Aus der Klinik und Poliklinik für Neurologie
(Direktorin Univ.- Prof. Dr. Agnes Flöel)
der Universitätsmedizin der Universität Greifswald

Thema:

Untersuchung der Wirkung einer prophylaktischen Therapie der episodischen Migräne mit CGRP-/Rezeptor-Antikörpern auf die dysfunktionelle Schmerzverarbeitung im Hirnstamm

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vorgelegt von:
Anne Thiele
geb. am: 24.08.1997
in: Strausberg

Dekan:	Prof. Dr. Karlhans Endlich
1. Gutachter:	Prof. Dr. Agnes Flöel
2. Gutachter:	Prof. Dr. Dagny Holle-Lee
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1 Abstrakt

1.1 Abstrakt (Deutsch)

Hintergrund

Migräne ist eine hochprävalente Erkrankung, die bei betroffenen Patient*innen eine hohe Belastung sowohl durch die Kopfschmerzen an sich als auch durch die Einschränkung ihres Sozial- und Berufslebens hervorruft. Die Therapie besteht aus einer Akuttherapie der Kopfschmerzattacken sowie einer prophylaktischen Therapie zur Reduktion der Kopfschmerzfrequenz und -schwere. In der Prophylaxe stehen mit Antikörpern gegen das Calcitonin-gene-related-peptide (CGRP) und dessen Rezeptor erstmalig für die Migräne entwickelte gezielte prophylaktische Therapien zur Verfügung. Es stellt sich jedoch hierbei die Frage, ob CGRP-Antikörper lediglich symptomatisch in der Peripherie des trigemino-vaskulären-Systems wirken oder auch im zentralen Nervensystem die zugrundeliegenden pathophysiologischen Mechanismen beeinflussen, was einer krankheitsmodifizierenden Wirkung entspräche. Ziel unserer Studie war es, die Nullhypothese einer rein symptomatischen Wirkung gegen die Alternativhypothese einer Krankheitsmodifikation und somit zentralnervösen Wirkung, zu prüfen, indem bei Patient*innen mit episodischer Migräne der nozizeptive Blinkreflex vor und nach der Behandlung mit CGRP-Antikörpern untersucht wurde.

Methoden

22 Patient*innen mit episodischer Migräne (21 Frauen, 46,2 ± 13,8 Jahre alt) und 22 alters- und geschlechts-gematchte Kontrollen wurden im Rahmen dieser prospektiven Beobachtungsstudie eingeschlossen. Sie erhielten einen umfassenden Fragebogen zur Erhebung demografischer Charakteristika sowie der Kopfschmerzanamnese. Es erfolgte eine Messung des Blinkreflexes (10 Durchgänge à 6 Stimuli) vor (V0) und 3 Monate (V3) nach der Behandlung mit CGRP-Antikörpern (Kontrollen wurden einmalig gemessen). Im Rahmen der Messung wurden wiederholt schmerzhafte Stimuli supraorbital appliziert, die direkte Rückschlüsse auf die zentralnervöse Erregbarkeit des Hirnstamms als pathophysiologisch zentralen Mechanismus im Rahmen der Migräneentstehung zulassen. Die Area-under-the-curve (AUC) der R2-Komponente

der Muskelsummenaktionspotentiale des Blinkreflexes sowie das Habituationsverhalten (Regressionskoeffizient über mehrere Blöcke) der stimulierten sowie nicht-stimulierten Seite wurden über 10 Blöcke hinweg evaluiert (primärer Endpunkt). Es wurde jeweils zuerst ein Test auf globale Veränderungen durchgeführt, der dann durch post-hoc-Analysen weiter spezifiziert wurde.

Ergebnisse

Alle Patient*innen zeigten eine signifikante Reduktion der Kopfschmerztage/Monat (V0: 12,4±3,3, V3: 6,6 ± 4,9) nach Beginn der Behandlung mit einem CGRP-/Rezeptorantikörper. Auf der stimulierten Seite reduzierte sich die AUC signifikant in den Blöcken eins, zwei sowie acht (F_{global}=5,86, p<0,001; block 1: R2a_s: -28%, p<0,001). Auf der nicht-stimulierten Seite zeigten sich Block eins, zwei, drei, acht sowie zehn als signifikant reduziert (F_{global}=8,22, p<0,001, block 1: R2a_ns: -22%, p=0,003). Die Veränderung der Habituation erwies sich in den Blöcken sechs, sieben, acht und zehn auf der nicht-stimulierten Seite als signifikant (F_{global}=3,07, p<0,001; block 6: R2h_ns: r=-1,36, p=0,007). Weder die AUC noch die Habituation des ersten Messtermins (V0) korrelierte mit dem späteren klinischen Ansprechen, sodass kein Prädiktor für das Therapieansprechen detektiert werden konnte (binär logistische Regression; alle Prädiktoren p>0,05).

Diskussion & Zusammenfassung

Die Ergebnisse dieser Studie zeigen, dass die dreimonatige Therapie mit CGRP-Antikörpern die Erregbarkeit des Hirnstamms als Antwort auf wiederholte schmerzhafte Stimuli bei Patient*innen mit Migräne normalisiert und liefert somit Hinweise für ein krankheitsmodifizierendes Potenzial. Veränderungen der Habituation korrelierten signifikant mit der Verringerung der Kopfschmerz-Frequenz, weitere Studien sind jedoch nötig, um zu eruieren, ob Parameter als Prädiktor geeignet sind um eine Voraussage über das Therapieansprechen und das Risiko einer Verschlechterung nach Beendigung der Therapie zu ermöglichen.

1.2 Abstrakt (Englisch)

Background

Migraine is a highly prevalent neurological disease, which causes severe headache for the affected patients and interferes with their social and work life. Therapy consists of acute treatment of the pain and a prophylactical treatment, which should reduce the headache frequency and severity. Antibodies against the calcitonin-gene-related peptide (CGRP) and his receptor are therefore the first pharmaceuticals, which were specifically developed for this purpose. This raises the question, if CGRP-antibodies are solely a symptomatic therapy acting in the periphery of the trigemino-vascular system or if they interfere with the underlying central nervous pathomechanisms of the disease and are therefore disease-modifying. This study aims to weigh the null hypothesis of a symptomatic therapy against the alternative hypothesis of central disease modifying activity by examining the nociceptive blink reflex on patients suffering from episodic migraine before and after the treatment with CGRP-antibodies.

Methods

22 patients with episodic migraine (21 female, 46.2 ± 13.8 years old) and 22 age and gender matched controls were examined for this prospective observational study. The patients were given a questionnaire to examine demographic as well as the headache characteristics. For the investigation they underwent an analysis of the supraorbital blink reflex (10 blocks à 6 stimuli) prior and 3 months after the application of CGRP-antibodies (controls were examined once). Therefore, painful stimuli were applied, which allowed to investigate the central excitability of the brain stem as an essential mechanism of the underlying pathophysiology of migraine. The area-under-the-curve (AUC), calculated from the R2 component of the summarized muscle action potential and the habituation (regression coefficient over the blocks) for the stimulated and non-stimulated site for ten blocks were analysed as the primary endpoint.

Results

All patients showed a significant reduction of headaches days per month (V0: 12.4±3.3, V3: 6.6 ± 4.9) after the beginning of a treatment with CGRP-antibodies. The AUC was

significantly reduced in the blocks one, two and eight on the stimulated site (F_{global}=5.86, p<0.001; block 1: R2a_s: -28%, p<0.001) and in the blocks one, two, three, eight and ten on the non-stimulated site (F_{global}=8.22, p<0.001, block 1: R2a_ns: -22%, p=0.003). The change in habituation was significant in the blocks six, seven, eight and ten on the non-stimulated site (F_{global}=3.07, p<0.001; block 6: R2h_ns: r=-1.36, p=0.007). None of the parameters could be used as a baseline predictor for the treatment response (binary logistic regression; all predictors p>0.05).

Discussion & Summary

The findings of this study show that a three-month therapy with CGRP-antibodies restores the brain stem excitability as an answer to repeated painful stimuli in patients with episodic migraine and provide evidence for a disease-modifying potential. The changes of the habituation correlated with a lower headache frequency; however, further studies should evaluate if the blink reflex can be used as a predictor for the treatment response and the risk of relapse after the treatment cessation.

2 Einführung

Migräne gehört zu den weltweit häufigsten neurologischen Erkrankungen und beeinträchtigt mit einer Prävalenz von etwa 10-20% einen erheblichen Teil der Bevölkerung in Europa. (1) Die Erkrankung zeichnet sich dabei nicht nur durch den charakteristischen Kopfschmerz aus, der sich als einseitig, stechend, von starker Intensität und meist für 4-72h anhaltend präsentiert. Es treten auch weitere Symptome wie Geräusch- sowie Lichtempfindlichkeit, eine begleitende Übelkeit, sowie in etwa 20% der Fälle eine Aura-Symptomatik auf, die sich am häufigsten durch flackernde Lichtblitze (sogenannte visuelle Aura) vor der Attacke einstellt. Klinisch lässt sich die Erkrankung in eine episodische Form (14 Kopfschmerztage oder weniger pro Monat) und eine chronische Form differenzieren (mehr als 14 Kopfschmerztage pro Monat). (2) Betroffene werden dabei nicht nur durch die häufigen Kopfschmerzen und deren Begleiterscheinungen an sich beeinträchtigt, sondern leiden auch unter massiven Einschränkungen ihres Sozial-, Familien- und Berufslebens, was auch durch eigene Studien belegt werden konnte. (3, 4) Gerade, weil diese Erkrankung einen erheblichen Anteil der insbesondere jungen Bevölkerung betrifft (Altersgipfel 35 Jahre) und somit neben vorgenannten individuellen Beeinträchtigungen mit einem erheblichen sozio-ökonomischen Schaden einhergeht (beispielsweise durch die Beeinträchtigung der Arbeitskapazität) (1, 3, 5), ist es umso wichtiger, Patient*innen mit Migräne eine Behandlung zu ermöglichen. Voraussetzung hierfür ist, sie einfach und zuverlässig in der Praxis zu identifizieren. Geeignet dafür ist eines der bekanntesten und am einfachsten anzuwendenden Screening Tools, der IDMigraine™. Dieser wurde zu diesem Zwecke begleitend zum Hauptprojekt in einer eigenen Studie für den deutschsprachigen Raum übersetzt und seine diagnostischen Eigenschaften bestimmt. (6) Sofern Patient*innen mit einer Migräne identifiziert wurden, gilt es, stärkere Kopfschmerzattacken einerseits mit einer optimierten Akuttherapie (z.B. mit Triptanen) zu kupieren. Andererseits gibt es weitere Medikamente, die die Frequenz und Schwere der Attacken senken sollen, sogenannte Prophylaktika. Neben vielen Medikamenten, die ursprünglich zur Therapie anderer Krankheiten entwickelt wurden (7), werden seit einigen Jahren Antikörper gegen das Calcitonin-gene-related-peptide und dessen Rezeptor (im Folgenden bezeichnet als „CGRP-Antikörper“) eingesetzt, die spezifisch für die Therapie der Migräne entwickelt wurden (vergleiche hierzu Abschnitt 2.2). (7, 8)

Die Behandlungsmöglichkeit mit CGRP-Antikörpern leitete eine neue Ära der Migräneprävention ein, da die spezifische Therapie eine erhöhte Effektivität und Tolerabilität ermöglicht. (9, 10) Trotz des breiten klinischen Einsatzes bleiben einige Fragen ungeklärt, insbesondere ist zu untersuchen, ob CGRP-Antikörper nur symptomatisch wirken oder ob sie darüber hinaus auch einen Langzeit- und somit krankheitsmodifizierenden Effekt aufweisen, der eine Änderung der zugrundeliegenden Pathomechanismen beinhalten würde. Krankheitsmodifizierend können nach Definition der Europäischer Arzneimittel-Agentur (EMA) Medikamente erachtet werden, die „den Symptomprogress verlangsamen oder stoppen und den zugrundeliegenden neuropathophysiologischen Prozess verzögern“ [aus dem Englischen übersetzt]. (11) Marteletti et. al. formulierten hierzu in Analogie für die disease-modifying-migraine-drugs (DMMD), dass ein krankheitsmodifizierender Effekt den natürlichen Verlauf der Migräne, eine Konversion von episodischer zu chronischer Migräne, verlangsamen bzw. verhindern sollte.(12, 13) Aktuelle Studien liefern Hinweise dafür, dass es nach Absetzen der Therapie mit CGRP-Antikörpern rasch zu einer Symptomverschlechterung kommt, was den prophylaktischen Effekt im Sinne einer Krankheitsmodifikation hinterfragen lässt. (14) Deshalb ist es umso bedeutender, zugrundeliegende Pathomechanismen während der Therapie näher zu betrachten, um einen krankheitsmodifizierenden Effekt zu bestätigen.

Das Ziel dieser Arbeit war es, die Alternativhypothese einer Krankheitsmodifikation durch die CGRP-Antikörper gegen die Nullhypothese einer rein symptomatischen Wirkung zu überprüfen. Hierzu wurden Patient*innen während der Behandlung mit CGRP-Antikörpern auf eine Veränderung ihrer Hirnstammerregbarkeit als Reaktion auf wiederholte schmerzhafte Stimuli untersucht, die sich als pathologisch in Patient*innen mit Migräne zeigten und repräsentativ für die zentralen Krankheitsprozesse stehen. (15, 16) Dafür wurde der nozizeptive Blinkreflex (BR) als Methode verwendet, der sich wiederholt als idealer neurophysiologischer Biomarker für die zentrale sensorische Verarbeitung im trigeminalen System erwiesen hat (siehe folgende Abschnitte).

Außerdem bestand die Frage, inwieweit sich der BR eignet, um ihn als Prädiktor für das klinische Ansprechen von Patient*innen auf die Therapie zu verwenden. Wäre es möglich, aus der Messung des BR abzuleiten, ob und wie gut Patient*innen auf eine Behandlung ansprechen, gelänge es möglicherweise, Patient*innen vorzuselektieren, um sie schneller einer wirkungsvollen Behandlung zuzuführen. Außerdem wäre ein

klinischer Biomarker sinnvoll, um neben dem Therapieansprechen der Patient*innen eine Aussage über den idealen Absetzungszeitpunkt zu treffen, was unmittelbare klinische und ökonomische Relevanz hat.

2.1 Pathophysiologie der Migräne

2.1.1 Der Migränezyklus

Migräne stellt sich als eine zyklische Erkrankung dar (vergleiche Abbildung I). Zusätzlich zu den Migräneattacken, die gekennzeichnet sind durch den Migräne-Kopfschmerz, gibt es davor bzw. danach Attacken-freie Intervalle. Gerade bei Patient*innen mit episodischer Migräne lassen sich diese Intervalle relativ gut abgrenzen, wobei es bei Patient*innen mit chronischer Migräne zum Fehlen dieser schmerzfreien Intervalle kommen kann. (17)

Obwohl in den attackenfreien (interiktalen) Intervallen die Kopfschmerzen fehlen, lassen sich oft Migräne-spezifische Symptome erkennen, die kurz vor (prodromal) oder nach den Attacken (postdromal) auftreten und die Patient*innen zusätzlich belasten und einschränken. Insbesondere in der Prodromalphase leiden Patient*innen oft unter anderem unter gastrointestinalen Beschwerden, Stimmungsschwankungen oder vermehrtem Gähnen. (18)

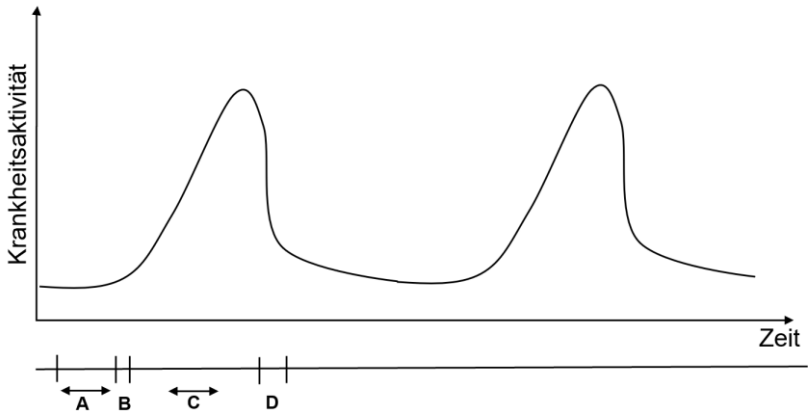


Abbildung I – Vereinfachte Darstellung des Migräne-Zyklus

Die Krankheitsaktivität schwankt periodisch und lässt sich in verschiedene Phasen unterteilen: **A** – prodromale Phase (bis zu 72h), gekennzeichnet durch Stimmungsschwankungen, Müdigkeit, Veränderungen des Essverhaltens, etc.; **B** – mögliche Aura-Phase (5-60min), zu 90% visuelle Aura; **C** – Kopfschmerz-Phase (4-72h); **D** – postdromale Phase, oft begleitet durch Müdigkeit, Konzentrationsprobleme; etc.. (15)

Analog zu diesem klinischen Erscheinungsbild lassen sich auch diagnostisch/elektrophysiologisch zentrale Veränderungen detektieren, die sich im Verlauf dieses Zyklus verändern (siehe Abschnitt Blinkreflex).(19)

2.1.2 Pathophysiologische Veränderungen als Grundlage des Migränezyklus

Man geht davon aus, dass es sich bei Migräne um eine Erkrankung mit multifaktorieller Genese handelt. Neben den eigentlichen, klinisch detektierbaren, Veränderungen im zentralen Nervensystem, spielen sowohl genetische als auch Einflussfaktoren aus der Umwelt eine Rolle. (20)

