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Evaluation klinischer und morphologischer Merkmale bei zerebellären Syndromen mittels MRT-Bildgebung und Mobilitätsparametern

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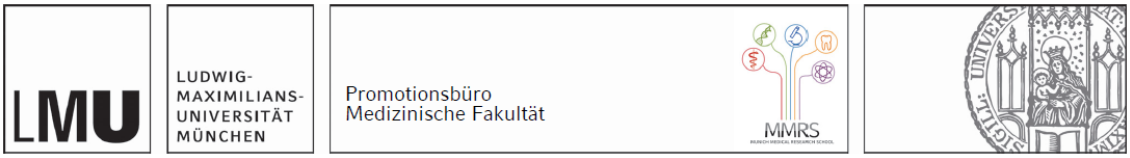
1. Affidavit



Eidesstattliche Versicherung

von

Anna Huppert

Ich erkläre hiermit an Eides statt, dass ich die vorliegende Dissertation mit dem Titel:

Evaluation klinischer und morphologischer Merkmale bei zerebellären Syndromen mittels MRT-Bildgebung und Mobilitätsparametern

selbständig verfasst, mich außer der angegebenen keiner weiteren Hilfsmittel bedient und alle Erkenntnisse, die aus dem Schrifttum ganz oder annähernd übernommen sind, als solche kenntlich gemacht und nach ihrer Herkunft unter Bezeichnung der Fundstelle einzeln nachgewiesen habe.

Ich erkläre des Weiteren, dass die hier vorgelegte Dissertation nicht in gleicher oder in ähnlicher Form bei einer anderen Stelle zur Erlangung eines akademischen Grades eingereicht wurde.

München, den 10.07.2024

Anna Huppert

2. Abkürzungsverzeichnis

ABC-d	Activities-specific Balance Confidence Scale
DBN	Downbeatnystagmus
FES-I	Falls Efficacy Scale-International
FGA	Functional Gait Assessment Score
MoCA	Montreal Cognitive Assessment
MRT	Magnetresonanztomographie
PET	Positronenemissionstomographie
SAOA	Sporadic adult-onset ataxia
SARA	Scale for the assessment and rating of ataxia
SCA	Spinozerebelläre Ataxie
SF-12	Short-Form Health Survey (SF-12)
SPECT	Single Photon Emission Computed Tomography
TUG	Timed up and Go Test
ZNS	Zentrales Nervensystem

3. Publikationsliste

Die vorliegende kumulative Dissertation umfasst zwei bereits publizierte Arbeiten:

Conrad J.*, **Huppert A.*,** Ruehl R. M., Wuehr M., Schniepp R., Eulenburg P. (2023) **Disability in cerebellar ataxia syndromes is linked to cortical degeneration**. *J. Neurol., 270: 5449–5460.* https://doi.org/10.1007/s00415-023-11859-z

*geteilte Erstautorenschaft

Schniepp R., **Huppert A.,** Decker J., Schenkel F., Dieterich M., Brandt T., Wuehr M. (2023). **Multimodal mobility assessment predicts fall frequency and severity in cerebellar ataxia.** *The Cerebellum, 22: 85–95.* https://doi.org/10.1007/s12311-021-01365-1

Weitere bereits publizierte Arbeiten, an denen als Koautorin mitgewirkt wurde:

Wuehr M., **Huppert A.,** Schenkel F., Decker J., Jahn K., Schniepp R. (2020). **Independent domains of daily mobility in patients with neurological gait disorders.** *J. Neurol., 267 (Suppl 1): S292-300.*x https://doi.org/10.1007/s00415-020-09893-2

Schniepp R., **Huppert A.,** Decker J., Schenkel F., Schlick C., n Rasoul A., Dieterich M., Brandt T., Jahn K., Wuehr M. (2021). **Fall prediction in neurological gait disorders: differential contributions from clinical, gait analysis, and daily-life mobility monitorin.** *J. Neurol., 268: 3421-3434.* https://doi.org/10.1007/s00415-021-10504-x

