended period of continuous medical therapy.

AUTHOR CONTRIBUTIONS

Jakob I. Doerrfuss: Conceptualization; data curation; investigation; formal analysis; visualization; writing – original draft. **Thea Hüsing:** Investigation; formal analysis; writing – review and editing. **Luise Graf:** Writing – review and editing; formal analysis. **Maria**

Ilyas-Feldmann: Conceptualization; writing – review and editing; supervision. **Martin Holtkamp:** Conceptualization; supervision; resources; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

JID, TH, LG and MIF declare no conflicts of interest with respect to the research, authorship, and/or publication of this article. MH reports personal fees from Arvelle, Bial, Desitin, Eisai, Jazz Pharma and UCB within the last 3 years, outside the submitted work.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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3. Diskussion

Die Diagnosestellung epileptischer Anfälle und deren prognostische Einschätzung beruhen auf der Berücksichtigung von Wahrscheinlichkeiten: Zunächst muss mit hinreichender Sicherheit geklärt werden, ob es sich bei einem paroxysmalen Ereignis überhaupt um einen epileptischen Anfall gehandelt hat. In Abhängigkeit vom aufgrund der durchgeführten Diagnostik erwarteten Risiko für ein Anfallsrezidiv entscheidet sich, ob eine Epilepsie vorliegt und ob eine Behandlungsindikation mit ASM besteht. Eine Empfehlung zum Fortführen oder Absetzen der Medikation im Verlauf wird schließlich unter Berücksichtigung der vermuteten Chance auf dauerhafte Anfallsfreiheit gegeben. Für die Einschätzung all dieser Wahrscheinlichkeiten werden diagnostische und prognostische Marker herangezogen. Ein besonderes Merkmal der Epileptologie sind dabei die fließenden Grenzen zwischen Diagnostik und Prognostik: Die *Diagnose* einer Epilepsie wird dann gestellt, wenn die *Prognose* nach erstmaligem unprovokierten Anfall hinsichtlich des Rezidivrisikos nach Anfall entsprechend ungünstig ist. Die *Diagnose* einer Epilepsie gilt als überwunden, wenn die *Prognose* hinsichtlich des Risikos weiterer Anfälle entsprechend günstig ist.

Die in dieser kumulativen Habilitationsschrift zusammengefassten Arbeiten beschäftigen sich mit diagnostischen Markern, die in der Einschätzung der Prognose – und damit auch der Diagnose – von epileptischen Anfällen eingesetzt werden sowie mit den sich daraus ergebenden klinischen Konsequenzen. Dabei wurden klinische, bildgebende und elektroenzephalographische Marker untersucht.

3.1 Klinische Marker können helfen, Patient:innen mit akut-symptomatischen Anfällen in der Notaufnahme zu identifizieren

Epileptische Anfälle sind das vierthäufigste neurologische Leitsymptom, das zur Vorstellung von Patient:innen in der Notaufnahme führt (Royle et al. 2010). Eine Vielzahl postiktaler Phänomene wie eine anhaltende Vigilanzminderung, Sprachstörungen oder Verwirrheitszustände erschweren häufig die initiale Einschätzung des/der Patient:in (Subota et al. 2019). Gleichzeitig stellt insbesondere jeder akut-symptomatische Anfall einen potenziellen neurologischen Notfall dar, da dieser auf eine schwere zugrundeliegende systemische oder zerebrale Erkrankung hindeuten kann. So lag in einer retrospektiven Studie mit insgesamt 410 Teilnehmer:innen die 30-Tages-Mortalität akut-symptomatischer Anfälle bei 21% – gegenüber einer 30-Tages-Mortalität von nur 3% nach unprovokierten Anfällen (Hesdorffer et al. 2009). Daraus ergibt sich die Notwendigkeit der Identifizierung von klinischen Markern, die bei der Diagnose akut-symptomatischer Anfälle nützlich sein können.

Drei derartige klinische Variablen konnten in der ersten hier vorgestellten Arbeit (2.1.1) identifiziert werden (Reinecke et al. 2022). In einer Auswertung aller konsekutiven, innerhalb

eines Jahres durchgeführten, Behandlungen aufgrund epileptischer Anfälle in zwei Notaufnahmen der Charité hatte ein Viertel der knapp 700 eingeschlossenen Patient:innen einen akut-symptomatischen Anfall. Es zeigte sich eine unabhängige Assoziation zwischen akut-symptomatischen Anfällen und männlichem Geschlecht, keiner Vordiagnose einer Epilepsie und bilateraler oder generalisierter tonisch-klonischer Anfallssemiologie (Reinecke et al. 2022). Diese Variablen können unterstützend herangezogen werden, um Patient:innen, bei denen mit höherer Wahrscheinlichkeit ein akut-symptomatischer Anfall vorliegt, frühzeitig zu identifizieren. Durch Einsatz eines in der vorliegenden Arbeit entwickelten Risiko-Scores, der die o.g. Variablen umfasst, kann je nach Konstellation mit einem positiven prädiktiven Wert von bis zu 57% das Vorliegen eines akut-symptomatischen Anfalls vorhergesagt werden. Dies entspricht zwar immerhin einer Verdopplung der Prätest-Wahrscheinlichkeit für das Vorliegen dieser Anfallsform, macht jedoch auch deutlich, dass laborchemische und bildgebende Verfahren für die Diagnose akut-symptomatischer Anfälle weiter unerlässlich bleiben.

Die Notwendigkeit einer akuten zerebralen Bildgebung nach epileptischem Anfall wird in der Literatur kontrovers diskutiert (Neidlinger et al. 2005, Salinsky et al. 2018). In unserer Studie wurde bei 83% der Patient:innen mit finaler Diagnose eines akut-symptomatischen Anfalls eine zerebrale Bildgebung durchgeführt. Bei knapp einem Viertel der Patient:innen konnte dabei eine akute Pathologie identifiziert werden. Bei Patient:innen mit finaler Diagnose eines unprovzierten Anfalls war dies nur bei 4% der Fall (Reinecke et al. 2022). Diese Ergebnisse sind vereinbar mit einer systematischen Übersichtsarbeit, in der gezeigt wurde, dass die Akutbildgebung mittels Computertomographie nach epileptischen Anfällen in der Rettungsstelle bei 9-17% der Patient:innen zu einer Änderung im Akutmanagement führt (Harden et al. 2007). Die aktuelle Leitlinie „Erster epileptischer Anfall und Epilepsien im Erwachsenenalter“ der Deutschen Gesellschaft für Neurologie empfiehlt die Durchführung einer Computertomografie nach einem epileptischen Anfall bei prolongierter Vigilanzstörung, neuem fokal-neurologischen Defizit oder Risikofaktoren für intrakranielle Traumafolgen. Unabhängig hiervon wird die Durchführung eines MRTs nach erstmaligem unprovzierten Anfall zur Identifizierung einer epileptogenen Läsion empfohlen (Holtkamp et al., 2023).