Die aktuelle medizinische Forschungslage geht davon aus, dass Migräne auf komplexen pathologischen Prozessen im zentralen Nervensystem basiert, die von einer Dysrhythmie im Thalamus ausgehen. (15) Die Verarbeitung von Reizen im zentralen Nervensystem von Patient*innen mit Migräne zeichnet sich einerseits durch eine Übererregbarkeit bzw. vermehrte Antwort des sensorischen Kortex auf Stimuli, als auch andererseits durch eine zentrale Sensitivierung des schmerzverarbeitenden Systems aus. Beide Prozesse sind energieintensiv und können im weiteren Verlauf in einer Migräne-Attacke gipfeln (vergleiche Abbildung II). (15) Die eigentliche Attacke beinhaltet dann eine neurogene Entzündung, im Rahmen derer oben erwähnte pathophysiologische Veränderungen im trigeminovaskulären System zur Ausschüttung vasoaktiver Substanzen führen. Eine besondere Rolle spielt hierbei das CGRP, das proinflammatorisch und schmerzsensibilisierend wirkt. Es resultiert eine Negativspirale, in der der zunehmende Schmerz eine weitere Ausschüttung von CGRP und anderer Substanzen verstärkt. (15)

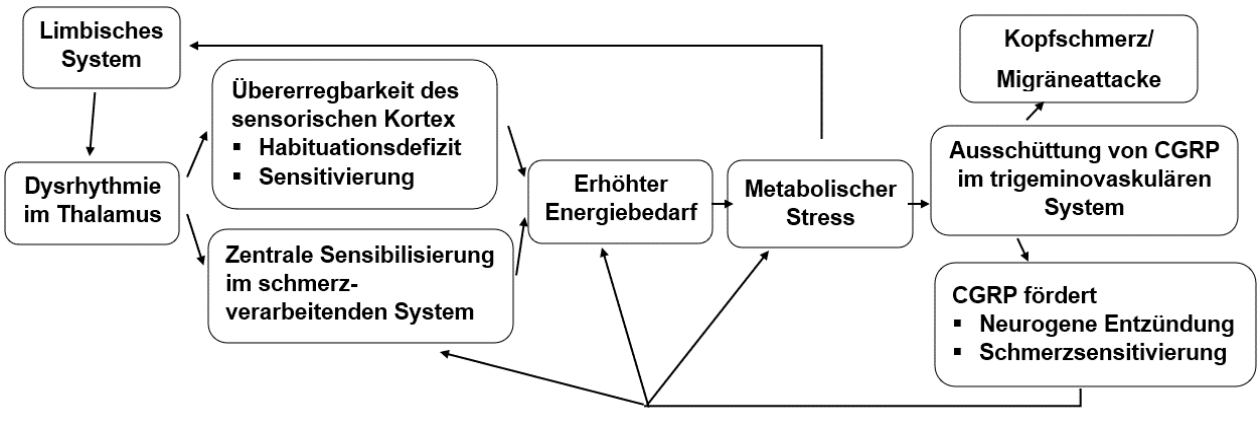


Abbildung II – Vereinfachte Darstellung der pathophysiologischen Komponenten und Prozesse der Migräne (abgewandelt nach De Tommasso et.al; (14))

2.2 CGRP-/-Rezeptor-Antikörper

Wie bereits im Abschnitt 2.1.2. erwähnt, spielt CGRP eine zentrale Rolle in der Entstehung von Migränen-Attacken. Es verstärkt sowohl die vasogene Entzündung als auch die Schmerzwahrnehmung. CGRP wirkt dabei über Rezeptoren, die sich an den Blutgefäßen der Dura, im trigeminovaskulären System, sowie direkt in schmerzverarbeitenden Strukturen des Gehirns finden. (8, 9) Im Rahmen dieser Studie wurden drei verschiedene Antikörper verabreicht: Galcanezumab und Fremanezumab als CGRP-Ligandenantikörper und Erenumab als CGRP-Rezeptorantikörper. (12)

Wie bereits angedeutet, weisen die CGRP-Antikörper eine erhöhte Verträglichkeit und ein geringes Nebenwirkungsprofil auf, was vor allem darauf zurückzuführen ist, dass sie als relativ große Moleküle die Blut-Hirn-Schranke nicht passieren können, was zentralnervöse Nebenwirkungen verhindert. (8) Im Gegensatz zu den bisherigen Prophylaktika, die ursprünglich für andere Indikationen entwickelt wurden (7), weisen CGRP-Antikörper somit ein insgesamt geringeres und günstigeres Nebenwirkungsprofil auf. Zu beobachtende Nebenwirkungen sind eine vorübergehende Nasopharyngitis und leichte grippale Symptome. Zusätzlich wurde bei Erenumab Obstipation beschrieben. (21) Gerade im Vergleich zu anderen Prophylaktika, Substanz(-gruppen) wie Betablockern, Amitryptilin, Flunarizin oder Antiepileptika stellt sich dies als großer Vorteil dar, da die Einnahme dieser für die Patient*innen mit häufigen und mitunter stärkeren Nebenwirkungen verbunden ist (unter anderem Gewichtszunahme, Hypotonie, Müdigkeit, Übelkeit). (7) Geringe Nebenwirkungen und eine nur einmalige subkutane Applikation pro Monat bieten für Patient*innen somit eine erhöhte Verträglichkeit bzw. Tolerabilität.

Des Weiteren bieten die Antikörper eine, auch im klinischen Setting bewiesene, erhöhte Effektivität, zum Beispiel im Vergleich zu Topiramat. (10) In Bezug auf episodische Migräne zeigt sich eine Reduktion der Migräne-Tage im Bereich von 2,9-4,7 Tagen/Monat mit 50%-Responderraten von 30-62% nach 3-6 Monaten. (8)

2.3 Blinkreflex

Der Blinkreflex (BR) ist ein Hirnstammreflex, der abgeleitet wird, indem man den supraorbitalen Ast des Nervus trigeminus medial an der Augenbraue stimuliert. Im Folgenden können zwei Signale abgeleitet werden: eine frühe, ipsilaterale, monosynaptische R1-Komponente und eine zweite, späte, bilaterale, polysynaptische R2-Komponente (vergleiche Abbildung III). (22, 23) Durch die Stimulation des trigeminalen Systems und der damit einhergehenden direkten Verarbeitung im Hirnstamm eignet sich der Blinkreflex insbesondere, um Aussagen über die zentrale (Hirnstamm-) Erregbarkeit zu treffen. (15) Die R2-Komponente kann hinsichtlich ihrer Amplitude, ihrer Fläche (Area-under-the-curve, AUC) sowie bei wiederholten Stimuli hinsichtlich ihres Habituationsverhaltens ausgewertet werden.

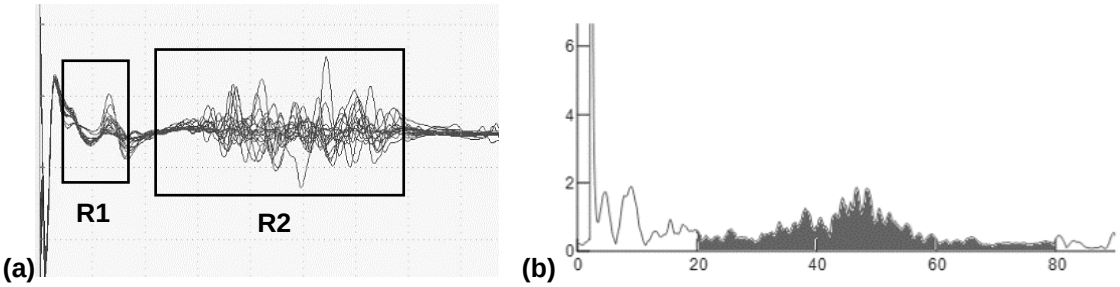


Abbildung III – Exemplarische Darstellung von Blinkreflex-Kurven und deren Auswertung. **a:** mehrere übereinander gelegte Ableitungen des BR mit Markierung der R1- sowie R2-Komponente. **b:** ein extrahierter Graf mit Markierung der AUC innerhalb der R2-Komponente. x-Achse: Zeit in ms. y-Achse: Amplitude in µV

Bei Patient*innen mit Migräne zeigt sich eine Veränderung der zentralen Reizverarbeitung, die sich bei der Ableitung des Blinkreflexes widerspiegelt. Insbesondere sind Patient*innen mit Migräne durch ein interiktales Habituationsdefizit charakterisiert, das sich während der Attacke normalisiert. (24)

2.4 Zusammenfassung der Studienziele

Die vorherigen Abschnitte dienten dazu, die pathophysiologischen Grundlagen der Migräne, deren medikamentöse Beeinflussung durch CGRP-Antikörper und auch die elektrophysiologischen Hintergründe des BR zu erläutern. Bevor es in den folgenden Abschnitten detailliert um die Methodik und Auswertung der Studienergebnisse geht, sollen noch einmal die zentralen Fragestellungen dieser Arbeit kurz dargestellt

werden. Zusammenfassend lassen sich folgende Hypothesen (mit zugehörigen Endpunkten) festhalten:

- Primärer Endpunkt: Area-under-the-curve und Habituationsverhalten der R2-Komponente des Blinkreflexes, wobei
  -keine Veränderung dieser Parameter einer rein symptomatischen Wirkung entspricht (Nullhypothese).
  -eine Veränderung dieser Parameter Hinweise auf eine zentral krankheitsmodifizierende Wirkung liefert (Alternativhypothese).
- Sekundäre Endpunkte: Veränderung der Kopfschmerzcharakteristika (Kopfschmerzfrequenz/-schwere) und der Einschränkung der Lebensqualität durch die Kopfschmerzen.

Auf Grundlage dieser Ergebnisse sollen folgende Fragestellungen beantwortet bzw. diskutiert werden:

- Bestehen Hinweise auf eine krankheitsmodifizierende Wirkung der CGRP-Antikörper?
- Wie ist das klinische Ansprechen der Patient*innen auf die CGRP-Antikörper?
- Kann der BR als klinischer Biomarker für ein Therapieansprechen genutzt werden?

3 Methodik

In den folgenden Abschnitten wird sowohl das zugrundeliegende Studiendesign und die Proband*innenpopulation dargestellt als auch gezeigt werden, wie die Daten erhoben und im Folgenden ausgewertet wurden.

3.1 Studiendesign & Proband*innen

Bei der Studie handelt es sich um eine prospektive Beobachtungsstudie, welche durch die Ethikkommission der Universitätsmedizin Greifswald bewilligt wurde (Ethikvotum BB 168/18) und prospektiv registriert wurde (clinicaltrials.gov (ID: NCT04019496, Datum der Registrierung: 15.07.2019)). Alle Patient*innen erhielten eine detaillierte schriftliche Studieninformation und -aufklärung und gaben ihr schriftliches Einverständnis zur Studienteilnahme. Es wurden Patient*innen mit episodischer Migräne ausgewählt, denen gesunde Alters- und Geschlechts-gematchte Kontrollproband*innen (±5 Jahre) zugeordnet wurden. Die Studienproband*innen wurden im Rahmen der neurologischen Kopfschmerzsprechstunde des Universitätsklinikums Greifswald rekrutiert. Ausgewählt wurden Patient*innen, die an episodischer Migräne erkrankt sind und die Indikation für eine Prophylaxe (mehr als 4 Kopfschmerztage im Monat) aufwiesen. Das Vorhandensein einer chronischen Migräne stellte ein Exklusionskriterium dar. Kontrollpatient*innen durften weder an einer neurologischen Erkrankung noch an einer Kopfschmerzerkrankung leiden. Darüber hinaus waren das Vorliegen eines Medikamentenübergebrauchskopfschmerzes oder die Einnahme von zentralnervös-wirksamen Medikamenten Ausschlusskriterium für beide Gruppen.

Sofern sie inkludiert wurden, wurden die Patient*innen für einen ersten Studientermin (V0) einbestellt. Im Rahmen dessen erfolgte die Beantwortung eines ausführlichen Fragebogens (allgemeine demografische Daten, Lifestyle-Parameter sowie eine ausführliche Kopfschmerzanamnese) und die erstmalige Messung des BR. Nachfolgend erhielten sie die erste Antikörperinjektion. In den folgenden drei Monaten wurden sie gebeten, einen Kopfschmerzkalender zu führen. Nach 90 Tagen (±14 Tage) wurden sie zur zweiten Studienvisite (V3) einbestellt, bei der die Messung

wiederholt wurde. Die gesunden Kontrollproband*innen wurden nur einmalig zur Messung einbestellt (vergleiche Abbildung IV).(25)

3.2 Datenerhebung

Die Messung des BR erfolgte nach standardisiertem Protokoll (vergleiche Abbildung IV). Nach der Aufklärung über die Methode wurde die Messung in einem ruhigen Raum durchgeführt. Die Mess- sowie die Stimulationselektrode (bipolare Oberflächenelektrode) wurden dabei montiert und fixiert. Es folgte die Bestimmung der individuellen Schmerzschwelle, wobei einzelne Stimuli im Abstand von 30 Sekunden verabreicht wurden, um eine Habituation vor der eigentlichen Messung zu vermeiden. Bei der eigentlichen Stimulation wurden insgesamt 60 Stimuli in 10 Blöcken à 6 Stimuli appliziert, wobei das Interstimulus-Intervall 15-17 Sekunden und das Interblock-Intervall 2 Minuten betrug. (25)

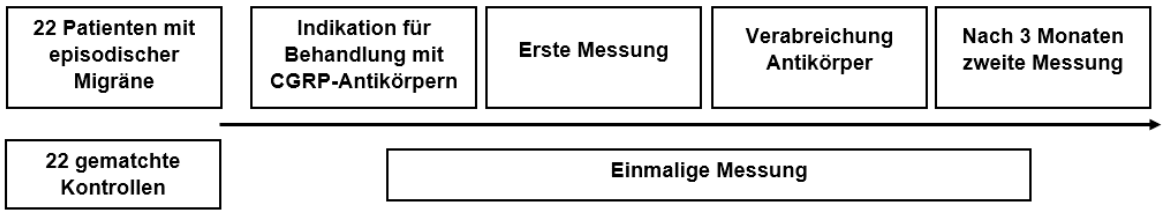


Abbildung IV – Darstellung des Studiendesigns

Die Messung bestand aus einem standardisierten Fragebogen und der Erhebung des Blinkreflexes, wobei insgesamt 60 Stimuli in 10 Blöcken à 6 Stimuli appliziert wurden.

3.3 Auswertung & Statistik

3.3.1 Endpunkte & statistische Analyse

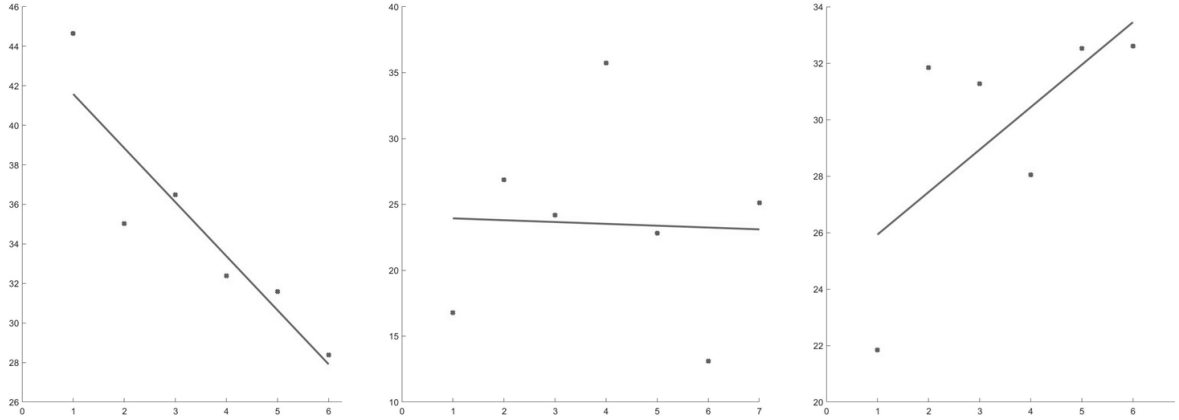
Als primärer kombinierter Endpunkt der Studie wurde eine Veränderung der Sensitivierung (entspricht der AUC) oder Habituation (bei wiederholter Stimulation) der R2-Komponente des Blinkreflexes nach dreimonatiger Therapie mit einem CGRP-Antikörper definiert. Die AUC der R2-Komponente diente hierbei als erstes Kriterium der zentralen Sensitivierung. Für die Evaluation der Habituation wurde die Entwicklung der AUC von Stimulus 1-6 betrachtet.