Schnabel L., Wuehr M., **Huppert A.,** Bardins S., Brandt T., Huppert D. (2022). **Age-dependent perturbation of the perceptual and postural vertical by visual roll vection and susceptibility to motion sickness in children.** *J. Neurol., 269: 5724–5730.* https://doi.org/10.1007/s00415-022-11017-x

4. Beitrag zu den Veröffentlichungen

Grundlage der vorliegenden kumulativen Doktorarbeit sind zwei Publikationen, die sich mit klinischen und morphologischen Merkmalen zerebellärer Syndrome mittels MRT-Bildgebung und Mobilitätsparametern beschäftigen.

4.1 Beitrag zur Publikation "Disability in cerebellar ataxia syndromes is linked to cortical degeneration"

Die Arbeit „Disability in cerebellar ataxia syndromes is linked to cortical degeneration“ wurde am 22. Juli 2023 online im “Journal of Neurology” veröffentlicht und liegt mittlerweile auch in gedruckter Version vor. In der Studie wurden die syndrombezogenen, klinisch relevanten Beeinträchtigungen von 30 Patienten mit Kleinhirndegeneration unterschiedlicher Ätiologie - DBN, SCA, SAOA - charakterisiert und miteinander korreliert. Bei allen Patienten sowie einer Kontrollgruppe von 29 gesunden, alters- und geschlechtsgleichen Kontrollpersonen ohne neurologische Erkrankungen in der Anamnese wurde eine hochauflösende, strukturelle MRT-Bildgebung auf einem 3-T-MRT-Scanner unter Verwendung voxel- und oberflächenbasierter Morphometrie durchgeführt, um die strukturellen Veränderungen im Kleinhirn bei den drei verschiedenen Gruppen von Kleinhirnerkrankungen untereinander sowie mit gesunden Kontrollprobanden vergleichen zu können. Anschließend wurden die objektivierten strukturellen Veränderungen im Zerebellum und Kortex mit den Ergebnissen aus den klinischen Untersuchungen und Messungen - standardisierte Anamnese inklusive Erhebung des Mobilitäts- und Sturzstatus, Komorbiditäten, subjektives Stabilitätsempfinden mittels FES-I, basale kognitive Leistungsfähigkeit mittels MoCA, Bewertung des Schweregrades der Ataxiesymptomatik mittels SARA-Score, Gangleistung, neurologischer und somatischer Status und Neuroorthoptik - korreliert, um mittels dieser Methoden Zusammenhänge zwischen morphologischen Befunden in der Bildgebung und der funktionellen Beeinträchtigung der Patienten herstellen zu können.

Die Zusammenarbeit zwischen der Doktorandin Frau Anna Huppert und Herrn Dr. med. Julian Conrad entstand durch das gemeinsame Forschungsgebiet der Untersuchung von Bildgebungsdaten und klinischer Evaluation bei Patienten mit Kleinhirnerkrankungen. Beide Autoren leisteten einen gleichwertigen Beitrag zu der Arbeit „Disability in cerebellar ataxia syndromes is linked to cortical degeneration“. Die Doktorandin führte selbstständig die Patientenrekrutierung im Deutschen Schwindel- und Gleichgewichtszentrum sowie die gesamte klinische und MRT-Datenerhebung durch und wertete die klinischen Ergebnisse vollständig statistisch aus. Herr Dr. med. Julian Conrad führte die statistische Analyse der Daten aus der strukturellen Bildgebung durch. Die Interpretation der Ergebnisse erfolgte zum überwiegenden Teil durch die Doktorandin. Das Manuskript wurde in Zusammenarbeit mit Herrn Dr. med. Julian Conrad erstellt, wobei Frau Anna Huppert den Bereich Einleitung, Methoden und Diskussion und Herr Dr. med. Julian

Conrad Ergebnisse und Diskussion verfasste. Schließlich folgte eine gemeinsame Überarbeitung und Zusammenführung nach Rücksprache mit dem Betreuer sowie den Ko-Autoren bis zur finalen Version. Aus diesem Grund handelt es sich bei dieser Veröffentlichung um eine geteilte Erstautorenschaft.