In der hier vorgestellten Studie hatten 19% der Patient:innen einen akut-symptomatischen Anfall struktureller Genese, bei den übrigen Patient:innen war die Genese metabolisch-toxisch. Auffällig war dabei der hohe Anteil von 74% an Patient:innen mit akut-symptomatischem Anfall aufgrund eines Alkoholentzugs, der höher liegt als in amerikanischen und japanischen Kohorten (Annegers et al. 1995, Leung et al. 2010). Bei Patient:innen mit akut-symptomatischem Anfall aufgrund eines Alkoholentzugs handelt es sich um eine besonders relevante Gruppe von Patient:innen, da diese die einzige ist, für die es evidenzbasierte Empfehlungen für eine vorübergehende anfallssuppressive Therapie gibt: In

einer randomisierten, Placebo-kontrollierten Studie konnte gezeigt werden, dass die Verabreichung von 2 mg intravenösem Lorazepam das Anfallsrezidivrisiko innerhalb der nächsten 6 Stunden signifikant um ca. 20% senken kann (D'Onofrio et al. 1999).

Wie aktuelle Daten aus einer multizentrischen, prospektiven Kohorte zeigen, ist das Risiko des Auftretens von unprovzierten Anfällen im Verlauf nach einem akut-symptomatischen Anfall nicht-struktureller Genese äußerst gering (Herzig-Nichtweiß et al. 2023). Ein höheres Rezidivrisiko besteht für Patient:innen mit akut-symptomatischen Anfällen aufgrund struktureller Ursachen, die anhand bildgebender Verfahren detektiert werden können. Es stellt sich hier also die Frage, ob durch eine ASM das Risiko für das Auftreten von unprovzierten Anfällen nach akuter struktureller Hirnschädigung reduziert werden kann. Hierbei würde es sich also um eine primärprophylaktische Therapie in Bezug auf das Auftreten unprovzierter Anfälle handeln. In einer randomisierten Studie zur ASM nach Schädel-Hirn-Trauma mit 404 Patient:innen konnte durch eine intravenöse Gabe von Phenytoin das Risiko für das Auftreten akut-symptomatischer, nicht aber unprovzierter Anfälle reduziert werden (Temkin et al. 1990). Auch für eine primärprophylaktische Valproat-Gabe nach intrazerebraler Blutung konnte in einer anderen Studie keine Reduktion der Häufigkeit unprovzierter Anfälle nachgewiesen werden (Gilad et al. 2011). Randomisierte Studien zur primärprophylaktischen Gabe von ASM nach struktureller Hirnläsion *und* akut-symptomatischem Anfall gibt es derzeit nicht. Daher sprechen sich die aktuelle Leitlinien gegen eine ASM nach akut-symptomatischem Anfall aus (Holtkamp et al. 2023, Holtkamp et al. 2017). Erstaunlicherweise weicht die tatsächliche Praxis hiervon ab und es wird beispielsweise bei akut-symptomatischen Anfällen nach Schlaganfall häufig eine ASM initiiert (Leung et al. 2017, Herzig-Nichtweiß et al. 2023, Sinka et al. 2023). In einer Umfrage unter 122 Ärzt:innen sprachen sich mehr als 50% der Befragten für eine mindestens dreimonatige Gabe einer ASM nach akut-symptomatischem Anfall in Folge eines Schlaganfalls aus (Herzig-Nichtweiß et al. 2023). Dies kann problematisch sein, wenn die eigentlich als vorübergehend geplante anfallssuppressive Therapie dauerhaft fortgesetzt wird, ohne dass eine Indikation hierfür besteht (Vorderwülbecke et al. 2018). Daher sind randomisierte, prospektive Studien zur Wirksamkeit sowie zur Dauer einer anfallssuppressiven Therapie nach akut-symptomatischem Anfall dringend erforderlich.

3.2 White matter lesions treten bei Patient:innen mit epileptischen Anfällen gehäuft auf

Die Relevanz der zerebralen Bildgebung in der Diagnostik von Epilepsien und epileptischen Anfällen wurde in der folgenden Originalarbeit (2.1.2) weiter unterstrichen (Dörrfuß et al. 2023a). Bei ungefähr der Hälfte der Patient:innen mit einer Epilepsie kann im cMRT kein epileptogener Fokus identifiziert werden (Tanaka et al. 2013, Dörrfuß et al. 2021a). Jedoch zeigen sich bei einem relevanten Anteil dieser Patient:innen mehr oder weniger ausgeprägte WML (Mao et al. 2016, Hanby et al. 2015). In einer Population älterer Patient:innen gelten

diese WML (in Abhängigkeit von ihrem Verteilungsmuster) als überwiegend vaskulärer Genese und bilden einen Teil des radiologisch definierten Symptomkomplexes einer „*cerebral small vessel disease*“ (CSVD) ab (Wardlaw et al. 2013, Erten-Lyons et al. 2013). Bislang ist unklar, ob diese Läsionen als epileptogen einzuschätzen sind und damit eine Behandlung mit ASM nach einmaligem unprovokierten Anfall rechtfertigen. Gemäß der aktuellen DGN-Leitlinie kann in dieser Konstellation eine ASM erwogen werden (Holtkamp et al. 2023).

Grundsätzlich wird für die Entstehung epileptischer Anfälle eine Beteiligung kortikalen Gewebes vorausgesetzt (Rosenow et al. 2001). Verschiedene Hypothesen, warum auch Läsionen der weißen Substanz zu epileptischen Anfällen führen könnten, wurden formuliert. So ist es möglich, dass diese 1.) zu einer Disruption thalamo-kortiko-thalamischer Bahnen führen (Maxwell et al. 2013), 2.) eine Waller'sche Degeneration und damit eine indirekte kortikale Schädigung auslösen (Kim et al. 2008), 3.) im Bereich neu auftretender Läsionen eine lokale Exzitotoxizität bedingen (Gibson et al. 2011) sowie 4.) selbst zwar nicht epileptogen sind, aber als Surrogatparameter für kleine kortikale Mikroinfarkte dienen, die im 7 Tesla MRT, nicht aber im 3 Tesla MRT detektiert werden können (Benjamin et al. 2015, Jouvent et al. 2011).