Die sekundären Endpunkte der Studie waren des Weiteren die demografischen Charakteristika und die Kopfschmerz-Charakteristika (unter anderem Kopfschmerzfrequenz und -intensität, Attackendauer sowie die Kopfschmerz-assoziierte Einschränkung des Alltagslebens), die mit Hilfe des Fragebogens erhoben wurden. (25)

Es wurde zuerst auf globale Effekte innerhalb und zwischen den Gruppen bei den Visiten untersucht, indem eine Varianzanalyse (ANOVA, Patient*innen gegen Kontrollproband*innen) bzw. eine Varianzanalyse mit Messwiederholung (rmANOVA, Patient*innen) durchgeführt wurde. Sofern diese, z.B. zwischen den Visiten detektiert wurden, wurden einzelne Parameter post-hoc weiter analysiert. Innerhalb der Gruppen wurde hierfür ein gepaarter t-Test (Migräne-Patient*innen) bzw. ungepaarter t-Test (Patient*innen gegen Kontrollproband*innen) verwendet. Sofern mehrere Vergleiche vorgenommen wurden, erfolgte eine Bonferroni-Korrektur. Als Signifikanzniveau wurde $p<0,05$ definiert. (25)

3.3.2 Auswertung des Blinkreflexes

Für die Analyse der Habituation wurde die Entwicklung der AUC der R2 Komponente über mehrere Stimuli hinweg betrachtet. Dafür wurde eine lineare Regression durchgeführt, wobei der β-Koeffizient der linearen Regression als Habituation definiert wurde. Hierbei gilt, dass ein negativer Koeffizient einer Habituation, ein positiver Koeffizient einer Bahnung und ein Koeffizient gleich Null keiner Veränderung des trigemino-zervikalen Komplexes als Antwort auf wiederholte Stimuli entspricht (vergleiche Abbildung V). Sowohl die AUC als auch die Habituation wurden sowohl für die stimulierte Seite als auch für die nicht-stimulierte Seite bestimmt. (25)



1 **2** **3**

Abbildung V – Darstellung der Analyse des Habituationsverhaltens.
1: Graf mit negativem Steigungskoeffizienten/Habituation. **2:** Graf mit Steigungskoeffizient annähernd 0/unverändert. **3:** Graf mit positivem Steigungskoeffizienten/Sensitivierung.
x-Achse: Anzahl der Stimuli. y-Achse: AUC in $\mu V^2/ms$

4 Ergebnisse

4.1 Demografische Charakteristika und klinisches Ansprechen auf die Prophylaxe

Es wurden 22 Patient*innen (21 Frauen, Durchschnittsalter 46,2±13,8 Jahre) in die Studie eingeschlossen, davon 4 Patientinnen mit Migräne mit Aura. Von diesen erhielten 12 Erenumab, 5 Galcanezumab und 5 Fremanezumab. Bei der Analyse der Kopfschmerzcharakteristika ergab sich eine Kopfschmerzfrequenz von 12,4±3,3 Tagen/Monat, die eine Dauer von 8,0±5,3 Stunden/Attacke aufwiesen. Dies senkte sich nach 3 Monaten der Behandlung signifikant ab auf 6,6±4,9 Tage/Monat (p<0,001) und eine Dauer von 5,4±4,2 Stunden/Attacke (p=0.014) (siehe Tabelle I). Parallel dazu sanken die Scores zur Messung der Einschränkung der Lebensqualität durch die Krankheit (Headache-Impact-Test-6 (HIT-6) und Migraine-Disability-Assessment (MIDAS)), was einer geringeren Einschränkung bzw. erhöhten krankheitsassoziierten Lebensqualität im Vergleich zu V0 entspricht (Tabelle I). Das klinische Ansprechen war nicht abhängig von den verabreichten Antikörpern. Des Weiteren war keines der demografischen Charakteristika ein Prädiktor für das Therapieansprechen.

	Vor Therapie (V0)	Nach Therapie (V3)
Kopfschmerzfrequenz (Tage/Monat)	12,4±3,3	6,6±4,9 (p<0,001)
Kopfschmerzdauer (Stunden/Attacke)	8,0±5,3	5,4±4,2 (p=0,014)
MIDAS-Score	61,7 ± 62,3	32,2 ± 61,2 (p=0,003)
HIT-6-Score	66,1 ± 4,9	54,9 ± 9,2 (p<0,001)

Tabelle I – Übersicht über die Kopfschmerzcharakteristika vor und nach der 3-monatigen Therapie mit CGRP-Antikörpern

4.2 Blinkreflex

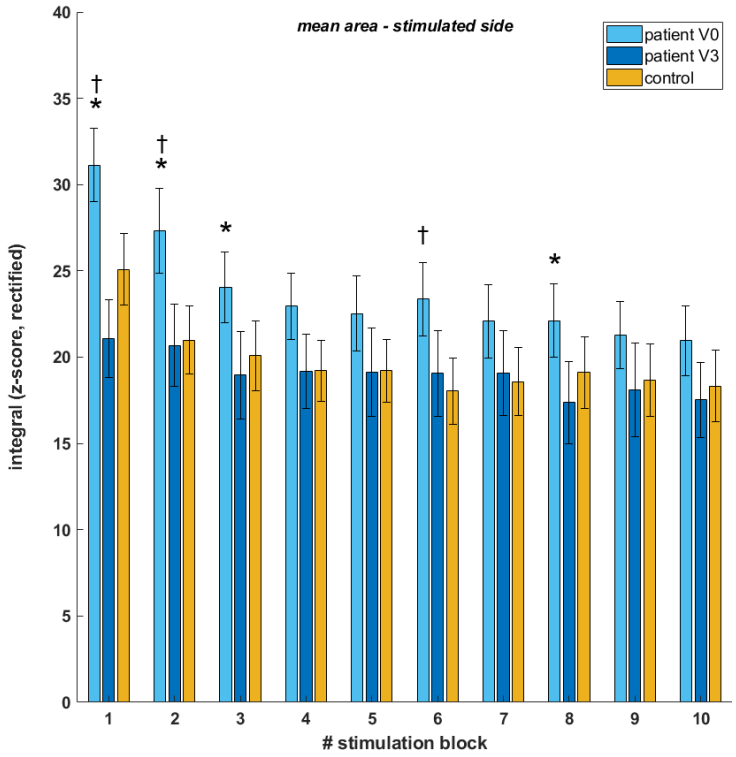
Sowohl auf der stimulierten (Kürzel „_s“) wie auch auf der nicht-stimulierten Seite (Kürzel „_ns“) ergaben sich für die Veränderung der AUC signifikante Veränderungen bei den behandelten Patient*innen mit einem signifikanten globalen Effekt für Veränderungen der Blöcke zwischen den Visiten (R2a_s ($F_{(19,597)}$=5,86), p<0,001);

R2a_ns ($F_{(19,597)}$=8,22), *p*<0,001). Auf der stimulierten Seite reduzierte sich die AUC signifikant in den Blöcken eins (-10,2±2,6, *p*<0,001), zwei (-6,7±2,8, *p*=0,028), drei (-5,1 ± 2,1, *p*=0,028) sowie acht (-4,7 ± 2,1, *p*=0,033). Auf der nicht-stimulierten Seite zeigten sich Block eins (-8,8 ± 2,6, *p*=0,003), zwei (-7,0 ± 2,5, *p*=0,010), drei (-6,0 ± 2,5, *p*=0,025), acht (-4,4 ± 1,9, *p*=0,028) sowie zehn (-4,1 ± 1,4, *p*=0,010) als signifikant reduziert (vergleiche hierzu Abbildung VI).

Bei Betrachtung der Habituation zeigten sich bei den Patient*innen nur auf der nicht-stimulierten Seite signifikante Ergebnisse ($F_{(19,597)}$=3,07), *p*<0,001), wobei die Veränderungen auf der stimulierten Seite nur grenzwertig nicht-signifikant waren ($F_{(19,597)}$=1,46, *p*=0,095). Somit wurde nur die nicht-stimulierte Seite weiter verglichen, woraus sich eine stärkere Minderung in den Blöcken sechs (-1,4 ± 0,5, *p*=0,007), sieben (-1,2 ± 0,4, *p*=0,010), acht (-1,0 ± 0,5, *p*=0,034) und zehn (-1,0 ± 0,4, *p*=0,034) im Vergleich zu V0 ergab (vergleiche Abbildung VII).

Beim Vergleich zwischen den Patient*innen und Kontrollen konnte nur ein signifikanter Effekt bei der AUC der stimulierten Seite ($F_{(19,420)}$=3,11, *p*<0,001) sowie für die Habituation der stimulierten ($F_{(19,420)}$=2,45, *p*=0,001) und nicht-stimulierten Seite ($F_{(19,420)}$=3,16, *p*<0,001) nachgewiesen werden.

a)



b)

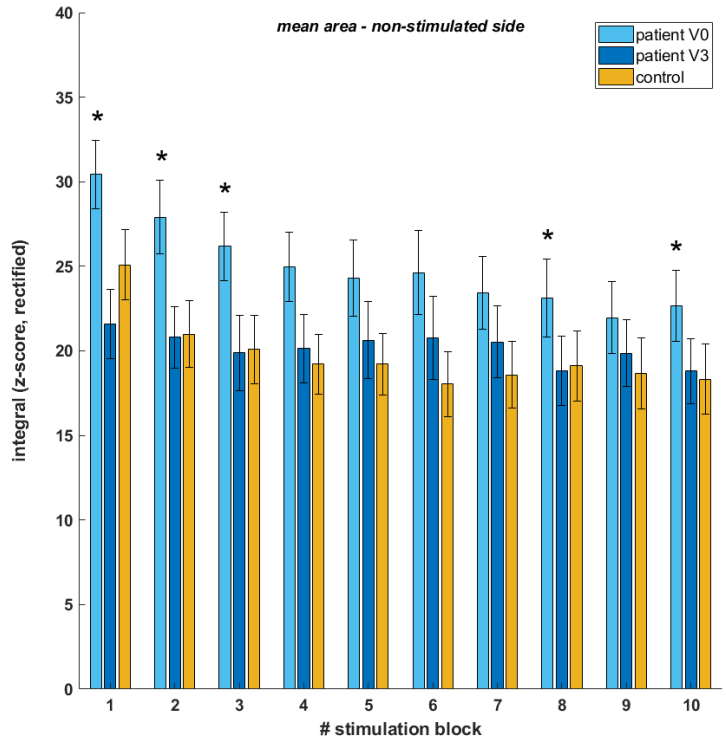


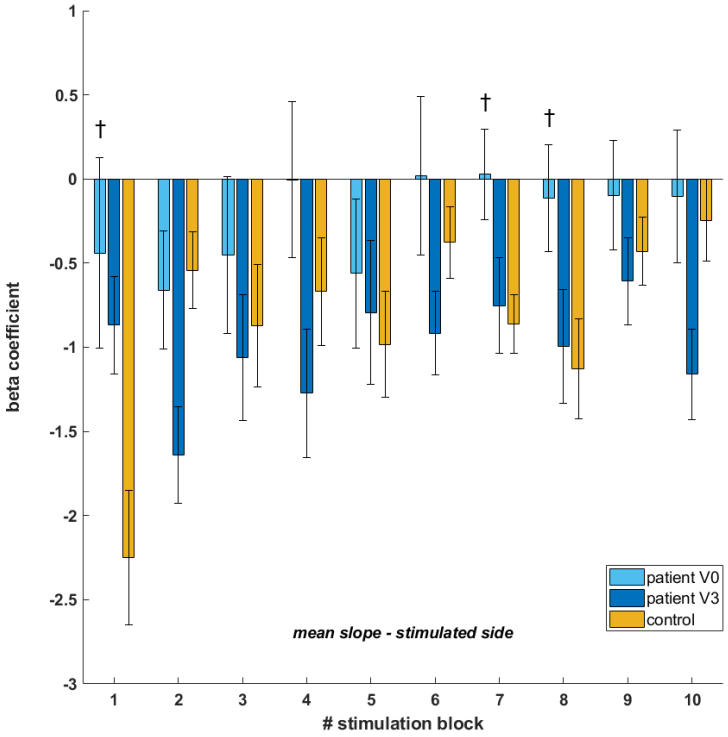
Abbildung VI – Veränderungen des Blinkreflexes in Hinblick auf die AUC mit Markierung der signifikanten Ergebnisse

a/b: Veränderungen der AUC auf der stimulierten (a) sowie nicht-stimulierten (b) Seite. (25)

* = statistische Signifikanz zwischen V0 und V3 bei Migränikern

† = statistische Signifikanz zwischen V0 und Kontrollen

a)



b)

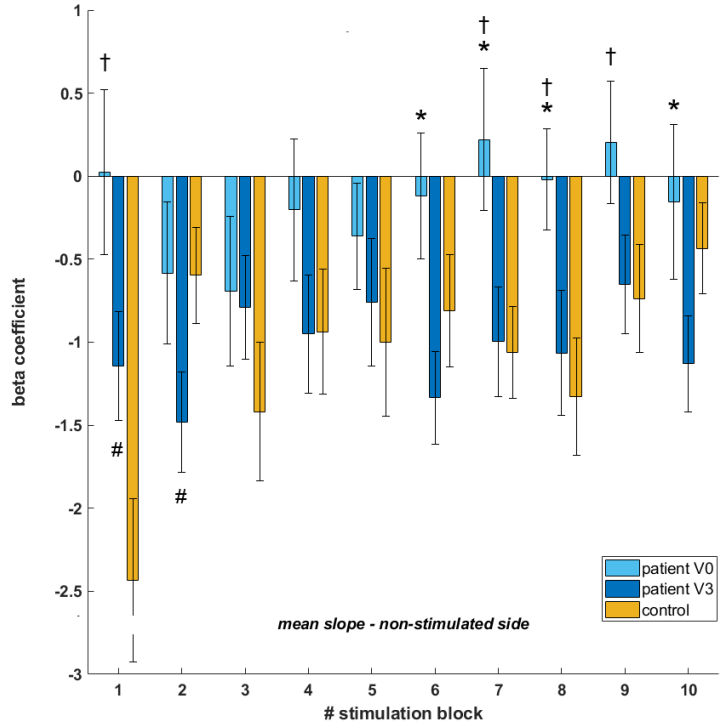


Abbildung VII – Veränderungen des Blinkreflexes in Hinblick auf die Habituation mit Markierung der signifikanten Ergebnisse

a/b: Veränderungen der Habituation (β-Koeffizient) auf der stimulierten (a) sowie nicht-stimulierten (b) Seite (25)

* = statistische Signifikanz zwischen V0 und V3 bei Migränikern

† = statistische Signifikanz zwischen V0 und Kontrollen

= statistische Signifikanz zwischen V3 und Kontrollen

4.3 Blinkreflex als Biomarker

Die Veränderungen der Habituation in Block fünf auf der stimulierten (r=0,56, *p*=0,010) sowie auf der nicht-stimulierten (r=0,45, *p*=0,045) Seite korrelierten signifikant mit den Veränderungen der Kopfschmerz-Frequenz. Nach zusätzlicher statistischer Korrektur der Zeit bis zur nächsten Attacke, konnten weitere Korrelationen für den Block drei auf der stimulierten (r=0,56, *p*=0,025) und nicht-stimulierten Seite (r=0,54, *p*=0,030) gezeigt werden (vergleiche Abbildung 4 (25)). Kein Parameter der AUC oder Habituation war ein Prädiktor für das Therapieansprechen in der logistischen Regression (alle *p*>0,05).

5 Diskussion

Das Ziel der Arbeit war es, die Veränderung der Hirnstammerregbarkeit als Reaktion auf wiederholte schmerzhafte Stimuli im Verlauf der Behandlung mit CGRP-Antikörpern zu untersuchen. Im Rahmen der Studie konnte die Alternativhypothese, wonach eine Krankheitsmodifikation durch CGRP-Antikörper besteht, bestätigt werden.

Es lässt sich zusammenfassend in Hinblick auf die eingangs definierten Fragestellung feststellen:

- In Bezug auf den primären Endpunkt war eine Normalisierung der AUC und des Habituationsverhaltens nachzuweisen, sodass Hinweise auf ein krankheitsmodifizierendes Potenzial der CGRP-Antikörper bestehen (Annahme der Alternativhypothese).
- Hinsichtlich der sekundären Endpunkte ließ sich eine deutliche Reduktion der Kopfschmerzfrequenz sowie Schmerzstärke und eine Besserung der krankheitsassoziierten Lebensqualität nach dreimonatiger Therapie registrieren.
- Die Veränderungen der Habituation korrelierten mit der Besserung der klinischen Parameter, jedoch konnte kein Prädiktor für ein Ansprechen auf die Therapie definiert werden.

Die hierzu durchgeführten Messungen bestätigten, dass die zentrale Hirnstammerregbarkeit und das Habituationsverhalten als Antwort auf wiederholte schmerzhafte Stimuli bei Patient*innen mit Migräne beeinträchtigt sind. Einerseits zeigte sich bei Patient*innen mit Migräne eine erhöhte Sensitivierung. Andererseits konnte ein deutliches Habituationsdefizit der Patient*innen, vor allem auf der nicht-stimulierten Seite, nachgewiesen werden. Die gestörte Hirnstamm-Erregbarkeit und Habituation als Reaktion auf schmerzhafte Stimuli ließen sich am deutlichsten in späten Blöcken der Stimulation und auf der nicht-stimulierten Seite belegen. Nach drei Monaten der Behandlung mit CGRP-Antikörpern kam es zu einer Normalisierung dieser pathologischen Muster. Zudem kann durch die Korrelation zwischen der Normalisierung des Habituationsverhaltens und des klinischen Ansprechens ein biologischer Gradient nachgewiesen werden, sodass eine kausale Interpretation der Behandlung mit CGRP-Antikörpern als Ursache für die Veränderungen der zentralen

Krankheitsaktivität möglich ist. Damit kann die Nullhypothese, wonach CGRP-Antikörper lediglich symptomatisch wirken, verworfen werden.

5.1 Sind CGRP-Antikörper krankheitsmodifizierend?

Wie in der Einleitung bereits beleuchtet, sollten krankheitsmodifizierende Medikamente das Potenzial haben, den natürlichen Verlauf der Krankheit zu verlangsamen. Im Verlauf dieser Arbeit konnte dargestellt werden, dass die Behandlung mit CGRP-Antikörpern zu einer klinischen Reduktion der Krankheitsschwere durch einen peripheren Wirkmechanismus führt. Dies wäre im Spontanverlauf nicht zu erwarten gewesen.(13) Des Weiteren konnte gezeigt werden, dass ein Einfluss auf zentrale Prozesse der Krankheit besteht. Dies deckt sich mit der EMA-Definition (siehe Einleitung, (11)). In aktuellen klinischen Studien findet sich außerdem Evidenz dafür, dass CGRP-Antikörper dazu beitragen, dass sich die Krankheitsaktivität von einer chronischen Migräne hin zu einer episodischen Migräne reduziert. (26) Dies unterstützt die These bezüglich des krankheitsmodifizierenden Potenzials, da der natürliche Verlauf eher eine Zunahme der Aktivität von episodischer hin zu chronischer Migräne vorsieht. (13, 26) Trotz dessen muss angemerkt werden, dass die klinische Besserung der Symptome sistiert, sobald die Behandlung eingestellt wird (14, 27, 28), was einer Krankheitsmodifikation widerspricht.