4.2 Beitrag zur Publikation "Multimodal mobility assessment predicts fall frequency and severity in cerebellar ataxia"

Die Arbeit „Multimodal mobility assessment predicts fall frequency and severity in cerebellar ataxia“ wurde am 4. Februar 2022 im Journal „The Cerebellum“ online und im Jahr 2023 gedruckt veröffentlicht. Schniepp et al. untersuchten Auftreten, Schweregrad und Folgen von Stürzen bei 93 Patienten mit erblichen, sporadischen und sekundären Formen zerebellärer Ataxien in einem prospektiven Zeitraum von 6 Monaten. Mithilfe multivariater logistischer Regressionsanalysen wurde evaluiert, inwiefern eine multimodale klinische und funktionelle Beurteilung sowie Mobilitätsmessungen, die sowohl als Ganganalyse im Labor als auch mittels Inertialsensoren im Alltag durchgeführt wurden, den Sturzstatus, die Sturzhäufigkeit und den Schweregrad von Stürzen im Lebensumfeld der Patienten vorhersagen können.

Die Doktorandin Frau Anna Huppert führte einen großen Teil der Datenerhebung sowie statistischen Auswertung selbstständig durch. Anschließend folgten die Interpretation der erhobenen Daten und die kritische Auseinandersetzung mit dem Entwurf und dem Manuskript im Austausch mit dem Erstautor und den weiteren Ko-Autoren.

5. Einleitung

5.1 Zerebelläre Ataxiesyndrome

5.1.1 Klinische Einführung

Ohne die dem griechischen Wort ἀταξία ursprünglich zugrundeliegende konkret moralisch-militärische Bedeutungskomponente von Zuchtlosigkeit und Insubordination wird in der allgemeinen Begrifflichkeit von Ataxie als einer Unordnung der neurologische Bedeutungsinhalt unmittelbar erkennbar (Klockgether 2010). Bezogen auf die komplexen koordinativen zerebellären Funktionen, also die Sicherstellung geordneter Bewegungsabläufe, meint Ataxie durch Läsionen in für jene Funktionen essentiellen neuronalen Strukturen verursachte Beeinträchtigungen von Statik und Motorik. Klinisch wird mit diesem Begriff übergeordnet eine Gruppe von Bewegungsstörungen bezeichnet, die neben dem häufigen zerebellären Ursprung beispielsweise auch durch spinale und primär frontale Läsionen bedingt sein können (Berlit 2020).

Die bekannten klinischen Symptome der Ataxie sind Gangstörungen, Standunsicherheit, dyskoordinative Bewegungen der Gliedmaßen, Dysmetrie, Dysdiadochokinese, Dysarthrophonie, Dysphagie und okulomotorische Symptome wie sakkadierte Blickfolge und pathologische Nystagmusformen wie Blickrichtungs- oder Downbeatnystagmus, wobei die motorisch- muskulären Parameter der ausführenden Muskelgruppen wie Trophik, Kraft und Tonus unauffällig erhalten sind. Die symptomatologischen Facetten ergeben sich aus der jeweiligen Lokalisation des pathologisch veränderten neuronalen morphologischen Substrats (Berlit 2020; Jacobi und Minnerop 2021).

Neben den zentralen Störungen der Koordination können auf der Grundlage eines sehr breiten Spektrums ataktischer Syndrome im Verlauf weitere, über die Kernsymptomatik der Ataxie hinausgehende nicht-zerebelläre Symptome hinzukommen. Dazu gehören kognitive Defizite bis hin zu demenziellen Syndromen, überdies Hirnnervensymptome, Polyneuropathien, extrapyramidale und pyramidale Zeichen wie Spastizität, Tremor, Rigor und Dystonie, die auf neurodegenerative Prozesse multipler Hirnregionen außerhalb des Cerebellums, wie Cortex, Hirnstamm und Rückenmark, sowie auf Läsionen kortikospinaler Projektionen zurückzuführen sind (Berlit 2020; Jacobi und Minnerop 2021).