In einer Meta-Analyse unter Einbeziehung von Primärdaten konnten wir nun nachweisen, dass die Läsionslast an WML bei Patient:innen mit epileptischen Anfällen erhöht ist (Dörrfuß et al. 2023a): Es zeigte sich eine signifikante Assoziation zwischen Vorliegen von epileptischen Anfällen und Nachweis (relevanter) WML, wie sie durch visuelle Analogskalen quantifiziert werden. Keine Assoziation bestand zwischen epileptischen Anfällen und dem Volumen von WML. Vermutlich liegt dies darin begründet, dass die Relevanz von WML auf die Entstehung von Anfällen führend von ihrer Lokalisation abhängt: Typischerweise werden WML nach ihrer Lokalisation in juxtakortikale, periventrikuläre und „tiefe“ WML unterteilt. Während sich die visuellen Analogskalen (wie in den Studien angewendet) vorwiegend auf tief gelegene WML konzentrieren, umfasst eine Volumetrie WML in jeglicher Lokalisation. Gerade die tief gelegenen WML scheinen besonders relevant für die Assoziation zwischen WML und Anfällen zu sein. Tiefe WML sind häufiger ischämischen Ursprungs als WML in anderen Hirnregionen (Gouw et al. 2011). Die Relevanz tief gelegener WML könnte für die Hypothese von WML als Surrogatparameter kleiner kortikaler ischämischer Mikroinfarkte sprechen (Dörrfuß et al. 2023a).

Auch juxtakortikalen WML scheint eine hervorgehobene Bedeutung zuzukommen. In einer kürzlich vorgestellten Arbeit zeigte sich ein nach juxtakortikal hin verschobenes Verteilungsmuster der WML bei Patient:innen mit erstmaligem Anfall und einem Lebensalter 60 Jahre im Vergleich zu einer Kontrollgruppe aus Patient:innen ohne epileptische Anfälle

(Nasca et al. 2023). Juxtakortikale WML sind auch ein typischer bildgebender Befund bei Multipler Sklerose, einer prototypischen, mit Veränderungen der weißen Substanz einhergehenden, Erkrankung (Brownell et al. 1962). Die juxtakortikalen WML sind häufig mit kortikalen Schädigungen assoziiert (Kidd et al. 1999, Futatsuya et al. 2016). Dennoch ist die Prävalenz von epileptischen Anfällen bei Patient:innen mit Multipler Sklerose mit ca. 4% als relativ gering anzusehen – vor allem vor dem Hintergrund, dass bei einem relevanten Anteil der Patient:innen auch alternative Ursachen der Epilepsie identifiziert werden konnten (Neuss et al. 2021, Burman et al. 2017).

In jedem Fall scheint eine alle WML umfassende Volumetrie der Komplexität einer möglichen mit WML assoziierten Epileptogenese nicht gerecht zu werden. Allerdings ist auch die Verwendung visueller Analogskalen für die Auswertung von WML nicht unproblematisch: Sieben Studien, die in die Meta-Analyse eingeschlossen wurden, verwendeten visuelle Analogskalen. Jedoch gab es zwischen allen Studien geringfügige Unterschiede in der Anwendung dieser Skalen, was die Vergleichbarkeit erheblich erschwert (Dörrfuß et al. 2023a).

In den meisten in dieser Meta-Analyse aufgenommenen Studien wurden zudem Patient:innen mit bereits bestehender Epilepsie eingeschlossen. Ob die WML schon bei Diagnosestellung der Epilepsie vorgelegen oder sich erst im Krankheitsverlauf gebildet haben, ist in dieser Konstellation unklar. Dass Anfälle selbst zur Entstehung neuer mikroangiopathischer Veränderungen führen, erscheint pathophysiologisch unwahrscheinlich (Izutsu et al. 2018). Es ist aber möglich, dass eine ASM die Entstehung neuer WML beeinflussen könnte. In einer retrospektiven Analyse von insgesamt 150 Patient:innen mit länger bestehender Epilepsie zeigte sich eine erhöhte Läsionslast bei Patient:innen mit enzyminduzierender im Vergleich zu nicht-enzyminduzierender ASM (Mao et al. 2016). Auch andere kardiovaskuläre Risikofaktoren wie eine Hyperlipidämie sind bei Patient:innen, die mit enzyminduzierenden ASM behandelt werden, erhöht (Mintzer et al. 2020). In zukünftigen Arbeiten zur Läsionslast der weißen Substanz sollte daher der Fokus auf Patient:innen mit einem erstmaligen epileptischen Anfall bzw. neu-diagnostizierter Epilepsie liegen.

Neben WML gehören auch Mikroblutungen und erweiterte perivaskuläre Räume zum radiologischen definierten Symptomkomplex der CSVD. Bezüglich Mikroblutungen ist die Studienlage begrenzt. Überraschenderweise war das Vorliegen von Mikroblutungen in zwei kürzlich veröffentlichten Analysen von Patient:innen mit zerebraler Amyloidangiopathie mit einem geringeren (sic!) Risiko epileptischer Anfälle assoziiert (Freund et al. 2023, Tabae Damavandi et al. 2023). Ob eine Assoziation zwischen epileptischen Anfällen und erweiterten perivaskulären Räumen besteht, wurde bislang noch nicht untersucht. Die mögliche Rolle von

erweiterten perivaskulären Räumen als potenzieller Biomarker einer Post-Stroke Epilepsie gewinnt jedoch zunehmend an Bedeutung (Hlauschek et al. 2023).

In unserem systematischen Review mit Meta-Analyse wurde als nächstes der Frage nachgegangen, ob das Vorliegen von WML mit einem erhöhten Rezidivrisiko weiterer unprovoked Anfälle assoziiert ist. In der systematischen Literaturrecherche konnten lediglich zwei Studien identifiziert werden, die diesen Aspekt aufgreifen: In einer retrospektiven Analyse von insgesamt 162 Patient:innen mit neu diagnostizierter fokaler Epilepsie unbekannter oder struktureller Ätiologie war das Vorliegen von WML unabhängig mit einem erhöhten Rezidivrisiko unprovoked Anfälle assoziiert (Tartara et al. 2022). In einer weiteren retrospektiven Studie war das Vorliegen von WML nicht mit der Häufigkeit von Anfällen assoziiert. Bemerkenswerterweise wurden in dieser Studie keine Patient:innen mit kardiovaskulären Risikofaktoren eingeschlossen (Uslu et al. 2021). Da, wie oben aufgeführt, insbesondere WML vaskulärer Genese für die Entwicklung epileptischer Anfälle relevant sein könnten, ist die Aussagekraft dieser Studie für die Beantwortung der vorliegenden Fragestellung vermutlich limitiert.