5.2 Die Nutzung des Blinkreflexes als klinischer Biomarker

Im Rahmen dieser Arbeit war es möglich, zu zeigen, dass die Veränderungen der Habituation mit den Veränderungen der Kopfschmerz-Frequenz korrelierten. Somit erfüllt der nozizeptive Blinkreflex die Kriterien als Biomarker (vergleiche hierzu die FDA Biomarker Working Group, (29)). Trotz dessen war es nicht möglich, einen Parameter zu bestimmen, der als Baseline-Prädiktor für das Therapieansprechen geeignet ist. Weiterhin bleibt ungeklärt, inwieweit der BR genutzt werden kann, um den Verlauf der Krankheitsaktivität nach Absetzen der Therapie vorauszusagen. Dies ist jedoch von höchster klinischer Relevanz, da die aktuelle klinische Forschungslage zeigt, dass bei vielen Patient*innen nach Absetzen der Therapie die Krankheitsaktivität wieder zunimmt und eine Erhöhung der Kopfschmerztage zu verzeichnen ist. (14, 27, 28)

Dadurch ergibt sich die Notwendigkeit, dass zukünftige Forschung weiter evaluieren sollte, wie sich der BR vor, während und nach der Therapie mit CGRP-Antikörpern verhält. Sofern sich die Nutzung des BR als Biomarker bestätigt, könnte dies von Nutzen sein, um die Therapie individuell auf die Patient*innen abzustimmen.

5.3 Künftige Forschungsschwerpunkte

Die Ergebnisse deuten auf eine mögliche Verwendung des Blinkreflexes als Biomarker für das Therapieansprechen während der Therapie hin. Nichtsdestotrotz wird es in Zukunft nötig sein, in weiteren Studien zu evaluieren, wie sich diese Veränderungen nach dem Absetzen der CGRP-Antikörper verhalten und tatsächlich einen Prädiktor für das anhaltende Therapieansprechen, d.h. einen prognostischen Biomarker, darstellen. Dies wäre ebenfalls sinnvoll, um weiter zu untersuchen, ob eine längere/abgewandelte Form der Messung doch Parameter konkretisieren kann, die als Prädiktoren verwendet werden können. So sollte der CGRP-spezifische nozizeptiv-spezifische BR mit dem hier durchgeführten nozizeptiven Blinkreflex verglichen werden. Des Weiteren muss in Betracht gezogen werden, dass eine Veränderung der Messparameter (kürzere Interstimulusintervalle, etc.) dazu führen könnten, die gezeigten Effekte besser darzustellen. Daher sollten kommende Studien untersuchen, welchen Einfluss Änderungen des Protokolls auf das Habituationsverhalten haben.

5.4 Zusammenfassung

Die im Rahmen dieser Arbeit durchgeführte Studie zeigt erstmalig, dass CGRP-Antikörper das Habituationsverhalten von Patient*innen mit Migräne bereits nach drei Monaten der Therapie normalisieren. Parallel dazu verbesserten sich auch die klinischen Kopfschmerz-Parameter. Daher ist erstmalig festzustellen, dass CGRP-Antikörper krankheitsmodifizierende Wirkung haben könnten. Es war außerdem möglich darzustellen, dass der nozizeptive Blinkreflex als möglicher Biomarker für die zentrale Krankheitsaktivität und somit auch den Behandlungserfolg in Betracht kommt.

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7 Anhang

7.1 Publikation Hauptprojekt

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The Journal of Headache and Pain

RESEARCH ARTICLE Open Access

Preventive treatment with CGRP monoclonal antibodies restores brain stem habituation deficits and excitability to painful stimuli in migraine: results from a prospective case-control study

Anne Thiele[1], Lara Klehr[1], Sebastian Strauß[1], Anselm Angermaier[1], Ulf Schminke[1], Martin Kronenbuerger[1,2], Steffen Naegel[3] and Robert Fleischmann[1*]

Abstract

Background & Objectives: Calcitonin gene-related peptide ligand/receptor (CGRP) antibodies effectively reduce headache frequency in migraine. It is understood that they act peripherally, which raises the question whether treatment merely interferes with the last stage of headache generation or, alternatively, causes secondary adaptations in the central nervous system and might thus possess disease modifying potential. This study addresses this question by investigating the nociceptive blink reflex (nBR), which is closely tied to central disease activity, before and after treatment with CGRP antibodies.

Methods: We enrolled 22 patients suffering episodic migraine (21 female, 46.2 ± 13.8 years of age) and 22 age-/gender-matched controls. Patients received assessments of the nBR (R2 component, 10 trials, 6 stimuli/trial) before (V0) and three months (V3) after treatment with CGRP antibodies started, controls were assessed once. The R2 area (R2a) and habituation (R2h; gradient of R2a against stimulus order) of the stimulated/non-stimulated side (_s/_ns) following repeated supraorbital stimulation provide a direct readout of brainstem excitability and habituation as key mechanisms in migraine.

Results: All patients showed a substantial reduction of headache days/month (V0: 12.4±3.3, V3: 6.6 ± 4.9). R2a_s (F_{global}=5.86, p<0.001; block 1: R2a_s: -28%, p<0.001) and R2a_ns (F_{global}=8.22, p<0.001, block 1: R2a_ns: -22%, p=0.003) were significantly decreased, and R2h_ns was significantly enhanced (F_{global}=3.07, p<0.001; block 6: R2h_ns: r=-1.36, p=0.007) from V0 to V3. The global test for changes of R2h_s was non-significant (F_{global}=1.46, p=0.095). Changes of R2h significantly correlated with improvement of headache frequency (R2h_s, r=0.56, p=0.010; R2h_ns: r=0.45, p=0.045). None of the nBR parameters assessed at baseline predicted treatment response.

* Correspondence: robert.fleischmann@uni-greifswald.de
[1]Department of Neurology, University Medicine Greifswald, Ferdinand-Sauerbruch-Str. 1, 17475 Greifswald, Germany
Full list of author information is available at the end of the article

Discussion: We provide evidence that three months of treatment with CGRP antibodies restores brain stem responses to painful stimuli and thus might be considered disease modifying. The nociceptive blink reflex may provide a biomarker to monitor central disease activity. Future studies should evaluate the blink reflex as a clinical biomarker to predict treatment response at baseline and to establish the risk of relapse after treatment discontinuation.

Trial registration: This trial was prospectively registered at clinicaltrials.gov (ID: NCT04019496, date of registration: July 15, 2019).

Keywords: Migraine, Headache, Prevention, Calcitonin gene-related peptide, Antibodies, Disease modifying drug, Blink reflex

Background

Migraine is among the most prevalent neurological disorders and substantially interferes with individuals' psychosocial health, family life and professional development [1]. An effective preventive treatment is considered key to ameliorate the negative impact of migraine [2]. Unfortunately, most approved preventive drugs are characterized by low tolerability and contraindications that impede their unconditional use in clinical routine [3, 4]. Monoclonal antibodies targeting calcitonin gene-related peptide (CGRP) or the CGRP receptor (hereafter collectively referred to as *CGRP mAbs*) have ushered in a novel era of migraine prevention by being specifically designed to target disease relevant mechanisms, which enables superior tolerability and efficacy to oral preventives [5, 6].

Some practical issues in clinical routine application of CGRP mAbs remain, importantly patient selection and duration of treatment, which are both essential to be resolved given associated treatment costs [7]. German guidelines recommend continuing treatment for about six to nine months if they were proven effective in a preceding three-month trial [3]. European guidelines are less absolute about the treatment duration but also advise to continue for about 6-12 months while the American Headache Society Consensus Statement considers reauthorization duration indefinite and should be guided by patient response and medical professional attestation [8, 9]. This discrepancy of guidelines reveals uncertainty about long-term effects of CGRP mAbs on the natural course of migraine, but it is generally acknowledged that the preventive treatment should potentially lead to a sustained amelioration of headache frequency as it is shown for oral preventives, which may be considered disease modifying [10–12]. While there is no unequivocal definition of disease modification in headache research, it might follow the European Medicines Agency's definition as "slowing or arrest of symptom progression and evidence of delay in the underlying […] pathophysiological disease processes" [13]. Martelletti proposed in analogy that a Disease-Modifying-Migraine-Drug (DMMD) should "slow down or freeze or revert the natural course of migraine" [14]. Currently, it is unclear if a course of CGRP mAbs possesses disease modifying potential. This concern is mainly due to the presumed peripheral mode of action, which is blocking the effect of CGRP release in the trigeminovascular system and not directly targeting central structures [5, 15, 16]. Furthermore, up to 80% of patients relapse to their prior headache frequency following discontinuation of the treatment with CGRP mAbs, which further challenges central disease modifying potential, but may be confounded by non-pharmacological effects [17, 18]. On the other hand, functional imaging studies revealed altered activity in brain regions such as the hypothalamus closely related to migraine pathophysiology following treatment with CGRP mAbs, which argues for disease modifying activity [19]. The discrepancy of pharmacological, clinical and imaging studies precludes conclusions whether or not long-term treatment with CGRP mAbs shapes the natural course of migraine. Consequently, there is no biomarker to select suitable patients and the ideal moment for discontinuation of treatment with CGRP mAbs.

This study aims to address this ambiguity of findings by investigating patients with migraine treated with CGRP mAbs for longitudinal changes of brain stem excitability and habituation to nociceptive stimuli, which were shown to be deficient in migraine and closely tied to central disease activity [15, 20]. The nociceptive blink reflex (nBR) was repeatedly proven to be an ideal neurophysiologic biomarker for this purpose since it provides a direct readout of central processing of trigeminal sensory (nociceptive) input, and is hence used as the primary endpoint to probe disease modification potential in this study [21–23]. Findings from this study may also yield implications for the nBR as therapeutic biomarker in migraine.

Methods

Ethical approval and study registration

This study was prospectively registered at clinicaltrials.gov (Identifier: NCT04019496) and approved by the ethics committee of the University Medicine Greifswald (Identifier: BB 168/18). All procedures adhered to the *Helsinki declaration* in its latest revision and were conducted in line with current guidelines for *good clinical*

practice (ICH E6(R2)). All patients and controls were provided detailed study information and gave their written consent for the study and the use of their data.

Study design and participant selection

This is a prospective case-control study with patients suffering episodic migraine serving as cases and healthy volunteers serving as matched controls. Matching was done for age (±5 years) and gender. Controls were required not to suffer from any neurological condition or a primary headache disorder (defined as headache frequency of <1/year and negative medical history).

Patients suffering migraine were identified among patients presenting to the specialized headache outpatient clinic affiliated with the Department of Neurology of a tertiary care university hospital in Northern Germany. Diagnosis of migraine was established according to international classification of headache disorders, 3rd revision, (ICHD-3) criteria [24]. Only patients with episodic migraine with an indication for preventive treatment with CGRP mAbs were considered. Chronic migraine was an exclusion criterion since at least a proportion of patients lacks a clear interictal phase that was required for BR assessments [25]. Further exclusion criteria for both groups were presence of a medication-overuse headache and chronic intake of central nervous system active drug.

Cases were investigated after washout of any previous preventive drug, defined as five half-lives, at least two days apart from any preceding headache attack, and before starting treatment with CGRP mAbs (visit at zero months of treatment, i.e. usually the day of the first injection, denoted as V0) and three months (±14 days) after treatment was initiated (denoted as V3). The rationale for a three-month interval between visits was treatment response is to be expected and can be assessed within that period [3, 5]. Controls were investigated only once at about the same time of the day.

Primary endpoint – blink reflex habituation and sensitization

The area under the curve (AUC) and habituation of the BR's R2-component following repeated stimulation were investigated as primary endpoints [26]. The nBR response was elicited and evaluated using well-established electrical stimulation parameters in migraine research in order to enable comparison to previous results [26, 27]. Painful electrical stimuli were applied to the supraorbital division of the trigeminal nerve on the main headache side (matched in controls) through a commercial electrophysiology setup (Neuropack X1, Nihon Kohden Europe, Rosbach, Germany) using a bipolar montage of gold cup electrodes, which were fixed using adhesive paste and tape. We decided to use a classic bipolar montage for two reasons. First, using ring electrodes with a circular anode and central cathode were shown to specifically activate Aδ-fibers, which elicits a nociception specific BR (nsBR), and may be influenced by direct peripheral antagonism of CGRP mAbs at the time of stimulation and confound assessments of central neuroplastic effects [28, 29]. Second, this approach was chosen for ready implementation of findings in electrophysiological laboratories. Surface electromyography was recorded using a bipolar montage with the refence being placed over the tip of the nose and active electrodes being placed over bilateral orbicularis oculi muscles [30]. Electrode positions were recorded and replicated at V3 in patients. Stimulation parameters were set as previously recommended by a panel of experts [26]. In brief, the pain threshold (PT) was established using stimuli, which were at least 30 s apart to avoid habituation, at increasing intensity. Then, 60 stimuli with a pulse width of 0.3 ms and 1.5x PT intensity were applied in 10 blocks each consisting of 6 stimuli with an interstimulus interval (ISI) of 15-17 s and an interblock interval of at least 2 min. Traces of recorded EMG responses were then exported into a MATLAB environment and the R2 component defined as responses that occurred in an interval of 30-80 ms (see Fig. 1).

Preprocessing of CMAPs was done using the fieldtrip toolbox and included rectification, detrending and z-transformation, which was done to enable comparisons of R2 AUC (R2a) intra- and interindividually, and between sides (indicated by suffix: _s = stimulated, _ns = not-stimulated) [31].

Secondary endpoints

Demographic characteristics were recorded in all participants, which included age and gender. We additionally assessed headache characteristics (headache frequency, mean headache intensity [rated on a numerical scale ranging from 0 to 10 points], attack duration, time the last headache occurred before and after the assessment) and headache-related disability (Migraine Disability Assessment [MIDAS], Headache Impact Test [HIT-6™]) in patients suffering migraine through tools highly recommended by the National Institute of Neurological Disorders and Stroke common data element initiative [32]. All patients were obliged to provide a headache diary starting 3 months before beginning CGRP mAb treatment and throughout the study period.

Sample size considerations, data evaluation and statistics

The mean effect size of previous studies using the R2 AUC and habituation for the assessment of treatment response found a mean effect size of 0.7 (Cohen's *d*) [15, 21, 26]. G*Power (v.3.1.9.2, University of Düsseldorf,

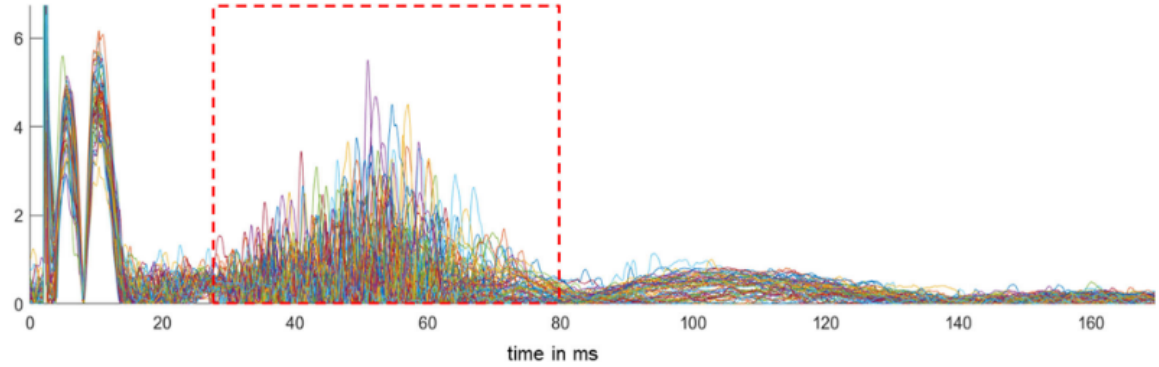

Fig. 1 Superimposed 60 nBR traces of one participant. The R2 component is indicated by a box of red dashed lines between 30-80 ms. Note the stimulation artifact at the start and the immediately following R1 component. The R1 component has a low variability given its monosynaptic pathway through the principal trigeminal nucleus. The R2 component is more variable in amplitude and time given its polysynaptic pathway through the trigemino-cervical complex. The R3 follows the R2 component and starts at about 80-90 ms. Its underlying pathways and functions are still debated

Germany) was used to calculated the sample size required to detect R2 changes between V0 and V3 in patients using a two-sided paired t-Test with an alpha-error of 0.05, power of 90% [33]. The power calculation revealed that 22 patients, and thus 22 controls, would be required to test our hypothesis. We aimed to include 25 participants in each group to account for about 10% drop-out rate.

NBR data were pre-processed as described above. The AUC of R2 responses (R2a) was computed using a trapezoidal approximation of its integral. Habituation (R2h) was quantified as the beta coefficient (i.e. β0, slope) of the linear regression: $f(R2a_i) = \beta0*R2a_i + \text{intercept}$ (i = stimulus order). A positive slope indicates facilitation, negative slope habituation and zero slope no change of the trigemino-cervical complex (TCC) to consecutive stimulation. Evaluations of R2a and R2h corrected for the time before the following headache attacks were included as exploratory endpoints.

Further statistical analyses were carried out using the Statistical Package for the Social Sciences (SPSS v25.0, IBM, Armonk, NY, USA). Continuous data were analysed for normal distribution using histogram plots before performing descriptive and inferential statistics. Unless stated differently, normal distribution was confirmed. Descriptive normal distributed data are presented as group means ± standard deviation. Inferential comparisons within and between group means were done using repeated-measures analysis for variance (rmANOVA, patients) or ANOVA (patients vs. controls) to test for global effects. If global effects, e.g. difference between visits, were present, single parameters were post-hoc compared pairwise and were corrected for multiple comparisons using the Bonferroni method. Frequencies are reported numerical.