5.1.2 Nosologie und Klassifikation

Zerebelläre Ataxien sind eine sehr heterogene Gruppe, die sowohl Erkrankungen genetischen Ursprungs als auch non-hereditäre Formen einschließt. Nach aktuellen ätiologiebasierten Klassifikationen lassen sich Ataxien in drei große Gruppen unterteilen: durch exogene oder endogene Faktoren erworbene, sekundäre Ataxien ohne genetische Ursachen, hereditäre Ataxien und nicht hereditäre, degenerative Ataxien (Klockgether 2010).

Bei den erblichen Formen der Ataxien wird ein autosomal-dominanter Erbgang von einem autosomal-rezessiven unterschieden. Die spinozerebellären Ataxieformen werden ebenso autosomal-dominant vererbt wie die episodischen Ataxien. In die Gruppe der autosomal-rezessiv vererbten Ataxieformen gehören unter anderem die Friedreich-Ataxie, die Ataxia teleangiectatica und weitere seltene Ataxieformen wie die Refsum-Krankheit und die Abetaliproteinämie. Daneben gibt es eine X-chromosomal vererbte Form beim Fragilen X-Tremor-Ataxie-Syndrom (Diener et al. 2018).

Nosologisch werden die hereditären Formen der Ataxien in der Internationalen Klassifikation von Krankheiten der Weltgesundheitsorganisation unter die „Vorwiegend das Zentralnervensystem betreffende Systematrophien“ subsumiert, während die nicht erblichen Formen in „Symptomatische Ataxien“ bei den jeweiligen Grunderkrankungen wie beispielsweise alkoholische oder durch andere neurotoxische Substanzen verursachte Kleinhirndegenerationen, paraneoplastische Syndrome, durch Malnutrition oder -absorption ausgelöste Vitaminmangelsyndrome, Wernicke-Enzephalopathie (Vitamin B1), funikuläre Myelose und Enzephalopathie (Vitamin B12), Zöliakie (Vitamin E) eingeordnet werden. Die gleiche klassifikatorische Kategorie gilt für ataktische Syndrome im Rahmen oder als Folge von ZNS-Infektionen, beispielsweise durch Varizellen, Epstein-Barr-Virus, Treponema pallidum verursacht oder auch die Creuzfeldt-Jakob-Erkrankung (ICD-10-GM-2023: ICD-10-GM - icd-code.de 2023).

Eine weitere nicht erbliche Ataxieform ist die als sporadische Ataxie des Erwachsenenalters (SAOA) bezeichnete Manifestation, bei der weder eine klare genetische Charakterisierung möglich ist noch sekundäre ätiologierelevante Faktoren gefunden werden können. Sie wird als Ausdruck degenerativer zerebellärer Prozesse gesehen. Ebenfalls als degenerative Ataxieform wird der zerebelläre Typ der Multisystematrophie eingeordnet, bei der neben der zerebellären Ataxie auch weitere Symptome wie Parkinson-Zeichen, Pyramidenbahnzeichen und autonome Funktionsstörungen auftreten können (Diener et al. 2018).

Gleichfalls Ausdruck eines zerebellären degenerativen Prozesses, der häufig mit einer Ataxiesymptomatik einhergeht, ist das DBN-Syndrom, der häufigste erworbene Fixationsnystagmus und in seiner syndromalen Ausgestaltung eine Kombination aus visueller und vestibulo-zerebellärer Ataxie, die sich in einer Fallneigung nach hinten, Vorbeizeigen nach oben bei Zielbewegungen und Störung der vertikalen Blickfolge manifestiert. Das klinische Syndrom des DBN wird überdies bei vaskulär-zerebellären Läsionen, vestibulärer Migräne, Intoxikationen, multipler Sklerose, Vitamin-B12 Mangel und auch den hereditären Ataxieformen beobachtet (Strupp et al. 2022).