Letztlich muss die Frage beantwortet werden, ob durch eine ASM bei Patient:innen mit erstem epileptischen Anfall bei Nachweis von WML das Rezidivrisiko gesenkt werden kann. In unserer Meta-Analyse konnten wir hierzu keine prospektiven Studien identifizieren (Dörrfuß et al. 2023a).

3.3 Auch ein spätes EEG kann für die Prognoseabschätzung nach Reanimation herangezogen werden

Ähnlich wie der Nachweis von WML einen Grenzfall für die Diagnosestellung einer Epilepsie abbildet, können spezifische EEG-Veränderungen bei Patient:innen mit vermuteter hypoxisch-ischämischer Enzephalopathie (HIE) eine diagnostische und therapeutische Herausforderung sein. Das EEG nach Reanimation wird sowohl zur Vorhersage des neurologischen Outcomes, als auch zur Diagnose von epileptischen Anfällen herangezogen. Für die Neuroprognostik von Patient:innen mit vermuteter HIE wird bislang eine Untersuchung innerhalb der ersten 72 Stunden oder wenigstens innerhalb der ersten 7 Tage nach Reanimation empfohlen (Sandroni et al. 2014, Taccone et al. 2017, Leithner et al. 2023). Allerdings entspricht ein früher Zeitpunkt – beispielsweise aufgrund fehlender personeller Kapazitäten – nicht immer der klinischen Realität. Zudem ist ein relevanter Anteil der Patient:innen in der Frühphase nach Reanimation noch sediert, was die Diagnostik beeinträchtigen kann (Agarwal et al. 2019). Bislang war ungeklärt, wie mit den Ergebnissen einer späteren EEG-Untersuchung in dieser Gruppe von Patient:innen umzugehen ist.

In der vorgestellten Arbeit (2.2.1) wurde die diagnostische Wertigkeit eines solchen „späten“ EEGs, 5 bis 14 Tage nach Reanimation, bei insgesamt 187 Patient:innen analysiert: Bei Patient:innen mit supprimierter EEG-Aktivität $< 10 \mu\text{V}$ über die gesamte Dauer der späten Ableitung bestand eine hohe Assoziation zu einem schlechten funktionellem Outcome. Allerdings kam es bei einer nicht-sedierten Patientin mit diesem EEG-Befund zu einem guten funktionellen Outcome bei Entlassung (Dörrfuß et al. 2021b).

Die Anforderungen an die Neuroprognostik sind sehr hoch: In einer Befragung von 640 Ärzt:innen gab die Mehrzahl (56%) an, dass für sie lediglich eine falsch-positiv Rate von 0,1% für die Prognostik eines schlechten neurologischen Outcomes akzeptabel wäre (Steinberg et al. 2019). Keine singuläre Untersuchung, die in der Neuroprognostik angewendet wird, erfüllt – unter Berücksichtigung der 95%-KIs – diese Anforderungen (Leithner et al. 2023). Die Relevanz der multimodalen Neuroprognostik wird auch in der in dieser Habilitationsschrift vorgestellten Arbeit unterstrichen. Bei der einzigen Patientin, bei der trotz einer EEG-Suppression $< 10 \mu\text{V}$ ein gutes funktionelles Outcome bei Entlassung bestand, sprachen weder der klinische Befund, noch die NSE-Werte oder die SSEPs für eine ungünstige Prognose (Dörrfuß et al. 2021b). Andererseits wurde bei sieben Patient:innen mit normaler NSE und normalen SEPs ein ungünstiges Outcome durch eine supprimierte EEG-Hintergrundaktivität korrekt prognostiziert.

Insgesamt ist der prognostische Wert einer supprimierten EEG-Aktivität $< 10 \mu\text{V}$ als sehr hoch einzuschätzen (Sandroni et al. 2020). Die Ergebnisse aus klinischen Beobachtungsstudien wurden auch in einer multizentrischen Studie, in der Ergebnisse der Neuroprognostik mit den Befunden einer Hirnautopsie verglichen wurden, bestätigt: Bei allen Patient:innen mit einer supprimierten EEG-Aktivität waren in der Autopsie Zeichen einer schweren HIE nachweisbar (Endisch et al. 2020).

Bei 41% der Patient:innen in unserer Studie waren im EEG generalisierte periodische Entladungen (GPDs) nachweisbar. Diese waren, wenn sie vor dem Hintergrund einer supprimierten EEG-Aktivität auftraten, immer mit einem ungünstigen neurologischen Outcome assoziiert (Falsch-positiv-Rate 0). Diese Assoziation war unabhängig vom Vorliegen einer medikamentösen Sedierung. Damit konnte gezeigt werden, dass GPDs mit supprimierter Hintergrundaktivität auch in spät durchgeführten EEGs ein verlässlicher neuroprognostischer Parameter sind. Bei nicht-supprimierter EEG-Hintergrundaktivität waren GPDs hingegen auch bei Patient:innen mit gutem Outcome nachweisbar (Dörrfuß et al. 2021b).

Sowohl GPDs bei supprimierter Hirnaktivität als auch eine kontinuierliche Hintergrundaktivität $< 10 \mu\text{V}$ ohne Entladungen gehören zu den „*highly malignant patterns*“, die auch bei frühen EEG-Messungen mit einem ungünstigen Outcome assoziiert sind (Westhall et al. 2016). Die

beiden weiteren „*highly malignant patterns*“, ein Burst-Suppression-Muster mit und ohne eingelagerte periodische Entladungen, kamen bei den Patient:innen in der vorgestellten Studie kaum vor. Die Ergebnisse bestätigen damit Vorarbeiten, in denen gezeigt wurde, dass Burst-Suppression-Muster relativ zeitnah nach Reanimation in unspezifische Muster übergehen (Hofmeijer et al. 2014). Ihre Relevanz für die Neuroprognostik scheint also bei späteren EEG-Untersuchungen deutlich abzunehmen.