Pearson correlation coefficients were determined to evaluate whether changes in electrophysiological parameters correlated with clinical response. Linear regression was used to evaluate whether electrophysiological parameters at V0 predicted treatment response in terms of headache days. Results of linear and binary regression analyses are presented using beta coefficients or odds ratios including their 95% confidence interval (95%CI), respectively.

P-values below 0.05 were considered significant, results below 0.001 are not reported exact but as 0.001.

Results

Demographics and clinical response to preventative treatment

We enrolled 22 patients (21 female, mean age 46.2 ± 13.8 years; 4 migraine with aura (MwA)) and 22 matched controls (21 female, mean age 47.6 ± 14.9 years). No patient or control was lost to follow-up, i.e. there were no drop-outs. Twelve patients received Erenumab, five patients Galcanezumab and five patients Fremanezumab monthly for an episodic migraine. Headache diaries yielded a mean headache frequency of 12.4 ± 3.3 days/month, mean duration of 8.0 ± 5.3 h/attack and mean headache intensity of 4.9 ± 1.9 at baseline. Following three months of CGRP mAb treatment, headache frequency (6.6 ± 4.9 days/month, $p<0.001$ vs. V0) and attack duration (5.4 ± 4.2 h/attack, $p=0.014$ vs. V0) significantly decreased, while headache intensity remained unchanged (5.1 ± 2.5, $p=0.96$ vs. V0). In line with headache frequency and attack duration, also MIDAS (V0: 61.7 ± 62.3, V3: 32.2 ± 61.2; $p=0.003$) and HIT-6™ (V0: 66.1 ± 4.9, V3: 54.9 ± 9.2; $p<0.001$) scores improved significantly following three months of treatment. Baseline characteristics or clinical response did not differ significantly between patients who received

CGRP ligand or receptor antibodies. Baseline demographic and headache characteristics were furthermore no predictors of treatment response.

Blink reflex assessments –R2a changes in patients

Results of R2a changes following three months of treatment with CGRP mAbs and their comparison to healthy controls are summarized in Fig. 2. There was a significant global effect for block-wise changes of R2a_s ($F_{(19,597)}$=5.86), p<0.001) and R2a_ns ($F_{(19,597)}$=8.22), p< 0.001) between visits. Post-hoc comparisons revealed that R2a_s significantly decreased in blocks one (-10.2 ± 2.6, p<0.001), two (-6.7 ± 2.8, p=0.028), three (-5.1 ± 2.1, p=0.028) and eight (-4.7 ± 2.1, p=0.033). R2a_ns significantly decreased in blocks one (-8.8 ± 2.6, p=0.003), two (-7.0 ± 2.5, p=0.010), three (-6.0 ± 2.5, p=0.025), eight (-4.4 ± 1.9, p=0.028) and ten (-4.1 ± 1.4, p=0.010).

Blink reflex assessments – R2h changes in patients

Results of R2h changes following CGRP mAb treatment and their comparison to healthy controls are summarized in Fig. 3. Global analysis for habituation only revealed significant changes on the non-stimulated side (R2h_ns; $F_{(19,597)}$=3.07), p<0.001) but effects on the stimulated side (R2h_s) were marginally non-significant ($F_{(19,597)}$=1.46, p=0.095). Thus, only R2h_ns effects were compared and revealed stronger attenuation of subsequent stimuli in blocks six (-1.4 ± 0.5, p=0.007), seven (-1.2 ± 0.4, p=0.010), eight (-1.0 ± 0.5, p=0.034) and ten (-1.0 ± 0.4, p=0.034) at V3 as compared to V0.

Blink reflex assessments – comparison of patients and controls

R2a_s ($F_{(19,420)}$=3.11, p<0.001), R2h_s ($F_{(19,420)}$=2.45, p= 0.001) and R2h_ns ($F_{(19,420)}$=3.16, p<0.001) differed significantly between patients at V0 and controls, while R2a_ns was indifferent ($F_{(19,420)}$=1.22, p=0.234). Neither R2a_s ($F_{(19,420)}$=0.69, p=0.826), R2a_ns ($F_{(19,420)}$=0.29, p= 0.978) nor R2h_s ($F_{(19,420)}$=1.38, p=0.195) differed between controls and patients at V3. There remained a significant global effect for R2h_ns ($F_{(19,420)}$=2.23, p=0.019). For presentational purposes, comparisons to controls are not reported exact but can be found in Figs. 2 and 3.

Electrophysiological parameters as biomarker

Changes of R2h_s (r=0.56, p=0.010) and R2h_ns (r=0.45, p=0.045) in block five significantly correlated with changes in headache frequency, while R2a on neither side was significantly correlated. When correcting for time to the next headache attack, additionally changes of R2h_s (r=0.56, p=0.025) and R2h_ns (r=0.54, p=0.030) in block three significantly correlated with improvement of headache frequency (Fig. 4).

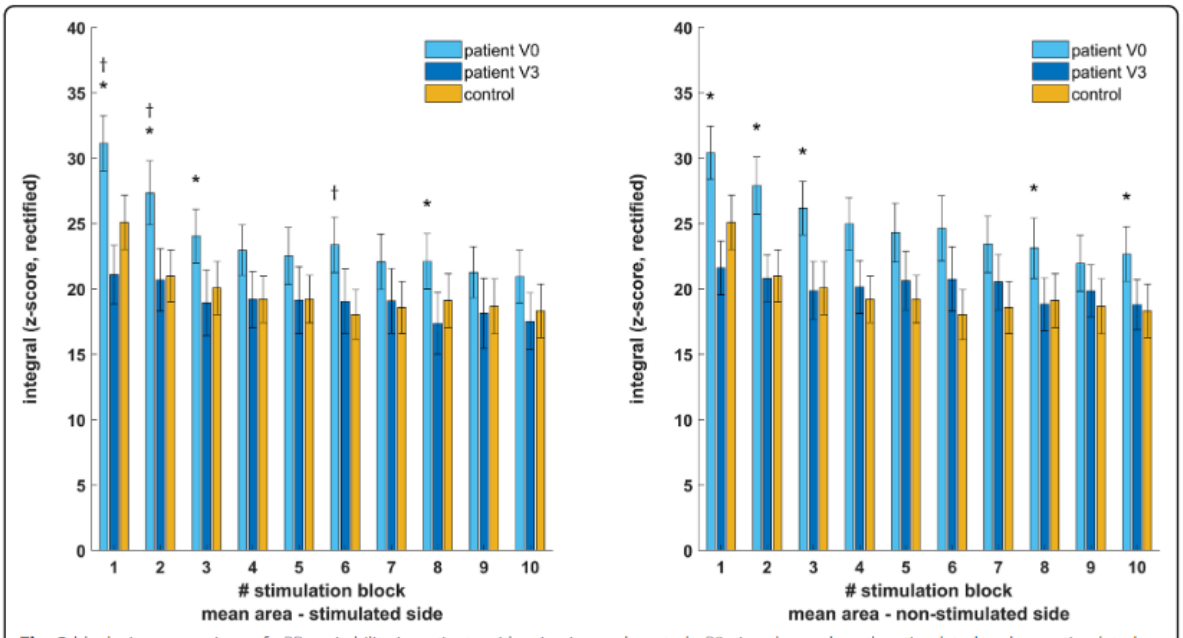

Fig. 2 blockwise comparison of nBR excitability in patients with migraine and controls. R2a is enhanced on the stimulated and non-stimulated side in migraineurs at V0, however only changes on the stimulated were significant given the high variance. These indicators of excessive brain stem excitability normalize after three months of treatment with CGRP mAbs and are then statistically indifferent from controls. * - indicates statistically significant difference between V0 and V3 in migraine. † - indicates statistically significant difference between V0 and controls

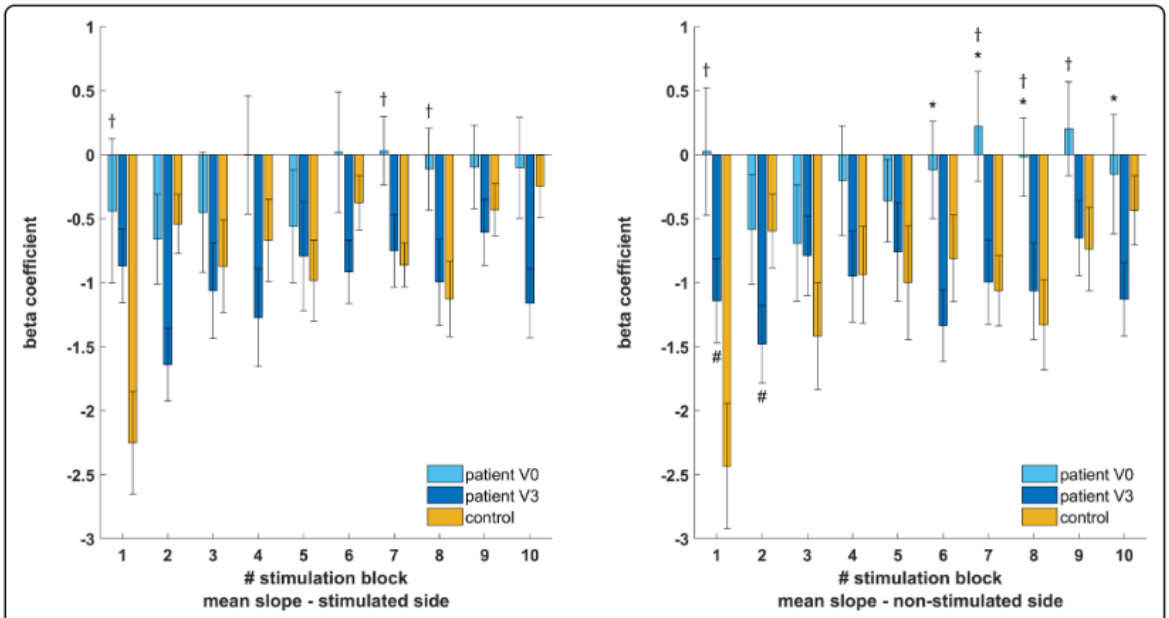

Fig. 3 blockwise comparison of nBR habituation in patients with migraine and controls. R2h is attenuated in migraine and has even a trend towards facilitation in later blocks at V0. After three months of treatment with CGRP mAbs, R2h normalizes and consecutive stimuli are inhibited in all blocks. There remains a significant difference between V3 and controls on the non-stimulated side. * - indicates statistically significant difference between V0 and V3 in migraine. † - indicates statistically significant difference between V0 and controls. # - indicates statistically significant difference between V3 and controls

We furthermore evaluated whether any parameter of R2a or R2h at V0 predicted treatment response. Forward stepwise linear regression revealed that neither R2a nor R2h were predictive. This was irrespective of the use of uncorrected or corrected data, and if reduction in headache days or any binary treatment response were used.

Discussion

We were able to show that brain stem excitability and habituation to painful trigeminal stimulation are impaired in patients with migraine eligible for a course of CGRP mAbs and restored with three months of treatment. Given the significant biological gradient between normalization of nBR habituation and clinical response, treatment with CGRP mAbs can be considered causative for changes of central disease activity based on Bradford Hill criteria [34]. Since CGRP mAbs are understood to act peripherally and nBR changes are tightly associated with central disease activity, our results furthermore provide evidence that treatment with CGRP mAbs may be considered disease modifying as early as three months of treatment.

Comparison to previous studies investigating the blink reflex as a biomarker of preventive treatment

Our literature search revealed only two studies that conducted electrophysiological investigations of the blink reflex to assess central effects of a preventive treatment. Tommaso and Delussi used the nsBR and found that treatment with Topiramate had a small effect on R2a and R2h [35]. Artemenko et al. found that duloxetine normalized the R3 threshold and habituation of the nBR [36]. However, the latter group assessed only patients with chronic migraine and it was shown that the blink reflex may not be a suitable biomarker in these patients since supraspinal structures are possibly more involved in these patients [37].

Ziegeler et al. investigated central effects following treatment with CGRP mAbs [19]. They used event-related functional magnetic resonance imaging and found a reduced hypothalamic activation in treatment responders, which supports the notion of central disease modification. Interestingly, it was shown that there is a close interaction between hypothalamic structures and the TCC in migraine pathophysiology [38]. Hence, our results are possibly a more direct and pain related readout of central effects treatment that extend into diencephalic structures.

There are comprehensive reviews available on electrophysiological methods to investigate changes in the visual, acoustic, sensory and multimodal systems [15, 26]. It remains elusive if treatment with CGRP mAbs also improves disturbed sensory processing in these domains, which was shown for prevention with beta blockers,

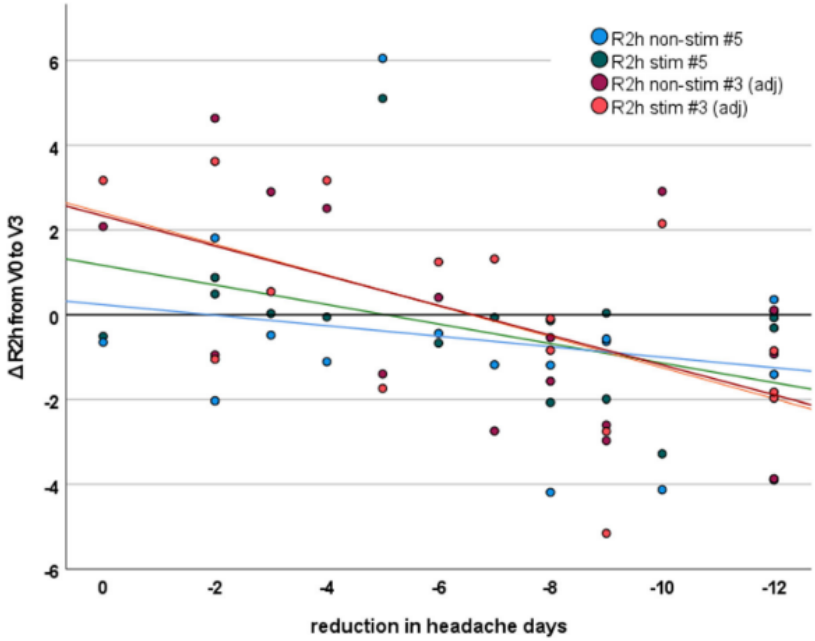

Fig. 4 reduction in headache days as a function of R2h changes after initiation of CGRP mAbs. There is a statistically significant correlation of the change in R2h slope from V0 to V3 on the stimulated and non-stimulated side in blocks three and five. Block three results are adjusted for the time before the next headache attack. Note that the correlation coefficients reported in the results section are by definition standardized while lines plotted here are based on raw data

levetiracetam and flunarizine. Changes of sensory processing in other domains would support the notion of disease modification since migraine is considered a disorder of global sensory processing [20].

Comparison of the nociception specific and nociceptive stimulation

There is a large heterogeneity in the literature considering the use of either the nBR or nsBR in the investigation of migraine pathophysiology. Pharmacological studies have shed light on divergent and shared pathways between both techniques and need to be considered. Migraine-associated changes of the nsBR were found to be restored by treatment with triptanes in two studies [39, 40]. Another study compared the nBR and nsBR using an adenosine receptor agonist, which is considered to inhibit release of neuropeptides on terminal trigeminal nerve fibers including CGRP. This study found that the nsBR but not nBR was changed by application of the agonist [29]. Thus, current understanding is that the nsBR and nBR share common central pathways involving the TCC and reflecting migraine pathophysiology, but the afferent input differs between both variants. The nsBR is largely mediated by Aδ-fibers and the nBR mainly depends on C-fiber activation, which renders the nsBR more susceptible to peripheral CGRP-mediated effects on trigeminal afferent pathways than the nBR. Assessments of the nBR are thus more robust against confounding effects of CGRP mAbs on a peripheral level and better suited to assess central effects in the TCC .

Utility of the nBR as biomarker in clinical practice

We found that changes of R2h correlated with changes of headache frequency. Hence, the nBR can be considered a biomarker by definition of the FDA Biomarker Working Group [41]. While we were able to provide evidence for the nBR as a biomarker to monitor treatment response, our results unfortunately did not reveal any parameter that predicts the treatment response at baseline. Following the evidence that the nsBR is possibly more specific for CGRP-dependent activation of the TCC, it might be better suited to predict treatment response and less suitable for monitoring the treatment (please also see discussion in the previous paragraph). It remains unclear at present if the nBR as monitoring biomarker can predict the risk of relapse after discontinuation of the preventive drug. This would be of significant clinical value since clinical response fades in about one third of patients as early as one month after discontinuation of treatment with CGRP mAbs, less than every second patient sustains a meaningful ≥30% or ≥50%

reduction in headache days and most patients consecutively restart treatment after three months [42–44]. Future studies should thus investigate changes of the baseline nBR during treatment, before and after discontinuation to assess its predictive value. If the nBR was a suitable biomarker, treatment duration might be tailored to individual needs.

Are CGRP mAbs disease modifying?

In the introduction, we summarized that a DMMD should slow down the natural course of the disease. We indeed found that a course of CGRP mAbs not only leads to a clinical response through peripheral antagonism of migraine attacks but restores the brainstem nociceptive system, which is in line with the EMA's definition of disease modification in neurodegenerative disease [13]. On a clinical level, Lipton et al. showed that CGRP mAbs can lead to a reversion from chronic to episodic migraine, which further supports the notion of CGRP mAbs as DMMD since the natural course of episodic migraine is to convert to chronic migraine at a rate of about 5%/year [45]. On the other hand, there is a lack of sustained reduction of headache frequency after discontinuation of treatment, which apparently contradicts disease modification [42–45]. Our study supports the notion of CGRP mAbs as DMMD but future studies need to assess if biomarker changes of central disease activity are sustained in the discontinuation period.