5.1.3 Epidemiologie

Epidemiologische Daten über die Gesamtgruppe der Ataxien gibt es nachvollziehbar aufgrund des breiten ätiologischen Spektrums von erblichen, nicht erblichen und erworbenen Ataxien nicht.

Auf der Grundlage weltweiter Erhebungen wurde die globale Prävalenz spinozerebellärer Ataxien zwischen 1-6/100 000 veranschlagt (Brooker et al. 2021). Generell ist von einer hohen Prävalenzvarianz auszugehen (Ruano et al. 2014). Weitere Studien zur Häufigkeit der autosomal-dominant vererbten zerebellären Ataxien fanden eine Prävalenz von 2,7/100 000 und bei der autosomal-rezessiv vererbten Form von 3,3/100 000 (Salman 2018). Die Heterogenität im Hinblick auf die Prävalenz spinozerebellärer Ataxien und die regionale Verteilung der Subtypen wurde in einer Literaturübersicht über die Jahre 1995-2017 wiederum bestätigt (Mattei et al. 2023). Zur Epidemiologie der SAOA wurden in Übereinstimmung mit klinischen Erfahrungen in regionalen europäischen Untersuchungen Prävalenzwerte von 6,9-8,4/100 000, also deutlich höher als bei den hereditären Formen, berichtet (Klockgether 2012).

Die statistische Dignität der Prävalenzdaten sieht sich einer Reihe von Einschränkungen gegenüber. Trotz relevanter diagnostischer Fortschritte bei der genetischen Charakterisierung, die die diagnostischen Unsicherheiten vor dem Hintergrund der großen klinischen Varianz dieser Erkrankungsformen erheblich reduzierte, ist die hereditäre Untergruppe von Ataxien insgesamt eine relativ seltene Erkrankung. Unsicherheiten in der Abgrenzung gegenüber ataktischen Syndromen sekundärer Genese bestehen jedoch weiterhin. Die Erkrankungsgruppe zeigt genetisch eine erhebliche Heterogenität. Die genetische Verifizierung klinisch als typisch erscheinender Störungsbilder erfolgt in epidemiologischen Studien mitunter nicht oder ist nicht nachvollziehbar. Darüber hinaus ist die Varianz des Symptombildes, des Verlaufs, sowie der individuellen Krankheitsschwere groß. Diese Konstellation hat zu einer kritischen und relativierenden Bewertung epidemiologischer Daten für erbliche und sporadische Ataxien generell geführt (Ruano et al. 2014; Brooker et al. 2021).

Dazu kommen in den Studien uneinheitlich definierte Ein- beziehungsweise Ausschlusskriterien, abweichende Rekrutierungsstrategien der Studienteilnehmer wie Feldstudien, klinische Patientenpopulation und Inanspruchnahmepopulation genetischer Abteilungen. Darüber hinaus spielen eine Reihe von unter anderem demographischen Variablen bei der Studiendurchführung und Teilnehmerauswahl eine Rolle. Hier sind geographische Situierung, Ethnie, Verwandtschaftsgrad, angeborene Risikofaktoren, Alter bei Erkrankungsbeginn, sowie Krankheitsdauer und Schwere mit Auswirkungen auf die Generativität und generell Erreichen des fortpflanzungsfähigen Alters zu nennen (Salman 2018). Dass die Prävalenz im Allgemeinen mit dem Alter zuzunehmen scheint, könnte auf blande Verlaufsformen wie auch einen späteren Erkrankungsbeginn mit milderen Verläufen hinweisen. Auch dieses wird als Hintergrund der weltweit gefundenen hohen Varianz der genetischen Subtypen und klinischen Erscheinungsformen diskutiert (Erichsen et al. 2009).