Die in unserer Arbeit erstmals gezeigte Wertigkeit später EEG-Untersuchungen für die Neuroprognostik nach kardiopulmonaler Reanimation wurde in einer kürzlich veröffentlichten Studie bestätigt: In einer multizentrischen Analyse von Patient:innen, die innerhalb von 1-14 Tagen nach Reanimation ein EEG zur Neuroprognostik erhielten, waren die Sensitivität und Spezifität von „*highly malignant patterns*“ in 181 EEG-Untersuchungen, die innerhalb von 5-14 Tagen durchgeführt wurden, vergleichbar mit den Ergebnissen von 756 Untersuchungen, die innerhalb von 1 bis 4 Tagen erfolgten (Turella et al. 2024).

Bei der Interpretation der Ergebnisse unserer – wie auch der im vorherigen Absatz vorgestellten – Studie ist zu beachten, dass die EEG-Veränderungen den behandelnden Ärzt:innen bekannt waren und damit Entscheidungen hinsichtlich Fortführung oder Beendigung einer lebenserhaltenden Therapie im Sinne einer „selbsterfüllenden Prophezeiung“ beeinflusst haben könnten (Geocadin et al. 2012). Daten aus Ländern, in denen Entscheidungen hin zu einer Beendigung der lebenserhaltenden Therapie selten sind, zeigen jedoch ähnliche Ergebnisse für die prognostische Wertigkeit von EEG-Untersuchungen nach kardiopulmonaler Reanimation (Scarpino et al. 2020).

Periodische EEG-Muster wie die oben beschriebenen GPDs finden sich bei 35% der Patient:innen nach Reanimation (Sandroni et al. 2020). Gemäß den *Kriterien der American Clinical Neurophysiology Society* liegen, ähnlich den Salzburg-Kriterien, elektrographische Anfälle vor, wenn die Frequenz periodischer Entladungen (ETPs oder scharf konfigurierte Entladungen) bei $> 2,5/s$ für 10 Sekunden liegt (Leitinger et al. 2015, Beniczky et al. 2013, Hirsch et al. 2021). Es bleibt jedoch unklar, ob es sich bei den periodischen EEG-Veränderungen nach Reanimation lediglich um einen Ausdruck einer strukturellen Hirnschädigung oder tatsächlich um eine epileptische Aktivität im engeren Sinne handelt. Die pathophysiologischen Entstehungsmechanismen von GPDs sind weiterhin unklar (Lin et al. 2018). Wahrscheinlich wird eine simple Dichotomisierung in struktureller vs. epileptischer Genese der Komplexität der elektrophysiologischen Hintergründe nicht gerecht. Vielmehr kann davon ausgegangen werden, dass der anteilige Beitrag struktureller Veränderungen gegenüber epileptischer Aktivität bei steigendem Grad einer Bewusstseinsstörung zunimmt (Bauer et al. 2010, Leitinger et al. 2021, Trinka et al. 2015b).

Bezüglich anfallssuppressiver Behandlungsindikation dieser beschriebenen EEG-Veränderungen bestand lange Unklarheit. In einer offenen, randomisiert-kontrollierten, multizentrischen Studie mit insgesamt 172 Patient:innen wurde der Einfluss einer ASM auf die Langzeitprognose erstmals prospektiv untersucht. Es konnte gezeigt werden, dass durch eine intensive sedierende und anfallssuppressive Therapie bei Patient:innen mit rhythmischer oder periodischer EEG-Aktivität nach Reanimation – der überwiegende Anteil hatte GPDs mit einer Frequenz von 0,5/s-2,5/s – keine Verbesserung des funktionellen Outcomes oder der Mortalität nach 3 Monaten erreicht werden kann (Ruijter et al. 2022). Ob eine ASM in bestimmten Konstellationen (z.B. bei erfüllten elektroenzephalographischen Kriterien eines Status epilepticus) dennoch sinnvoll sein könnte, ist noch unklar.

3.4 Post-Stroke Epilepsien haben eine gute Prognose

Mit der zugrundeliegenden Ätiologie wurde in der nächsten vorgestellten Studie (2.2.2) ein weiterer prognostischer Marker untersucht. In der Epilepsiechirurgie gilt die Art der die Epilepsie verursachenden Hirnschädigung als einer der wichtigsten Prädiktoren für postoperative Anfallsfreiheit (Englot et al. 2012, Jones et al. 2016, McIntosh et al. 2001, Tonini et al. 2004). Bezüglich medikamentöser Therapie gab es bislang lediglich zwei Studien, die vor mehr als 20 Jahren veröffentlicht wurden, in denen eine Assoziation zwischen Ätiologie und Outcome hinsichtlich Anfallsfreiheit untersucht wurde (Stephen et al. 2001, Semah et al. 1998). Seitdem wurde eine Vielzahl neuer ASM zugelassen, und es gab erhebliche Verbesserungen in der zerebralen Bildgebung zur Feststellung der Ätiologie, sodass eine Neubewertung notwendig wurde (Golyala et al. 2017, Goodman et al. 2021).

In unserer Studie konnte nachgewiesen werden, dass Epilepsien als Folge eines ischämischen Schlaganfalls das beste Outcome aller untersuchten Ätiologien hatten. Die Rate an mindestens zwölfmonatiger Anfallsfreiheit lag hier bei > 70%. Epilepsien nach ischämischem Schlaganfall waren zudem unabhängig mit Anfallsfreiheit assoziiert. Die niedrigste Rate an Anfallsfreiheit zeigte sich hingegen bei Patient:innen mit Hippocampusklerose und kortikaler Malformation (Dörrfuß et al. 2021a).

Die vorgestellte Arbeit ist die erste, in der die Medikationslast an Anfallssuppressiva zwischen verschiedenen Ätiologien verglichen wurde. Patient:innen mit Epilepsie nach ischämischem Schlaganfall hatten nicht nur die günstigste Prognose hinsichtlich des Erreichens von Anfallsfreiheit, sondern brauchten hierfür auch die geringsten Dosen an ASM (Dörrfuß et al. 2021a). Dieses Ergebnis ist wichtig, da hierdurch gezeigt werden konnte, dass die gute Prognose der Post-Stroke Epilepsien nicht durch eine erhöhte Dosierung von ASM, die wiederum mit mehr unerwünschten Arzneimittelwirkungen einhergehen kann, „erkauft“ wird.