Limitations

We investigated only episodic migraine since at least a proportion of patients with chronic migraine is known to lack a clear interictal phase that impedes electrophysiological assessments outside a migraine attack [25]. Nonetheless, central disease modifying activity should not differ between episodic and chronic migraine since both are known to be ameliorated by CGRP mAbs [3]. Future studies, however, that investigate any variant of the blink reflex as clinical biomarker should include patients with chronic migraine since their disease burden is particularly high and they are more likely to receive a treatment with CGRP mAbs [7, 46]. Subsequent studies should also include repeated measurements of control subjects, since there might be an adaptation or natural fluctuation of the nBR response. This approach would enable a more precise estimate of the sole effect caused by CGRP mAbs. The direction of findings from this study, however, would remain unchanged since we already found a non-physiological nBR response in patients with migraine at baseline, which is not to be expected in controls based on multiple studies using the same protocol [23, 26].

Another limitation is that we cannot exclude non-pharmacological effects on central disease activity. Our patients revealed a treatment response that is in line with what is to be expected, which improved their ability to pursue non-pharmacological interventions such as physical activity and relaxation techniques [47]. Unfortunately, we did not record these interventions but in a study that investigated the nsBR in the context of biofeedback, the authors did not find a change of habituation, which we found to correlate with pharmacological treatment response [35].

Any variant of the blink reflex can be elicited at different interstimulus intervals with shorter intervals causing more habituation [23]. We used an interstimulus interval that was most often used in previous studies and thus enables comparisons to previous studies. We cannot rule out the possibility that shorter interstimulus intervals would have led to different results. Future studies should thus include a set of discrete time intervals.

Conclusions

The correlation of changes of the nBR habituation with clinical response provides evidence for disease modifying potential of three months of treatment with CGRP mAbs. Our findings render the nBR habituation a potential biomarker to monitor treatment response in clinical practice. Unfortunately, we were unable to find that any nBR parameter predicted treatment response. Future studies should evaluate both variants of the BR, i.e. the nBR and nsBR, for their utility as clinical biomarkers to predict treatment response at baseline and to establish the risk of relapse after treatment discontinuation.

Acknowledgements

Not applicable.

Authors' contributions

Conception and design of the study: RF, MK. Review of methods: US, SN. Electrophysiological data acquisition and pre-processing: AT, LK and RF. Clinical data acquisition: RF, SS, AA and MK. Interpretation of results: RF, SN. Drafting the manuscript: AT, RF. All authors reviewed and approved the final version of manuscript.

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Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due to data protection regulations that impede distribution but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was prospectively registered at clinicaltrials.gov (Identifier: NCT04019496) and approved by the ethics committee of the University Medicine Greifswald (Identifier: BB 168/18). All procedures adhered to the *Helsinki declaration* in its latest revision and were conducted in line with current guidelines for *good clinical practice* (ICH E6(R2)). All patients and controls were provided detailed study information and gave their written consent for the study and the use of their data.

Consent for publication
Not applicable.

Competing interests
The author(s) declare(s) that they have no competing interests.

Author details
[1]Department of Neurology, University Medicine Greifswald, Ferdinand-Sauerbruch-Str. 1, 17475 Greifswald, Germany. [2]University Hospital of Old Age Psychiatry and Psychotherapy, University of Bern, Bern, Switzerland. [3]Department of Neurology, Martin Luther University Halle-Wittenberg and University Hospital Halle, Halle (Saale), Germany.

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Publisher's Note

7.2 Publikationen assoziierter Projekte

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Article

Treatment Realities of Headache Disorders in Rural Germany by the Example of the Region of Western Pomerania

Anne Thiele [1], Sebastian Strauß [1], Anselm Angermaier [1], Lara Klehr [1], Luise Bartsch [1], Martin Kronenbuerger [1,2], Sein Schmidt [3] and Robert Fleischmann [1,*]

[1] Department of Neurology, University Medicine Greifswald, 17475 Greifswald, Germany; anne.thiele@stud.uni-greifswald.de (A.T.); sebastian.strauss@uni-greifswald.de (S.S.); anselm.angermaier@uni-greifswald.de (A.A.); lara.klehr@stud.uni-greifswald.de (L.K.); luise.bartsch@med.uni-greifswald.de (L.B.)
[2] Medical School OWL, University of Bielefeld, 33615 Bielefeld, Germany
[3] Clinical Research Unit, Charité Campus Mitte, Berlin Institute of Health, 10117 Berlin, Germany; sein.schmidt@charite.de
* Correspondence: robert.fleischmann@uni-greifswald.de

Abstract: (1) Background: Headache disorders are among the most disabling medical conditions but the supply with experienced providers is outpaced by the demand for service. It is unclear to what extent particularly patients in rural regions are affected by limited access to comprehensive care. Furthermore, it is unknown what role general practitioners (GPs) play in headache care. (2) Methods: First-time consultations to a specialised headache clinic at a tertiary care centre were asked to participate. Their socio-demographic background, general and headache-specific medical history, disability and quality of life (QoL) were assessed. Additionally, 176 GPs in neighbouring districts were contacted regarding headache management. (3) Results: We assessed 162 patients with first-time consultations (age 46.1 ± 17.0 years, 78.1% female), who suffered from migraine (72%), tension type, cluster and secondary headaches (each 5–10%). About 50% of patients received a new headache-diagnosis and 60% had treatment inconsistent with national guidelines. QoL was significantly worse in all domains compared to the general population. About 75% of GPs see headache patients at least several times per week, and mostly treat them by themself. (4) Conclusions: More than every second headache patient was neither correctly diagnosed nor received guideline adherent treatment. Headache-related disability is inferior to what is expected from previous studies. Access to specialised health care is more limited in rural than in urban regions in Germany and GPs request more training.

Keywords: migraine; headache; disability; treatment; health care delivery; health care quality; outpatient; quality of life

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1. Introduction

Migraine and other headache disorders range among the most prevalent and most disabling diseases worldwide [1]. Suffering from a headache disorder significantly impairs multiple domains of personal life such as employment, physical, social and family activities [2] and is associated with substantial costs for health care providers and society [1]. Despite the individual and economic impact of headache disorders, the World Health Organization recognises that "they are under-recognized, under-diagnosed and under-treated" [3]. The unmet medical need was recently confirmed in a German population of migraineurs who utilised a specialised headache clinic in a metropolitan area [4]. About 36% of patients were not treated according to national guidelines and 53% never received a preventive treatment despite clear indication [4]. This finding is particularly surprising given the density of the medical infrastructure in the geographic region assessed and since 90% of the patients previously consulted a general practitioner (GP) and 75% of patients

consulted a neurologist [4]. In line with this notion, the Vancouver Declaration on Global Headache Patient Advocacy found that lifting the burden of headache not only requires effective therapies but that patients should have reliable access to comprehensive medical care [5]. Ineffective delivery of specialised care might be explained by insufficient training of healthcare providers, but also lack of awareness for the incapacitating character of severe headache disorders such as migraine [6]. Insufficient interaction and exchange between general and specialised health care providers may pose another limitation, but this is less well studied. GPs are on the frontlines of primary care and often first approached by headache patients, thus understanding their role in headache care may be a critical step to address missed opportunities. Management of headache disorders in rural areas may be particularly affected by management in primary care since access to specialists is limited.

In order to fill this gap, this study aims to clarify treatment realities of headache disorders in rural Germany and their association with primary care in two steps. We first hypothesise that the lower availability of specialist care in rural regions negatively impacts on the adherence of headache management with national guidelines. This hypothesis is tested by investigating data from a headache population treated in a specialised headache clinic in Western Pomerania, one of the most rural areas of Germany [7], and comparing these results to treatment patterns observed in an urban area [4]. We then conducted an exploratory investigation of routine headache management among regional GPs and discuss their possible contribution to observed treatment patterns.

2. Materials and Methods

The study was approved by the local ethics committee (protocol number BB 161/18) and conducted in line with the Declaration of Helsinki in its latest revision. Data were acquired in a specialised headache clinic, which is affiliated with the Department of Neurology at the University Medicine of Greifswald. The headache clinic provides an outpatient service to headache patients referred for consultation by their primary care physician or medical specialist. Data collection and evaluation required written informed consent from either patients or GPs.

2.1. Part 1—Headache and Sociodemographic Characteristics of First-Time Consultations to the Headache Clinic

All first-time consultations to the headache clinic between August 2018 and December 2019 were considered without exclusion criteria to avoid a selection bias. All patients routinely filled-in a questionnaire as part of their initial evaluation, which allowed for patient self-report of general information about age, gender, social environment, their living situation, family status and profession and their medical history. Additionally, detailed information about their headache disorder was gathered, including duration of the headaches in years, headache days per month, headache duration per attack, family history, previous contacts to specialists and information about the use of acute and prophylactic medication. Moreover, all patients were assessed regarding their functional abilities and quality of life (QoL) utilising the Migraine Disability Assessment (MIDAS) and Patient-Reported Outcomes Measurement Information System Profile 29 (PROMIS-29), which assesses seven QoL domains as well as general QoL [8]. Data obtained provide the treating physician with a bio-psycho-social context of the patient's living situation and conditions, and the headache disorder. First-time consultations usually take about 45–60 min to provide the patient with a solid diagnosis, or suggestions for further diagnostic work-up, and a treatment plan. Furthermore, as part of this study, the headache specialist in charge documented whether or not there was an indication for preventative treatment according to national guidelines and whether or not the indication was met.

2.2. Part 2—Assessment of Routine Headache Management by Primary Health Care Providers

We additionally contacted 176 GPs in the three neighbouring districts of Western Pomerania (Vorpommern-Rügen, Vorpommern-Greifswald, Mecklenburgische Seenplatte) including a consent form and study information. These general practitioners work inde-

pendent of the headache clinic but constitute the majority of primary care physicians that can directly refer their patients for consultation. Their number vastly outpaces that of neurologist or pain specialists in the vicinity. The aim was to further explore the role of GPs as the first contact for patients with headache disorders. We provided a questionnaire with seven multiple-choice questions assessing their routine management of headache patients, including questions about the estimated frequency of patients they treated for headache disorders, how they dealt with particular primary headaches, knowledge of and reasons to consult specialised healthcare providers and their interest in further education. An English translation of the questionnaire can be found as Supplementary Materials Table S1. GPs returned questionnaires anonymously, which was accomplished to ascertain data confidentiality.

2.3. Data Evaluation and Statistics

All patient data were pseudonymised and entered into an electronic data capture system. Data provided by GPs were anonymised and digitalised in analogy to patient data. All descriptive analyses and statistical evaluations were accomplished using Statistical Package for the Social Sciences (SPSS v25.0, IBM, Armonk, NY, USA).

2.4. Evaluation of Data from First-Time Consultations to the Headache Clinic

Patient data were first investigated using descriptive statistics to assess sociodemographic factors (age, gender, living and working situation), substance use (smoking, alcohol, other drugs), headache characteristics (headache history, frequency, MIDAS) and quality of life (PROMIS-29) of patients presenting for the first time to the outpatient clinic. Results from PROMIS-29 evaluations were transformed into population standardised T-scores using the database provided by the German PROMIS national reference center. T-Scores of 50 represent by definition the reference population mean, standard deviations are standardised to scores of 10, i.e., two standard deviations above mean would yield a T-score of 70.

2.5. Statistics of Data from First-Time Consultations to the Headache Clinic

Continuous data were analysed for normal distribution using histogram plots before performing descriptive and inferential statistics. Unless stated differently, normal distribution was confirmed. Sociodemographic factors and substance use were analysed regarding their influence on headache frequency and headache duration using a generalised linear regression model of main effects including nominal and ordinal data as factors and continuous data as covariates. Predictors are presented with their beta coefficient and 95% confidence intervals (95%CI) in square brackets. Medians and interquartile ranges (IQR) of the seven PROMIS domains (i.e., anxiety, depression, fatigue, sleep, physical and social functioning, pain interference) and global QoL score were calculated given that histograms revealed a non-normal distribution of data. One-sample Wilcoxon signed rank tests were used to evaluate whether the headache population's results differ from the nearest T-Score and standardised standard deviation. Finally, we evaluated whether PROMIS results correlated with headache characteristics, and which PROMIS domains correlate most with the MIDAS as a widely used tool to assess disability of migraineurs, using linear analyses and the Pearson correlation coefficient.

2.6. Evaluation and Statistics of Survey Responses from General Practitioners

Descriptive analyses were performed using contingency tables since multiple choice data generally returns response frequencies. Statistical significance of differences of responses were either evaluated using chi-square tests (nominal data, binary responses) or univariate analysis of variance (ANOVA, continuous data).

3. Results

3.1. Part 1—Demographic and Headache Characteristics of First-Time Outpatient Consultations

There were 162 first-time consultations (age 46.1 ± 17.0 years, 78.1% female) in the study period. Detailed patient characteristics are summarised in Table 1.

Table 1. Sociodemographic and headache characteristics of first-time consultations grouped by their headache diagnosis. The vast majority of patients was diagnosed with a migraine. Migraineurs tended to be younger than patients with other primary or secondary headache disorders, however, standard deviations are large and indicate a heterogeneous patient population. The frequency of students among migraineurs was larger than in other headache disorders, which probably explains the lower rate of children. Other sociodemographic characteristics were comparable between groups. Missing values are due to missing data, i.e., patients did not wish to disclose that information to their treating physician.

	Migraine	**Tension-Type Headache**	**Cluster Headache**	**Other Primary, Sedcondary Headache or Facial Pain Syndromes**
Number of patients	116	15	10	21
Age	43.4 ± 16.3	52.0 ± 20.3	54.67 ± 14.6	53.33 ± 15.8
Gender	86% female	64% female	33% female	67% female
Headache days per month	14.57 ± 7.6	23.42 ± 7.7	22.67 ± 8.7	24.75 ± 8.2
Headache duration in years	19.39 ± 13.4	4.75 ± 4.3	22.33 ± 15.8	7.36 ± 11.5
Marital status	Single 31% Married 50% Widowed 1% Divorced 16%	Single 36% Married 43% Widowed 7% Divorced 7%	Single 22% Married 56% Widowed 11% Divorced 11%	Single 16% Married 42% Widowed 0% Divorced 21%
Number of children	1.4 ± 1.2	2 ± 0.8	1.8 ± 1.5	1.9 ± 1.1
Living situation	Alone 17% Shared flat 21% Partner 48% Family 9%	Alone 43% Shared flat 21% Partner 29% Family 0%	Alone 11% Shared flat 33% Partner 56% Family 0%	Alone 23% Shared flat 31% Partner 31% Family 0%
Work status	Employed 35% Retired 19% Student 14% Unemployed 7% Others 14%	Employed 36% Retired 36% Student 7% Unemployed 0% Others 0%	Employed 33% Retired 33% Student 0% Unemployed 11% Others 0%	Employed 36% Retired 32% Student 5% Unemployed 5% Others 0%

Referrals to the headache clinic were carried out by GPs (78.8%), neurologists (17.9%), psychiatrists (1.3%), dentists (1.3%) and gynaecologists (0.7%). The prevalence of primary headaches was 71.8% migraine (22% of these chronic migraine), 9.2% tension-type headache, 6.1% cluster headache, 8.0% other primary headache syndromes and 4.8% secondary head or facial pain syndromes. Seventeen percent of patients presented with a medication-overuse headache. Headache frequency was on average 16.8 ± 8.2 days per month. Patients suffered for 17.1 ± 13.8 years from the headache syndrome leading to the consultation, yet 46% of patients were given a first-ever or new headache diagnosis as a result of the consultation. About 60% of the patients did not receive acute or prophylactic treatment according to national guidelines. 82% of patients met the indication for a prophylactic treatment, but only 52% of these received one. Patients with the correct diagnosis before consultation had significantly higher odds to receive guideline adherent treatment (OR 9.2 [95%CI: 3.7–22.4]).

3.2. Part 1—Influence of Sociodemographic Factors on Headache Frequency

Headache frequency per month was significantly influenced by the living situation. Living with the family was associated with −7.2 [95%CI: −1.1–−13.5] ($p = 0.022$) headache days per month as compared to living alone. Age, gender, family status, number of

children and profession did not influence headache days per month. Being a non-smoker was associated with −3.9 [95%CI: −0.2–−7.7] ($p = 0.042$) headache days per month while alcohol consumption or drug use were no significant predictors.

3.3. Part 1—Disability and Quality of Life in First-Time Outpatient Consultations

The distribution of the MIDAS score was non-normal. Its median value was 42.5 days (IQR 22.5–75.3, range 0–180). The results of the PROMIS evaluations are summarised in Table 2. In brief, patients performed significantly worse in all domains compared to a German reference population, i.e., their T-scores for anxiety, depression, fatigue, sleep disturbance and pain interference were significantly higher and those for physical and social functioning, and global health, significantly lower. More severe headache frequency was negatively correlated with physical ($\rho = -0.25$, $p = 0.005$) and social functioning ($\rho = -0.24$, $p = 0.005$), and positively correlated with pain interference ($\rho = 0.25$, $p = 0.004$). The MIDAS score significantly correlated with all PROMIS domains except for fatigue and sleep disturbance, however correlations with anxiety and depression T-scores were only weak (i.e., $\rho < 0.30$).