5.1.4 Diagnostik

5.1.4.1 Klinik

Typische Erscheinungsbilder ataktischer Syndrome stellen die rein klinische Einordnung in der Regel nicht vor Probleme. Wie bei vielen Erkrankungen ist die klinische Symptomatik für sich genommen oft ebenso heterogen wie ihre Auswirkungen auf unterschiedliche Funktionalitätsbereiche der Betroffenen. Bei Patienten mit unterschiedlichen Formen zerebellärer Ataxien sind Gangstörungen eine häufige und beeinträchtigende Komplikation und wirken sich erheblich auf die Fähigkeiten der Patienten zur unabhängigen Lebensführung und die Lebensqualität aus (Buckley et al. 2018). Wesentliche Folge eines eingeschränkten Gehvermögens bei zerebellärer Ataxie ist ein erhöhtes Risiko für Stürze, welche häufig mit sekundären Komorbiditäten und dem Verlust der funktionellen Unabhängigkeit verbunden sind (Schniepp et al. 2016; Schlick et al. 2017). Insofern ist es naheliegend, die Diagnostik über die phänomenologische, klinisch-qualitative Definition hinaus zu erweitern. Im Fokus sollten dabei also innerhalb der betroffenen Patientengruppe mögliche risikoerhöhende Faktoren der Gangstörung wie ätiologische Zuordnung, objektivierte Charakterisierung des individuellen Mobilitätsvermögens sowie Identifikation weiterer prädiktiver Variablen, die das Sturzrisiko bedingen, stehen (Aizawa et al. 2013; Silva et al. 2019). Dass einer auf diese Weise ermittelten Risikogruppe im Hinblick auf interventionelle und präventive Maßnahmen zur Verhinderung von Stürzen und sturzbedingten Verletzungen besonderes klinisches und therapeutisches Augenmerk zu widmen wäre, erscheint folgerichtig (Fonteyn et al. 2010).

Im Einzelnen umfasst die klinische Diagnostik neben einer unabdingbaren Erhebung der Medikamentenanamnese eine standardisierte somatisch-neurologische Untersuchung, in die eine Erhebung der Gehfähigkeit und der funktionellen Mobilität beispielsweise mittels TUG und FGA eingehen (Podsiadlo und Richardson 1991; Thieme et al. 2009). Besonderes Augenmerk gilt einer differenzierten Anamnese vorausgegangener Sturzereignisse nach Frequenz und Schwere, mithilfe standardisierter Untersuchungsinstrumente wie der Hopkins-Falls-Grading-Scale (Davalos-Bichara et al. 2013). Weitere anamnestische Informationen können durch Patientenbefragungen zum subjektiven Stabilitätsempfinden mittels FES-I und ABC-d gewonnen werden (Greenberg 2012; Powell und Myers 1995). Kognitive Parameter können beispielsweise mit dem MoCA-Test, sowie Parameter zur Lebensqualität mit dem SF-12 erfasst werden (Fisher und Li 2004; Nasreddine et al. 2005). Der SARA-Score beurteilt den Schweregrad der Ataxiesymptome (Schmitz-Hübsch et al. 2006). Ein objektivierendes Verfahren der Gehfähigkeit ist die Ganganalyse im Labor, bei der verschiedene räumlich-zeitliche Gangparameter quantifiziert werden. Um Mobilitätsbeeinträchtigungen im Alltag zu evaluieren, wurden Messtechniken entwickelt, mithilfe derer Mobilitätsparameter wie Bewegungsintensität, Bewegungsumfang und Gehverhalten exemplarisch aufgezeichnet und ausgewertet werden können (Lord et al. 2011).

Da insbesondere spinozerebelläre Ataxien progrediente Erkrankungen sind, ist die langstreckige ärztlich-medizinische Verlaufsbegleitung von besonderer Bedeutung, um prognostische Aussagen über Progredienz und etwaige Auswirkungen auf die Lebenserwartung treffen zu können (Jacobi et al. 2023). Im Rahmen großer Kohortenstudien (z.B. EuroSCA) wurden mittels inzwischen gut validierter, reliabler und weit verbreiteter Untersuchungsinstrumente wie dem SARA-Score für unterschiedliche Subtypen variierende Verlaufsformen gefunden (Jacobi et al. 2022). Überdies zeigten global durchgeführte epidemiologische Studien abweichende Progredienzgeschwindigkeiten sowohl bei den einzelnen Subtypen als auch in der geographischen Verteilung (Klockgether 2012). Vor diesem Hintergrund ist nicht nur die Initialdiagnostik bedeutsam, sondern gleichfalls eine intermittierende Bewertung der Krankheitsschwere, um am Krankheitsverlauf orientierte adäquate therapeutische Maßnahmen implementieren zu können.