Die günstige Prognose von Epilepsien nach ischämischem Schlaganfall ist erfreulich, kann aber auch zu noch mehr „Ehrgeiz“ in der Behandlung dieser Gruppe von Patient:innen motivieren (Zelano 2016). Bislang gibt es lediglich zwei randomisierte, kontrollierte Studien zur spezifischen Behandlung von Post-Stroke Epilepsien. In einer ersten Studie wurde eine Monotherapie mit Lamotrigin gegenüber einer Monotherapie mit retardiertem Carbamazepin verglichen. Hier konnte knapp kein statistisch signifikanter Unterschied in der Wirksamkeit von Lamotrigin nachgewiesen werden, wobei die Studie mit einer Anzahl von 64 Patient:innen sehr klein war. (Gilad et al. 2007). In einer anderen Studie wurde Levetiracetam mit retardiertem Carbamazepin verglichen. Auch hier zeigte sich kein signifikanter Unterschied hinsichtlich des Erreichens von Anfallsfreiheit, wobei Levetiracetam besser verträglich war als Carbamazepin. Das ursprüngliche Rekrutierungsziel wurde allerdings deutlich unterschritten, sodass davon ausgegangen werden kann, dass auch diese Studie nicht über ausreichend statistische Power verfügte (Consoli et al. 2012). In den beiden größten randomisiert-kontrollierten Studien zur anfallssuppressiven Therapie fokaler Epilepsien im Allgemeinen zeigte sich die beste Retention für Lamotrigin. Allerdings hatten in beiden Studien weniger als 10% der eingeschlossenen Patient:innen einen Schlaganfall in der Vorgeschichte (Marson et al. 2007a, Marson et al. 2021a).

Patient:innen mit einer Post-Stroke Epilepsie sind in der Regel älter und haben mehr kardiovaskuläre Risikofaktoren sowie Komedikationen als Patient:innen mit Epilepsien anderer Ursache (Redfors et al. 2020, Zelano et al. 2020, Dörrfuß et al. 2021a). An die ASM sind daher besondere Anforderungen zu stellen: Sie sollten wenig Interaktionspotenzial mit anderen Medikamenten haben und sich nicht ungünstig auf das kardiovaskuläre Risikoprofil der Patient:innen auswirken. Zudem sollte die Therapie mit niedriger Dosierung einschleichend begonnen werden (Rohracher et al. 2021). Große, randomisiert-kontrollierte Studien, die untersuchen, welches ASM in dieser Konstellation am geeignetsten ist, sind erstrebenswert.

Im Gegensatz zu den beiden älteren Studien zur Ätiologie-spezifischen Prognose von Epilepsien wurde in unserer Arbeit zwischen ischämischen und hämorrhagischen Schlaganfällen unterschieden. Dabei war die Prognose von Epilepsien nach ischämischen Schlaganfällen besser als nach hämorrhagischen Schlaganfällen (Dörrfuß et al. 2021a). Hämorrhagische Schlaganfälle sind im Vergleich zu ischämischen Schlaganfällen mit einem größeren Risiko für eine Post-Stroke Epilepsie assoziiert (Merkler et al. 2018). Auch die epileptogenen Mechanismen unterscheiden sich zwischen beiden Arten von Schlaganfällen (Yang et al. 2018, Doria et al. 2019). Die Ergebnisse dieser Arbeit bestätigen die Bedeutsamkeit einer Unterscheidung zwischen diesen beiden zerebrovaskulären Ätiologien fokaler Epilepsien.

Eine schlechte Prognose zeigte sich bei Patient:innen mit Hippocampussklerose sowie bei denen mit kortikaler Malformation (Dörrfuß et al. 2021a). Passend hierzu waren in einer histopathologischen Analyse von > 9.500 Resektaten diese beiden Ätiologien die häufigste (36,4%) und die dritthäufigste (19,8%), die bei epilepsiechirurgischen Eingriffen entfernt wurden (Blumcke et al. 2017). Die Zuweisung von Patient:innen zur prächirurgischen Diagnostik ist häufig mühsam und zeitverzögert, in der oben zitierten Studie betrug die mediane Dauer der Epilepsie vor Resektion 20,1 Jahre (Blumcke et al. 2017). Die Ergebnisse unserer Studie unterstreichen, dass eine rein medikamentöse Therapie für diese beiden Ätiologien in der Mehrzahl der Fälle nicht zu Anfallsfreiheit führt und dass Patient:innen daher früh zu chirurgischen Therapieansätzen beraten werden sollten.

Bei fast der Hälfte der in der vorgestellten Studie eingeschlossenen Patient:innen war die Ätiologie unbekannt. Bei einem relevanten Anteil dieser Patient:innen sahen wir WML als Ausdruck einer CSVD, deren möglichen Einfluss auf die Entstehung einer Epilepsie oben (2.1.2 und 3.2) diskutiert wurde. Die Prognose von mit CSVD assoziierten Epilepsien wurde vor dem Hintergrund des noch unklaren Einflusses von WML auf das Rezidivrisiko epileptischer Anfälle in der vorliegenden Studie noch nicht untersucht, sollte aber Gegenstand zukünftiger Arbeiten werden.

3.5 Das Thematisieren eines Absetzversuchs der ASM ist immer lohnenswert

In der im vorherigen Abschnitt diskutierten Arbeit war insgesamt ungefähr die Hälfte der Patient:innen mit fokaler Epilepsie unter ASM anfallsfrei (Dörrfuß et al. 2021a). Werden auch generalisierte Epilepsien berücksichtigt, liegt die Rate an Anfallsfreiheit noch höher (Chen et al. 2018, Cockerell et al. 1997, Shorvon et al. 2013). Welche klinischen Konsequenzen bezüglich der Fortführung und des Absetzens der ASM gezogen werden, thematisiert die letzte in dieser Habilitationsschrift vorgestellte Arbeit (2.2.3).

Wird eine langjährige Anfallsfreiheit erreicht, stellt sich häufig die Frage, ob die ASM fortgesetzt oder abgesetzt werden sollte. Üblicherweise wird für einen Absetzversuch ein anfallsfreies Intervall von mindestens zwei Jahren vorausgesetzt (Holtkamp et al. 2023, Gloss et al. 2021, Beghi et al. 2013). In der hier vorgestellten Arbeit wurde bei 81,7% der für einen entsprechenden Zeitraum anfallsfreien Patient:innen die ASM unverändert fortgesetzt. Bei 11,5% wurde die ASM abgesetzt und bei 6,8% wurde die Dosis um 25% reduziert (Dörrfuß et al. 2023c).