Table 2. Quality of life in patients presenting to the specialised headache outpatient clinic. Headache patients were self-administered an assessment of quality of life (QoL) through these patients reported outcome measurement information system profile with 29 items (PROMIS-29), which provides a disease independent estimate of 7 domains of and global QoL. By definition, the population mean is a T-score of 50 and standard deviations are standardised to a T-score of 10 (e.g., a T-score of 70 indicates two standard deviations above population mean). Median T-scores of the headache population were tested for statistical difference against a T-score of 50, i.e., whether headache patients score significantly worse or better than the mean population. Pain interference was also tested against a T-score of 60. We found that headache patients perform significantly worse in all PROMIS domains and that particularly pain interferes with their QoL. */** = difference statistically significant against a T-score of 50 or 60.

	Anxiety	Depression	Fatigue	Sleep Disturbance	Physical Functioning	Social Functioning	Pain Interference	Global Quality of Life
PROMIS T-Score (Median)	55.8 *	53.9 *	56.1 *	56.1 *	45.3 *	44.2 *	63.8 **	45.1 *
PROMIS T-Score (IQR: 25–75%)	51.2–61.4	49–61.8	51–62.7	48.4–61.7	37–56.9	40.5–50	58.5–66.6	40.3–50

3.4. Part 2—Treatment Patterns in Primary Care

About 45% of GPs ($n = 76$) contacted participated in the survey. 72% of GPs reported to treat headache patients either daily (25%) or several times a week (47%). Treatment patterns for individual headache disorders are summarised in Figure 1. In brief, GPs always or often treat migraine and tension type headache by themself, while patients with symptomatic headache syndromes or unknown diagnoses are more likely to be referred to a specialist. Reasons for referral to a specialist other than the headache diagnosis were insufficient treatment response (84%) and patient's request (63%). Lack of therapeutic options (31%) and inability to provide treatment according to guidelines (12%) rarely caused referrals. GPs reported that they would most likely refer headache patients to either a general neurologist (95%) or pain specialist (48%). Only 23% of GPs would refer a patient to a headache specialist, however 61% of GPs reported to know neither a headache specialist nor a specialised headache clinic in their region. About 85% of GPs would appreciate further training for the treatment and diagnosis of headache disorders.

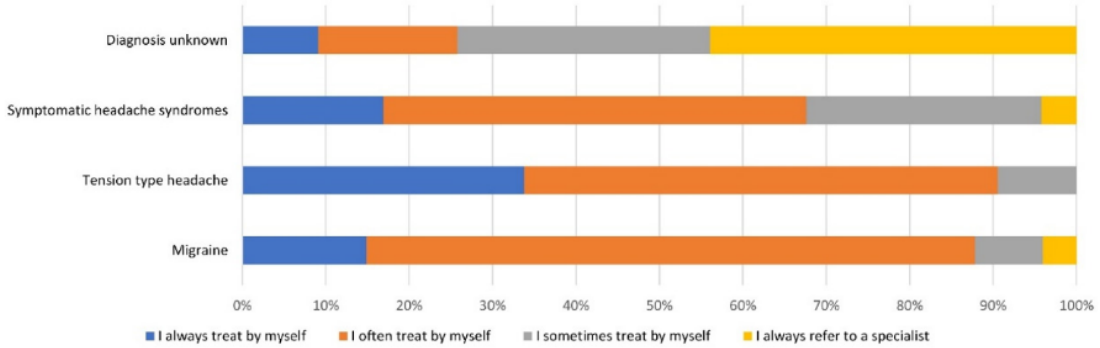

Figure 1. Treatment patterns reported by general practitioners. Seventy-six general practitioners (GP) from the neighbouring districts of the specialised outpatient clinic reported, which patients they usually treat by themselves and which patients they usually refer to a specialist. Migraine is in 86% of cases either always (n = 11) or often (n = 54) treated by general practitioner. Tensions type headaches are equally frequently, i.e., 88%, treated in the majority of cases by the GP. In contrast, patients with symptomatic headaches or an unknown diagnosis are more often not treated by GPs but referred in 30% or 64% of cases, respectively.

4. Discussion

This study conducted in patients presenting to a specialised headache clinic not only replicates evidence for the under-recognition and under-diagnosis of primary headache disorders, but our findings also extend on previous reports by providing insights into predictors of headache frequency and showing that all domains of bio-psycho-social health are affected by headache frequency. Finally, observed treatment patterns in primary care provide possible explanations for inadequate headache care and starting points for alleviating patient burden.

4.1. Comparison to Headache Treatment in Urban Areas of Germany and Internationally

Under-treatment and under-diagnosis of primary headache disorders are well documented phenomena. The range of correct diagnoses in patients ranges internationally from 27% in an Italian multicentre population to 56% in a US population [9,10]. We were unable to find similar data for Germany and thus provide first evidence that the proportion of patients with an adequate headache diagnosis is in the upper international range but equally insufficient. This is even more surprising given that the mean duration patients suffered from their headaches was more than 17 years. The diagnostic delay was accompanied by inadequate acute and prophylactic treatment since patients with a correct diagnosis were 9-times more likely to receive guideline adherent treatment. About 50% of the patients with an indication for prophylactic treatment never received any before consultation in our department. Ziegeler et al. found that even 61% of patients of their urban headache population did not receive a prophylactic treatment despite indication according to national guidelines [4]. This apparent superiority of guideline adherence in our study does not hold true when the total patient population is considered, which renders the proportion of patients without guideline-adherent preventative use in our population even higher, i.e., 39% vs. 34% (see Table 3 for comparison of the studies). The higher rate of medication overuse headaches (17% vs. 9%) furthermore indicates inadequate use of acute medication, which is supported by lack of triptans for acute treatment of migraine attacks. Adding another 10% of patients with inadequate acute medication use, 60% of our patient population did not receive guideline adherent treatment. While Ziegeler et al. did not provide information on acute medication, two Italian studies found that triptan use in migraineurs is suboptimal and one-year persistence is lower than 50% [11,12]. In summary, our data support that an under-treatment of 50–60% of patients should be expected in a German headache population. This is particularly unfortunate because it was shown that adequate treatment can lead to an improvement in more than 70% of patients [4].

Sociodemographic factors did not reveal a pattern that would provide treating physicians with risk factors for the identification of severely affected patients. Yet, we were able to show that being correctly diagnosed is a significant predictor of adequate treatment, and thus screening tools may pose a suitable and viable option to enhance headache treatment. Short instruments such as the ID Migraine™ provide a sensitivity of about 98% for the identification of migraine with only three questions that can be easily implemented in any outpatient setting [13].

Table 3. Overview of the population characteristics investigated in the current study and its comparison to a population in an urban area. It can be seen that patients in the rural area tended to be older, more severely affected in terms of medication overuse and headache days and less likely to receive guideline adherent prophylactic treatment. In apparent contradistinction, the rate of chronic migraineurs seems to be lower. This is resolved by the fact that the current study also investigated other headache disorders, including chronic tension type headache.

	Current Study	**Urban Cohort [4]**
Period of data acquisition	August 2018–December 2019	2010–2018
Number of included patients	162	1935
Age	46.1 ± 17.0 years	37.3 ± 13.3
Gender (female)	78.1%	81.6%
Percentage of migraineurs with chronic migraine	22.0%	29.1%
Headache days/month	16.8 ± 8.2	12.1 ± 9.6
Rate of patients with medication-overuse headache	17.0%	9.2%
Rate of patients NOT receiving preventatives according to guidelines	39%	34%

4.2. *Disability and Quality of Life in First-Time Outpatient Consultations*

Already in 1946, the World Health Organisation defined health "as a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" [14]. In line with this notion, headache patients are not only affected by pain itself but consider their overall health, daily activities, working abilities, social and family life significantly impaired due to their headaches [15]. While headache severity accounts for some of the variance, Malone et al. found that migraineurs are additionally affected by negative life events due to psycho-emotional, e.g., worries to disappoint people, and social-interactive, e.g., impact on professional advancement, stress [16]. Two large studies conducted, the American Migraine Prevalence and Prevention (AMPP) and Chronic Migraine Epidemiology and Outcome (CaMEO) study, evaluated measures of the associated patient burden among migraineurs, which help put our results into context [17,18]. The median MIDAS scores in both studies were 3–7 in episodic and 32–45 in chronic migraineurs. The median MIDAS score in our population was about 43 with a 25% quartile of 23, which indicates that patients presenting for the first time show significantly higher disability than one would expect in a general population of migraineurs [19]. We were able to show that the MIDAS score moderately corelated with physical and social functioning, and pain interference, but that it not sufficiently represents other domains of health. The PROMIS-29 revealed that patients suffer from fatigue and sleep disturbances and are additionally affected by affective disorders. This is expected given a prevalence of depression and anxiety disorders in 40–50% of cases [20]. In summary, 75% of patients revealed a lower global health than the average population. To our knowledge, this is the first study to demonstrate this disease independent multi-domain impairment of QoL in a German population of headache patients. These results underline that patients require specialised treatment to approach all domains of headache-related disability and impaired bio-psycho-social health. Importantly, headache frequency alone did not even show a modest correlation with most of the QoL domains, which additionally highlights the need for specialist care and routine

administration of instruments enabling assessment of these domains [5,21]. Specialists can provide access to multi-modal interventions that were shown to provide moderate to strong effect sizes to enhance affective symptoms, QoL and disability [22].

4.3. Standard of Headache Care Provided by General Practitioners in the Study Population

We were surprised by the high participation rate and the response behaviour of GPs suggests a strong motivation and interest in headache management. This may be due to high frequency that GPs encounter headache patients (that is mostly several times per week) and that treatment seems to be unsatisfactory in some cases. Indeed, another study found that one in twenty patients presenting to the GP in Germany complains about headaches [23]. In contradiction to poor guideline adherence, most GPs treat patients (in particular migraineurs) by themself and incapability of guideline adherent treatment is rarely a reason for GPs to refer a patient to a headache specialist. However, it is important to note that the Eurolight study found that treatment by GPs is superior to self-medication. Additionally, this study showed that having seen a GP for headaches is a predictor for access to specialist care. Furthermore, and as revealed by our study, GPs were highly interested in receiving training about headache management [24]. Yet, treatment patterns did not significantly differ between tension type headache patients and migraineurs in our population, hence strategies to inform GPs about the debilitating character of migraine on multiple domains and to increase their awareness could be important steps for optimising care for headache patients. Cooperative networks including general practitioners, neurologists, pain specialists and associated disciplines are a suitable platform to streamline headache management and provide health care delivery as needed [9].

4.4. Limitations

It remains unclear to what extent our study population represents the general population in the geographical region studied, yet we believe that this bias should be minor since no further exclusion criteria were defined and the study period comprised 12 months, which should account for fluctuations due to GP availability and waiting lists for consultations. It is furthermore possible, that the rate and interest in referrals by GPs to a specialist would have been higher if there was a longer history and knowledge of a specialised headache clinic. The outpatient clinic affiliated with the Department of Neurology was founded about two years before the study period and there was no comparable service available. Hence, treatment patterns may be different with more years having passed. If this was true, it would underline the necessity and impact of specialised headache services for the management in the surrounding area. Another possible limitation is that GPs were not interviewed directly but received only a short questionnaire in order to enhance return rates. This impedes drawing more detailed conclusions from the responses, yet it provides a surprisingly solid starting point to further investigate factors influencing headache management in rural areas and primary care.

5. Conclusions

Our study revealed that about 50–60% of headache patients, 75% of which being migraineurs, presenting to a specialised headache clinic are neither correctly diagnosed nor receive guideline adherent treatment, even though they suffer on average for more than 17 years from headaches. Headache-related disability was inferior to what is expected from previous studies and QoL was below population average on all domains investigated. Patients are generally treated by GPs, indicating that access to specialised health care delivery is worse in rural as compared to urban regions in Germany. GPs are generally interested in and regularly approached for management of headaches. However, GPs request more training and our data support that awareness for the debilitating impact of headache disorders on multiple domains of bio-psycho-social health is required.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/brainsci11070839/s1, Table S1: Questionnaire.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

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Translation and validation of an extended German version of *ID Migraine*™ as a migraine screening tool

Anne Thiele, Sebastian Strauß, Anselm Angermaier, Martin Kronenbuerger, and Robert Fleischmann

Abstract

Background and purpose: Diagnosing a patient with headache as a migraineur is critical for state-of-the-art migraine management. Screening tools are imperative means to improve the diagnostic yield in the primary care settings and specialized clinics. This study aims to translate and assess the diagnostic accuracy of a German version of the *ID Migraine*™ as a widely used and efficient screening instrument.

Methods: The Functional Assessment of Chronic Illness Therapy translation methodology was used to translate the original three-item *ID Migraine*™, including a fourth question for aura, from the English language into the German language. Diagnostic accuracy of the German *ID Migraine*™ and predictors of false screening results were assessed among patients presenting to a headache outpatient clinic of a tertiary care center in Germany over a 6-month period.

Results: The translation procedure yielded a harmonized German *ID Migraine*™ and its diagnostic accuracy was assessed in 105 patients (80 female, 46.5 $\pm$ 17.2 years of age), including 79 patients (75.2%) with migraine. The three-item German *ID Migraine*™ provides a sensitivity of 99%, specificity of 68%, and positive and negative predictive values of 90% and 95%, respectively, using a cutoff of $\geq$2. Positive and negative predictive values in a general headache population are estimated to be 74% and 98%, respectively. The aura question identified 18 out of 20 migraineurs with aura.

Conclusions: The German *ID Migraine*™ is an accurate screening tool for migraine even in a challenging population of a specialized outpatient clinic. Its diagnostic accuracy indicates a potential utility for screening in primary health care.

Keywords

diagnosis, migraine, screening tool

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Introduction

Migraine is a highly prevalent neurological condition, which affects about 10–15% of the world's population and substantially interferes with patients' daily activities and vocational and social life.[1] Furthermore, it is associated with significant costs for the economy, the society, and the health-care system due to loss of productivity, psychiatric comorbidities, and medical complications.[2,3] The availability of novel acute and prophylactic treatment options, including calcitonin gene-related peptide (CGRP) antibodies, and increasing acknowledgment of non-pharmacological treatment strategies lead to a new era of migraine care which enables effective treatment even in the most severely affected patient.[4,5] Unfortunately, the proportion of patients with access to evidence-based management of their migraine is

Department of Neurology, University Medicine Greifswald, Greifswald, Germany

Corresponding author:
Robert Fleischmann, Department of Neurology, University Medicine Greifswald, Ferdinand-Sauerbruch-Str. 1, 17475 Greifswald, Germany.
Email: robert.fleischmann@uni-greifswald.de

Table 1. German version of the *ID Migraine*™ (with original English items).[a]

German translation	English original[b]
Bemerkten Sie während der letzten 12 Monate folgende Begleiterscheinungen zu Ihren Kopfschmerzen:	During the last 12 months, did you have the following with your headache:
(1) Beeinträchtigte Ihr Kopfschmerz für mindestens einen Tag Ihre Fähigkeit zu arbeiten, zu lernen, oder das zu tun, was zu erledigen war?	(1) Your headache limited your ability to work, study, or do what you needed to do for at least 1 day?
(2) Verspürten Sie Übelkeit oder das Gefühl sich übergeben zu müssen?	(2) You felt nauseated or sick to your stomach?
(3) Fühlten Sie sich sehr durch Licht gestört (oder deutlich mehr als ohne Kopfschmerzen)?	(3) Light bothered you (a lot more than when you don't have headaches)?
(4) Hatten Sie kurz vor Beginn dieser Kopfschmerzen Sehstörungen (z.B. Blitze, dunkle Punkte, Flackern)?	(4) Just before these headaches, did you have any visual disturbances (flashes, dark spots, vibrations . . .)?

[a]The left column contains the finalized and harmonized German translations of the instrument. Note that the screening period is extended from 3 months to 12 months and that, in analogy to the French version, the German version includes a fourth question about visual aura phenomena.
[b]Item 4 is not part of the original three-item *ID Migraine*™ and derived from the French version.

limited since two-third of patients are incorrectly diagnosed and only 1 out of 10 migraine patients is seen by a headache specialist.[6] This clearly indicates that comprehensive migraine care does critically depend on not only treatment options but also its access. The first and critical step to improve the situation of these patients is to correctly diagnose migraine. Screening tools are powerful as well as well-appreciated means for this purpose, particularly for the health-care provider in the primary care environment.

The *ID Migraine*™ is an easy-to-use screening tool that identifies migraineurs through three questions with a sensitivity and specificity of about 80% by using the criteria of the second edition of the International Classification of Headache Disorders (*ICHD-2*).[7] *ID Migraine*™ has been translated into several languages and successfully implemented in primary care settings.[7,8] An extended version consists of four items including a question which inquiries about the aura phenomena.[8] Until today, a validated translation of the *ID Migraine*™ into the German language including an assessment of its diagnostic accuracy using *ICHD-3* criteria has not been available. The aim of this study was to fill this gap. Successful validation of this screening tool may enhance its use in German-speaking countries.

Methods

Study population and setting

This prospective study was conducted at the headache outpatient clinic of the University Hospital in Greifswald, Germany, a tertiary care center. Referrals are routinely made by neurologists, general practitioners, and rarely by physicians from other specialties, such as pain specialists. Patients are assessed, diagnosed, and treated by board-certified neurologists with very advanced expertise in headache care. All patients presenting for the first time to the headache clinic within the second half of 2019 were screened and asked to provide written informed consent to participate in this study. Further inclusion criteria were age of ≥18 years and being a native speaker of the German language. There were no exclusion criteria in order to avoid selection bias. The study was approved by the local ethic committee (BB 161/18). Its report adheres to *Standards for Reporting Diagnostic accuracy studies* (STARD).[9]

Translation of the questionnaire

The author of the *ID Migraine*™, Professor R Lipton, kindly authorized its use for the intended purpose of this study. The original version includes three questions about headache characteristics and accompanying symptoms (see Table 1 for original items).[7] In analogy to the French version of the *ID Migraine*™, we included a fourth question about aura symptoms and extended the assessed time period from 3 months to 12 months to account for cases of low attack frequency.[8]

The translation into German was done using the established Functional Assessment of Chronic Illness Therapy (FACIT) translation methodology, which can be found online including a full description of the translation procedure.[10] In brief, three German native speakers (including one with a professional qualification in English language and literature studies) conducted a forward translation from English to German blinded to each other's translations. The three versions were then reviewed by all three and a concerted translation was established. A professional translator, who is also an English native speaker, then performed a back-translation from German into English. The agreement of original *ID Migraine*™ items and back-translated items was assessed by the author of the original English version, Professor R Lipton. Comments were subsequently discussed between the three German translators and a reconciled translation of the established items. The resulting translation was again translated back, evaluated, and approved. The harmonized version finally underwent a cognitive debriefing by 10 individuals, who were asked to rate the clarity and comprehensibility of the German *ID Migraine*™ items.