5.1.4.2 Genetik

Waren Diagnostik und nosologische Klassifikation zerebellärer Ataxien aufgrund heterogener klinischer Erscheinungsbilder und der relativen Seltenheit der Erkrankung nicht zuletzt im Hinblick auf die Durchführung von epidemiologischen und Verlaufs- Studien wenig valide und reliabel, wurden sie mit der genetischen Differenzierung der hereditären Ataxien auf eine neue Grundlage gestellt (Ruano et al. 2014; Harding 1983). Unterschied Harding ursprünglich noch 3 Formen spinozerebellärer Ataxien wurden mit den in den letzten Jahrzehnten entwickelten Methoden genetischer Sequenzierung bei einer hohen Forschungsdynamik weiterer Typisierungen inzwischen 48 Subtypen spinozerebellärer Ataxien charakterisiert und nach der Reihenfolge ihrer Identifikation der zugrunde liegenden Mutation durchnummeriert (Brooker et al. 2021; Scott et al. 2020). Bei einem vielfältigen Mutationsspektrum über die Gesamtheit spinozerebellärer Ataxien genetischer Ätiologie ist als die häufigste Ursache eine Ausdehnung der CAG-Trinukleotid-Wiederholungen gefunden worden, die einen Polyglutaminabschnitt in Proteinen kodieren. Diese Formen, als SCA 1,2,3,6,7,17 bezeichnet, machen mehr als die Hälfte der bekannten spinozerebellären Ataxien aus und sind genetisch am besten charakterisiert (Brooker et al. 2021). Generell können die genetisch verursachten SCA-Formen in zwei große Subgruppen eingeteilt werden: Mutationen, die mit Ausdehnung der genannten Trinukleotid-Wiederholungen einhergehen und solche ohne diese Charakteristik (Klockgether et al. 2019).

Die Diagnose einer spinozerebellären Ataxie ist dann zu stellen, wenn ein charakteristisches klinisches Symptombild auftritt, eine positive Familienanamnese eruiert, eine andere Ätiologie ausgeschlossen werden kann und ein SCA-Genotyp gefunden wird (Klockgether et al. 2019). Ergänzende diagnostische Maßnahmen wie Bildgebung, Messung der Nervenleitgeschwindigkeiten und kognitive Leistungsdiagnostik können einerseits Begleitsymptome ermitteln, andererseits erworbene oder andere sekundäre Ataxieformen identifizieren.

5.1.4.3 Bildgebung

Paraklinische Befunde wie die Bildgebung sind unter Umständen nicht nur für die diagnostische Zuordnung klinischer Syndrome bedeutsam, sondern ermöglichen auch, ein nicht auf einen ausschließlich zerebellären Ursprung zurückzuführendes Symptombild diagnostisch abzusichern und einer zerebralen Lokalisation zuzuordnen. Neuroanatomische Untersuchungen haben in Modellen von Haltungs- und Bewegungskontrolle sowie der Initiation willkürlicher Bewegungen die systemische Organisation mittels Netzwerken auf sensorischer, muskulärer, spinaler, im Hirnstamm lokalisierter nukleärer sowie supraspinaler Ebene formuliert (MacKinnon 2018). Im Einzelnen wurden durch Tracer- und Bildgebungsstudien eine Vielzahl motorischer Projektionen zwischen Zerebellum-Thalamus-motorischem Kortex, sowie vom Zerebellum zu präfrontalen, zingulären, parietalen, temporalen und okzipitalen Kortexregionen beschrieben (Pisano et al. 2021; Xue et al. 2021). Diese neuronale Vernetzung ist als Hintergrund mitunter zu beobachtender neuropsychologischer Symptome bei Ataxiesyndromen anzunehmen (Klinke et al. 2010; van Overwalle et al. 2019).