In der Entscheidungsfindung bezüglich des Absetzens wird in erster Linie das Risiko eines Anfallsrezidivs berücksichtigt (Terman et al. 2023b). Zwei randomisierte, kontrollierte Studien haben die Wahrscheinlichkeit von Anfallsrezidiven im Falle eines Absetzens gegenüber dem Fortsetzen der ASM untersucht: In einer Studie mit gut 1.000 Patient:innen blieben 78% der

Patient:innen, bei denen die Medikation fortgeführt wurde und 59% der Patient:innen, bei denen sie abgesetzt wurde, innerhalb der ersten 24 Monate anfallsfrei (Medical Research Council 1991). Die Raten an Anfallsfreiheit nach 12 Monaten lagen in einer etwas neueren, kleineren Studie bei 93% bzw. 85% (Lossius et al. 2008). In einer Meta-Analyse von 10 Studien mit insgesamt 1.769 Patient:innen und einem medianen Follow-Up von 5,3 Jahren, kam es bei 46% zu Rezidivanfällen nach Absetzen der ASM. Die meisten Rezidivanfälle traten innerhalb der ersten 2 Jahre nach Absetzen auf. (Lamberink et al. 2017).

Rezidivanfälle gehen mit relevanten medizinischen und sozialen Implikationen einher und können für Patient:innen belastender sein als eine niedrigdosierte anfallssuppressive Therapie (Stenzel 1987, Lossius et al. 2008). Andererseits kann auch die Fortführung der ASM problematisch sein: Diese ist häufig mit Nebenwirkungen assoziiert, wodurch die Lebensqualität reduziert sein kann (Baker et al. 1997, Beghi et al. 1986, Jacoby et al. 2009). Zudem bestehen bei Einnahme einer ASM Einschränkungen hinsichtlich der Ausübung mancher Berufe: So dürfen Tätigkeiten mit erhöhter Absturzgefahr (Dachdecker, Schornsteinfeger etc.) oder Berufe mit Dienst an der Waffe in den meisten Fällen nur nach fünfjähriger Anfallsfreiheit ohne ASM ausgeübt werden (Deutsche Gesetzliche Unfallversicherung 2019, Kommando Sanitätsdienst der Bundeswehr 2019). Gleiches gilt für das Führen von Kraftfahrzeugen über 3,5 Tonnen und damit auch für Berufskraftfahrer (Möller et al. 2023, Bundesamt für Straßenwesen 2019). Auch die subjektive Krankheitsbewältigung kann durch die Fortführung der ASM negativ beeinflusst werden (Cole et al. 2008).

Vier Variablen waren in unserer Studie unabhängig mit der unveränderten Fortführung der ASM assoziiert: Bilateral tonisch-klonische Anfälle, eine hohe Last an ASM, ein gescheiterter Absetzversuch sowie ein sporadisches Anfallsrezidiv in der Vorgeschichte (Dörrfuß et al. 2023c). Nur die ersten beiden dieser Variablen sind auch etablierte Risikofaktoren für ein Anfallsrezidiv nach Absetzen. Ob auch vorangegangene fehlgeschlagene Absetzversuche und sporadische Anfallsrezidive tatsächlich mit einem erhöhten Risiko für Anfälle nach Absetzen einhergehen, wurde bislang noch nicht untersucht – pathophysiologisch wäre beides gut vorstellbar.

Eine Vielzahl von Risikofaktoren für ein Anfallsrezidiv nach Absetzen wurde bereits beschrieben (Lamberink et al. 2015, Lamberink et al. 2017). In einem Risiko-Score, dem *AED withdrawal risk retrieval tool*, werden 12 Variablen integriert. So kann – mit Hilfe eines unter www.epilepsypredictiontool.info online verfügbaren Kalkulators – das individuelle 2- und 5-Jahres-Rezidivrisiko berechnet werden (Lamberink et al. 2017, UMC Utrecht 2017). Dieser Score wurde mittlerweile in mehreren externen Kohorten validiert und kann herangezogen werden, um Patient:innen hinsichtlich des Für und Widers eines Absetzversuchs zu beraten

(Chu et al. 2021, Contento et al. 2021, Lin et al. 2020). Voraussetzung hierfür ist, dass ein Absetzversuch überhaupt thematisiert wird. In unserer Arbeit war dies bei 54% der letzten Visiten im anfallsfreien Intervall der Fall. Ähnliche Zahlen zeigten sich in einer kürzlich veröffentlichten multizentrischen, retrospektiven Arbeit. Hier wurde ein Gespräch über einen Absetzversuch zwischen Behandelnden und Patient:innen bei nur gut der Hälfte aller Patient:innen jemals dokumentiert (Terman et al. 2023a).

Im oben erwähnten Risikoscore zu Anfallsrezidiven nach Absetzen der ASM wurde die Ätiologie der Epilepsie nicht berücksichtigt. Die Ergebnisse der weiter oben vorgestellten Arbeit zum Ätiologie-spezifischen Ansprechen auf eine ASM (2.2.2) sollten Anlass dazu geben, auch mögliche Assoziationen zwischen Ätiologie und Anfallsrezidivrisiko nach Absetzen der Medikation zu untersuchen.

Für die klinische Praxis ist auch die zeitliche Dynamik von Absetzversuchen relevant. In der vorgestellten Arbeit wurden zu jedem Zeitpunkt der Anfallsfreiheit Absetzversuche unternommen (Dörrfuß et al. 2023c). Wir hatten ursprünglich angenommen, dass ab einer gewissen Dauer der Anfallsfreiheit die Rate an Absetzversuchen abnehmen würde, da die Patient:innen entweder eine finale Entscheidung bezüglich des Absetzens getroffen oder die Behandler:innen einen Absetzversuch „aufgegeben“ hätten. Das Gegenteil war der Fall: In der Gruppe der Patient:innen mit einer Anfallsfreiheit von 10 Jahren Dauer waren Absetz- und Reduktionsversuche am häufigsten. Es gab also keinen „*point of no return*“, ab dem nicht mehr abgesetzt wird (Dörrfuß et al. 2023c). Für die klinische Praxis kann daraus abgeleitet werden, dass es bei anfallsfreien Patient:innen auch nach zuvor langjähriger Fortführung der ASM sinnvoll sein kann, einen Absetzversuch zu thematisieren.