Data collection and processing

Patients were given the finalized German *ID Migraine*™ as part of their initial assessment at the headache outpatient clinic. They were handed out a printed version including checkboxes to agree or disagree with the four questions about their headaches using a paper-and-pencil method. The results of the questionnaire were pseudonymized and entered along with routine clinical data (patient age, gender, and employment status) and further headache characteristics (disease and attack duration and attack frequency) to an electronic data capture system for statistical analyses.

Statistics

Customized MATLAB scripts (R2018a, Natick, Massachusetts, USA) were used for data preprocessing, which included calculation and storage of binary true and false positive or negative screening results for various cutoffs tested, respectively. Statistical evaluations were done using SPSS (version 25, IBM, Armonk, New York, USA). Results from descriptive statistics are reported as group means $\pm$ standard deviations following confirmation of normal distribution of data. Results from inferential statistics are reported with their appropriate coefficients and, if applicable, odds ratios (OR) including 95% confidence intervals in square brackets and p values denoting the statistical significance. The values of p equal to or lower than 0.05 are considered significant. To address the multiple comparison problem when testing more than one hypothesis, we used the Bonferroni correction method.

Statistical performance of the translated *ID Migraine*™ was evaluated using receiver operating characteristics (ROC). The area under the curve (AUC), sensitivity, specificity, and predictive values were evaluated for the original three- and extended four-item questionnaire using cutoffs of $\geq$2 and $\geq$3 positive answers. Since predictive values critically depend on the disease prevalence in the target population, we additionally calculated predictive values for a migraine prevalence of 48% that is expected in a headache population according to health insurance data.[11,12] Predictors for false positive and negative screening results were evaluated using a generalized linear model with a logit link function and binomial response distribution, and including patient age, gender, attack frequency, disease duration, presence of nausea and/or phono-/photophobia, and employment status as predictive factors. Independence of predictors was confirmed using correlation analyses (see Supplemental Table 1).

Results

The study population consisted of 105 patients (80 female, 46.5 $\pm$ 17.2 years of age). The mean duration of the headache disorder before presentation was 17.9 $\pm$ 13.3 years. Employment status of patients was as follows: 39% employed (n = 41), 2% self-employed (n = 2), 4% unemployed (n = 4), 28% retired (n = 29), 11% students (n = 12), 5% trainees (n = 5), and 11% did not provide an answer (n = 12). Seventy-nine patients (75.2%) were clinically diagnosed with migraine; of these, 27% (n = 21) had a chronic migraine. Other diagnoses were cluster headache (7.6%, n = 8), tension-type headache (4.8%, n = 5), and other headache syndromes (12.4%, including trigeminal neuralgia (n = 3), nummular headache (n = 2), hypnic headache (n = 1), idiopathic intracranial hypertension (n = 2), and other symptomatic headache syndromes (n = 5)).

Translation procedure

The FACIT methodology could be followed without protocol deviations. The finalized translation can be found in Table 1. The introduction sentence was slightly modified in the first reconciliation to better express temporal continuity (use of "während" instead of "in den letzten") and the aspect of conscious perception of headache by the patient ("Bemerkten Sie . . ." instead of "Hatten Sie . . ."). A revision was furthermore necessary concerning the question about nausea and vomiting after the back-translation to properly express the feeling of nausea and/or discomfort in the stomach area in the German language. The remaining three questions could be included without changes after the back-translation. Cognitive debriefing did not reveal any further issues with the translated items but confirmed their intelligibility.

Diagnostic performance of the German *ID Migraine*™

The diagnostic performance and results of the ROC analyses are summarized in Figure 1 and Table 2. The AUC was 0.88 for both, the classic three-item *ID Migraine*™ (excluding the aura question) and the extended four-item version (including the aura question). Further diagnostic measures, however, substantially differed depending on the cutoff and number of items used. A cutoff of $\geq$2 yielded a sensitivity of 99% irrespective of the total number of items while specificity was 68% and thus substantially higher using the three-item instead of the four-item version. Specificity for both, the classic and extended version, was enhanced using a cutoff of $\geq$3 and was 86% while the sensitivity was lower than 80%. Positive and negative predictive values were generally greater than 90% considering the prevalence in the study population, except for negative predictive values using a cutoff of $\geq$3 for both *ID Migraine*™ variants. Calculation of predictive values for a reference population, that is, a general headache population with a migraine prevalence of 48% (see the "Methods" section for details), revealed a positive and negative predictive value of 74% and 98%, respectively, for the three-item *ID Migraine*™ using a cutoff of $\geq$2. Positive predictive values were greater than 80% applying a $\geq$3 cutoff to the classic and

extended version, yet negative predictive values decreased to about 80%. The aura question identified 18 out of 20 patients with migraine with aura. The two unidentified patients suffer from a vestibular and sensory aura with paresthesia, respectively.

Predictors for false positive and negative rates

Neither attack frequency, disease duration, employment status, patient age, nor gender were predictive of false positive or negative screening results. Yet, migraineurs without nausea or vomiting during attacks had higher odds to be classified false negative (OR = 3.66 [1.37–9.74], $p = 0.009$).

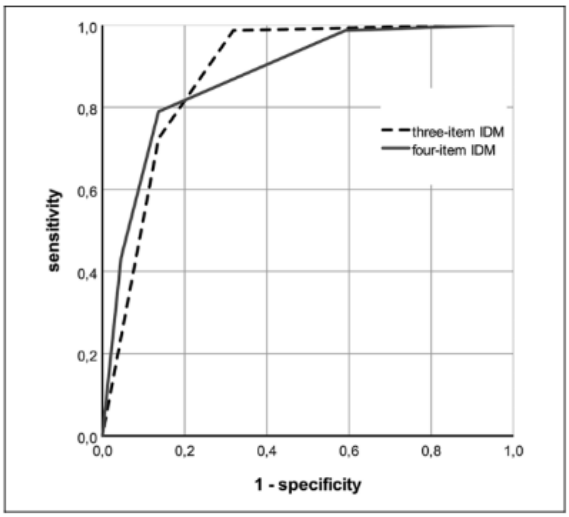

Figure 1. ROC curve illustrating the diagnostic performance of the German *ID Migraine*™ (IDM). Note that ideal operating points of the three- and four-item screening instrument yield a sensitivity of about 80% and specificity of greater than 80%. AUCs are about 0.88 and thus almost equal between both variants. ROC: receiver operating characteristic; AUC: area under the curve.

Discussion

We applied a validated translation methodology to the *ID Migraine*™ as one of the most widely used migraine screening tools and yielded a validated extended German *ID Migraine*™. We furthermore assessed its diagnostic accuracy and found that it is an accurate tool for the detection of migraine, even in a diverse and at times challenging headache population at a specialized headache center. Excellent predictive values, assuming a more general headache population, are encouraging and suggest its use in the primary care setting.

Translation procedure

The FACIT translation methodology is a more rigorous version of the double-back-translation method considered to be superior to single translation and translation by committee.[13] The ultimate goal of any translation is to achieve equivalence between instruments so that any difference detected is the result of true differences and not inherent to the measurement tool.[14] The most difficult item to translate and construct to assess was nausea. This is unsurprising since subjective thresholds for feeling nauseated and its description exist.[15] Multiple quality control measures were implemented to enhance equivalence. Independent review and finally approval of back-translations of the interim and reconciled translations by the author of the original *ID Migraine*™ support the agreement of the versions in both languages (English and German). We furthermore conducted cognitive debriefing interviews of the final German *ID Migraine*™ on an item-by-item basis that did not reveal any translation errors or misinterpretations of the items.

Diagnostic performance

Measures of diagnostic accuracy critically depend on the selection of cutoffs for a positive screening result and the number of items. The original three-item *ID Migraine*™ has shown to provide a sensitivity and a specificity of 81% and 75%, respectively, using a cutoff of ≥2 in a primary care setting.[7] The German *ID Migraine*™ yielded a

Table 2. Diagnostic performance of the German *ID Migraine*™.[a]

					Study population		Reference population	
Items	Cutoff	AUC	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	PPV (%)	NPV (%)
Three items	≥2	0.883	98.7	68.2	90.4	94.5	74.1	98.3
	≥3		72.4	86.4	94.2	50.8	83.1	77.2
Four items	≥2	0.876	98.7	40.9	83.5	91.2	60.1	40.1
	≥3		78.9	86.4	94.6	57.4	84.3	81.6

AUC: area under the curve; PPV: positive predictive value; NPV: negative predictive value.

[a]The diagnostic performance was tested in a specialized tertiary care outpatient headache clinic of a German university hospital. Sensitivities and specificities of the instruments are generally about or greater than 80%, except for a lower specificity when a cutoff of ≥2 is used, particularly in the four-item variant. Predictive values underline the suitability of the three-item German *ID Migraine*™ as a screening tool for migraine in the study population and assuming the migraine prevalence of a general headache population when a cutoff of >2 is used. A score lower than 2 in the three-item variant renders a migraine highly unlikely.

Table 3. Comparison of *ID Migraine*™ translations in five different languages, including the present translation into German.[a]

	German	English	French	Italian	Portuguese
Item number	4	3	4	3	3
Considered time frame (months)	12	3	12	3	3
Cutoff	≥2	≥2	No information	≥2	≥2
Sensitivity/specificity	98.7%/68.2%	81%/75%	87.5%/100%	94%/70%	94%/60%

[a]Note that there are differences in the time frame considered. Irrespective of the number of items, that is, whether or not a fourth aura question is included, the cutoff is generally chosen as ≥2, however, uncertainty remains regarding the French version. Sensitivity is higher than 80% in all and higher than 90% in three translations. Specificity, however, varies significantly and is reported to be between 60% and 100%.

substantially higher sensitivity and fairly lower specificity in a more specialized setting. While differences in the population's migraine prevalence provide an intuitive explanation for this difference, test sensitivity and specificity are generally independent of disease prevalence.[12] This does not exclude the possibility that migraine features are more prominent in a severely affected headache population and therefore enhance the patient's ability to recognize symptoms as belonging to their headaches, thereby enhancing test sensitivity. On the other hand, patients with non-migraine headaches may have more debilitating features than average causing a decreased specificity. This interpretation requires validation in primary care settings, which will also yield a more accurate estimation of the true diagnostic accuracy outside a specialized care facility. Reported diagnostic performances of the *ID Migraine*™ in other languages are, however, closer to our findings and thus leave the possibility that our results are already close to that of a more general headache population. To be more precise, versions in other languages provide a sensitivity and specificity of 87.5% and 100% in the French version, 95% and 72% in the Italian, and 94% and 60% in the Portuguese version.[8,16,17] A summary of the translations' characteristics and their diagnostic performance can be found in Table 3.

It is finally possible that the overrepresentation of chronic migraineurs in our population, that is, 27% in our versus 9% in the general migraine population,[18] needs to be taken into account since chronic migraineurs may present with headache features that differ from a classical migraine. This may therefore impede the detection of these individuals through a screening tool.[19] Unfortunately, the proportion of chronic migraineurs is not reported in most of the previous studies which limits comparison.

Potential applications and value for primary headache care

Migraine management has opened a new era of multimodal non-pharmacological approaches and specific pharmacological treatment options, including highly effective antibodies against CGRP.[5,20] Access to state-of-the-art care for migraine is, however, substantially limited and hinders a more widespread application of guidelines. It is well established that about 40% of patients do not know that they actually suffer from migraine. Additionally, about three-quarters of patients are without access to health-care providers for their headaches, which includes access to primary care physicians and headache specialists.[6,21] A recent study reported that about 70% of migraineurs would benefit from specialized treatment for their migraine.[22] In line with this notion, a simple three-item screening tool with a substantial diagnostic performance to rule in and, importantly, rule out migraine as an underlying primary headache disorder provides the intriguing perspective to enhance recognition and improve management of migraine through its widespread application in primary care settings. Based on a previous study, the time required to fill in the screening form is estimated to be lower than a minute, which underlines its applicability in real-world settings.[23] Future studies may address this point in the German health-care system. Another intriguing application of the screening tool would be its implementation in mobile applications or paper-based patient education material. This could facilitate the identification of potential migraineurs and their referral to pain specialists in areas with limited access or during pandemic situations.

Limitations

The study population included patients presenting to a specialized tertiary care center, which may have caused selection bias. Applying the test in primary care center could therefore affect predictive values since it depends on the prevalence in the target population. It is furthermore important to consider that this study was conducted on a German-speaking population in Germany. This leaves the possibility that the comprehensibility and diagnostic accuracy of the German *ID Migraine*™ may differ in Austria and Switzerland, as other German-speaking countries. Confirmatory studies of the German *ID Migraine*™ in these countries may a viable approach to test its validity.

Conclusions

The German version of the *ID Migraine*™ is a valid and easy-to-use screening tool to identify migraineurs, even in a challenging population of a specialized headache clinic.

Clinical implications

- A German *ID Migraine*™ as migraine screening tool is now available.
- The diagnostic accuracy of the German *ID Migraine*™ underlines its potential utility for primary care settings.

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Supplemental material

Supplemental material for this article is available online.

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7.3 Abbildungsverzeichnis & Tabellenverzeichnis

7.4 Selbstständigkeitserklärung & Anteilserklärung

Hiermit erkläre ich, dass ich die vorgelegte Doktorarbeit mit dem Thema

Untersuchung der Wirkung einer prophylaktischen Therapie der episodischen Migräne mit CGRP-/Rezeptor-Antikörpern auf die dysfunktionelle Schmerzverarbeitung im Hirnstamm

eigenständig verfasst und keine anderen als die im Literaturverzeichnis angegebenen Quellen, Darstellungen und Hilfsmittel benutzt habe. Dies trifft insbesondere auch auf Quellen aus dem Internet zu. Alle Textstellen, die wortwörtlich oder sinngemäß anderen Werken oder sonstigen Quellen entnommen sind, habe ich in jedem einzelnen Fall unter genauer Angabe der jeweiligen Quelle, auch der Sekundärliteratur, als Entlehnung gekennzeichnet. Ich erkläre hiermit weiterhin, dass die vorgelegte Arbeit zuvor weder von mir noch – soweit mir bekannt ist – von einer anderen Person an dieser oder einer anderen Hochschule eingereicht wurde. Darüber hinaus ist mir bekannt, dass die Unrichtigkeit dieser Erklärung eine Benotung der Arbeit mit der Note "nicht ausreichend" zur Folge hat und dass Verletzungen des Urheberrechts strafrechtlich verfolgt werden können.

Greifswald, den 15.04.2024 Unterschrift: 

Publikation des Hauptprojektes:

Anne Thiele, Lara Klehr, Sebastian Strauß, Anselm Angermaier, Ulf Schminke, Martin Kronenbuerger, Steffen Naegel, Robert Fleischmann. Preventive treatment with CGRP monoclonal antibodies restores brain stem habituation deficits and excitability to painful stimuli in migraine: results from a prospective case-control study. The Journal of Headache and Pain (2021), https://doi.org/10.1186/s10194-021-01364-x

Die Promovendin war maßgeblich an der Methodenetablierung sowie Durchführung der Messungen beteiligt. Sie trug zur Datenaufbereitung und -auswertung bei. Die Interpretation der Ergebnisse erfolgte zusammen mit Herrn Dr. Robert Fleischmann. Die Promovendin war am Erstentwurf des Papers sowie allen Revisionen beteiligt. Das finale Paper wurde von allen Autoren revidiert und akzeptiert.

Publikationen assoziierter Projekte:

Anne Thiele, Sebastian Strauß , Anselm Angermaier, Lara Klehr, Luise Bartsch, Martin Kronenbuerger, Sein Schmidt, Robert Fleischmann. Treatment Realities of Headache Disorders in Rural Germany by the Example of the Region of Western Pomerania. Brain Sciences (2021). https://doi.org/10.3390/brainsci11070839

Die Idee zu dem Projekt und die Projektplanung entstand zwischen der Promovendin und Herrn Dr. Robert Fleischmann. Die Promovendin entwickelte den Fragebogen zusammen mit Herrn Dr. Robert Fleischmann. Sie führte die Befragungen durch und war maßgeblich an der Datenaufbereitung und -auswertung beteiligt. Die Promovendin verfasste den Erstentwurf und war an der Revision beteiligt. Das finale Paper wurde von allen Autoren revidiert und akzeptiert.

Anne Thiele, Sebastian Strauß, Anselm Angermaier, Martin Kronenbuerger, and Robert Fleischmann. Translation and validation of an extended German version of ID Migraine™ as a migraine screening tool. Cephalalgia Reports (2020). https://doi.org/10.1177/2515816320962773

Die Idee zu dem Projekt und die Propjektplanung entstand zwischen der Promovendin und Herrn Dr. Robert Fleischmann. Die Promovendin war maßgeblich an der Datenakquise, -aufbereitung und -auswertung beteiligt. Sie verfasste den Erstentwurf und war an der Revision beteiligt. Das finale Paper wurde von allen Autoren revidiert und akzeptiert.

Unterschrift der Doktorandin: …Anne Thiele……

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