Am Ende sollte die Entscheidung für oder gegen das Absetzen der ASM im Konsens zwischen Ärzt:in und Patient:in getroffen werden. In der vorliegenden Studie haben alle Patient:innen, bei denen eine Verlaufsuntersuchung vorlag, die Entscheidung zum Absetzen letztlich auch umgesetzt. Welche individuellen Faktoren die Entscheidungsprozesse von Patient:innen und Behandelnden letztlich beeinflussen, muss in prospektiven Beobachtungsstudien untersucht werden.

4. Zusammenfassung und Ausblick

Die in dieser kumulativen Habilitationsschrift zusammengefassten Arbeiten beschäftigen sich mit prognostischen Markern in der Epileptologie, ihrem Einfluss auf die Diagnosestellung einer Epilepsie sowie den sich daraus ergebenden therapeutischen Konsequenzen.

In einer ersten Arbeit konnten wir zeigen, dass klinische Parameter bei der Identifizierung von akut-symptomatischen Anfällen in der Notaufnahme unterstützend herangezogen werden können. Bezüglich medikamentöser Therapie von akut-symptomatischen Anfällen besteht eine große Diskrepanz zwischen Empfehlungen zur Therapie (sie wird generell nicht empfohlen) und tatsächlicher Praxis (sie wird häufig durchgeführt). Die Sinnhaftigkeit und die Dauer einer derartigen Therapie müssen weiter untersucht werden.

In zwei Arbeiten wurden grenzwertige Befunde in der Abgrenzung von Epilepsien und in der Neuroprognostik untersucht:

In einer Meta-Analyse wurde gezeigt, dass bei Patient:innen mit epileptischen Anfällen Läsionen der weißen Substanz mutmaßlich vaskulärer Genese gehäuft auftreten. Dabei sind Prävalenz und Schweregrad – nicht aber das Volumen der WML – unabhängig mit dem Vorliegen epileptischer Anfälle assoziiert, was auf eine hervorgehobene Bedeutung der Lokalisation der WML hindeutet. Entscheidend für die Bewertung der Epileptogenität von WML wird die Beantwortung der Frage nach dem Einfluss der WML auf das Anfallsrezidivrisiko nach erstmaligem unprovokierten Anfall sein. Hierzu führen wir eine prospektive, multizentrische Beobachtungsstudie (Deutsches Register Klinischer Studien (DRKS)-ID 00031052) durch, in der untersucht wird, ob die WML-Last in dieser Gruppe von Patient:innen unabhängig mit der Anfallsrezidivrate assoziiert ist.

Neben WML im MRT wurde mit periodischen EEG-Veränderungen nach Reanimation ein weiterer diagnostischer Marker untersucht. In einer Studie über EEG-Veränderungen bei Patient:innen mit HIE konnte gezeigt werden, dass auch ein spätes EEG in der Neuroprognostik herangezogen werden kann. Der Nachweis von GPDs bei supprimierter Hirnaktivität war mit einer falsch-positiven Rate von 0 der sicherste EEG-Prädiktor für ein ungünstiges Outcome. Die Identifikation einer Patientin mit günstigem Outcome bei vollständig supprimierter EEG-Aktivität ohne GPDs unterstreicht die Notwendigkeit eines multimodalen Ansatzes in der Neuroprognostik.

In einer weiteren Arbeit wurden Epilepsien ischämischer Genese näher untersucht und es konnte gezeigt werden, dass Post-Stroke Epilepsien eine bessere Prognose hinsichtlich des Erlangens von Anfallsfreiheit haben als fokale Epilepsien anderer oder unbekannter Ätiologie. Diese bessere Prognose war nicht Folge einer intensiveren medikamentösen Therapie. Im

Gegenteil: Patient:innen mit einer Epilepsie aufgrund eines ischämischen Schlaganfalls hatten die geringste Medikationslast, was erneut das gute Ansprechen von Epilepsien dieser Ätiologie auf ASM unterstreicht. Die Ergebnisse sollten Anlass dazu geben, in der klinischen Behandlung dieser Gruppe von Patient:innen Anfallsfreiheit anzustreben. Ein Forschungsschwerpunkt sollte darauf liegen, zu untersuchen, ob spezifische Anfallssuppressiva bei Post-Stroke Epilepsien wirksamer sind als andere. Wir untersuchen derzeit zudem die Assoziation der Ätiologie von Epilepsien mit anderen Outcome-Parametern, wie beispielsweise dem Auftreten von sporadischen Anfallsrezidiven.

Wie in der klinischen Praxis mit Epilepsien guter Prognose verfahren wird, war Gegenstand der letzten hier vorgestellten Arbeit. Es wurde gezeigt, dass ein Großteil der mehrjährig anfallsfreien Patient:innen ihre Medikation unverändert fortsetzt. Trotzdem erscheint die Erörterung eines Absetzversuchs immer lohnenswert. Denn diese wurden zu jedem Zeitpunkt der Anfallsfreiheit versucht und waren sogar am häufigsten bei Patient:innen, die mehr als 10 Jahre anfallsfrei waren. Welche Faktoren aus Sicht der Patient:innen und der Behandelnden die Entscheidung zur Fortführung der Therapie beeinflussen, wird derzeit von der Arbeitsgruppe Klinische und experimentelle Epileptologie an der Klinik für Neurologie der Charité – Universitätsmedizin Berlin prospektiv untersucht (DRKS-ID 00030094).

Die vorgestellten Arbeiten sowie die derzeit laufenden Studien haben das gemeinsame Ziel, diagnostische und prognostische Marker in der Epileptologie sowie deren klinische Implikationen besser zu verstehen. Es ist die Hoffnung des Autors dieser Habilitationsschrift, dass die Ergebnisse dazu beitragen können, die Beratung und Behandlung von Patient:innen mit epileptischen Anfällen und Epilepsien zu verbessern.

5. Literatur

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Eidesstattliche Erklärung

Erklärung

§ 4 Abs. 3 (k) der HabOMed der Charité

Hiermit erkläre ich, dass

- weder früher noch gleichzeitig ein Habilitationsverfahren durchgeführt oder angemeldet wurde
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- mir die geltende Habilitationsordnung bekannt ist.

Ich erkläre ferner, dass mir die Satzung der Charité – Universitätsmedizin Berlin zur Sicherung Guter Wissenschaftlicher Praxis bekannt ist und ich mich zur Einhaltung dieser Satzung verpflichte.

Berlin, 05.02.2024

Dr. med. Jakob Dörrfuß