Mit bildgebenden Verfahren wie der funktionellen Magnetresonanztomographie wurde es auch möglich, im Tiermodell gefundene Loci und Mechanismen supraspinaler Bewegungskontrolle in Hirnstamm und Kleinhirn am Menschen nachzuvollziehen (Jahn et al. 2008). Die Identifizierung von Aktivierungs- und Deaktivierungsmustern in definierten Hirnstrukturen bei imaginierten motorischen Funktionen von Probanden führte zu Modellen einer hierarchischen Organisation zerebraler Strukturen von Stand und Gang, wobei der Einfluss zerebellärer motorischer Zentren mit dem Automatisierungsgrad von Bewegungen (Laufen, Gehen, Stehen) korrelierte (Jahn et al. 2004). Mittels der Anwendung an gesunden Probanden evaluierter funktioneller Bildgebung bei Patienten mit Ataxie konnten nicht nur Ataxieformen unterschiedlicher Ätiologie morphologisch genauer charakterisiert werden, sondern auch der Schweregrad eines ataktischen Syndroms mit einem morphologischen Substrat korreliert werden (D'Agata et al. 2011; Hernandez-Castillo et al. 2016; Döhlinger et al. 2008). Auf diese Weise konnte das pathophysiologische Verständnis klinischer Symptome wie Gangstörungen vertieft werden. Defiziten wie kognitiven Störungen, die auch bei Berücksichtigung zerebellärer Funktionalität in multiplen neuronalen Netzwerken auf über ausschließlich zerebelläre Lokalisation hinausgehende Läsionen hinwiesen, konnte bei genetisch definierten spinozerebellären Ataxieformen wie der SCA 7 ein morphologisches, hier kortikales Korrelat zugeordnet werden (Hernandez-Castillo et al. 2016; Schmahmann 2019).

Das Auftreten von Gangstörungen ist diagnostisch häufig als Beginn der klinisch relevanten Ataxiesymptomatik anzusehen, auch wenn Koordinationstests bei Risikopersonen für die Erkrankung wie Verwandte 1. Grades von SCA 1,2,3,6-Mutationsträgern ohne noch manifeste klinische Ataxiesymptome bereits schlechter ausfallen als bei Nicht-Mutationsträgern. Desgleichen wurden auch andere neurologische Symptome wie

Blickrichtungsnystagmus, Muskelkrämpfe und sensible Defizite bei dieser Personengruppe häufiger gefunden (Jacobi et al. 2013). Magnetresonanztomographiestudien an Risikopatienten wiesen vorauslaufenden Substanzverlust in Kleinhirn und Hirnstamm nach, der progredient mit zeitlicher Annäherung an die explizite klinische Manifestation der Ataxie zunimmt (Jacobi et al. 2013).

Daneben zeigen auch die genetisch differenzierten Subtypen spinozerebellärer Ataxien abweichende Prädilektionsregionen des Substanzverlusts. So wurden Volumenverluste im Zerebellum und Hirnstamm bei SCA 1,2,3,6,17 gefunden, Volumenverluste der weißen und grauen Substanz in Kleinhirn und Hirnstamm bei SCA 1,2,3; bei SCA 3 und 6 in Rückenmark, Basalganglien und Vermis des Kleinhirns, in SCA 6 und 17 hingegen im Caudatum (Brooker et al. 2021). Mittels funktioneller Bildgebungstechniken wie PET und SPECT und Metabolisierungsstudien konnten weitere Biomarker für einige der spinozerebellären Ataxieformen identifiziert werden (Brooker et al. 2021). Da die differenzialdiagnostische Zuordnung der SCA-Unterformen primär mittels genetischer Diagnostik erfolgt, haben Biomarker derzeit vor allem ihren Stellenwert in der Verlaufsprädiktion, d.h. insbesondere für die Konversion von einem asymptomatischen Stadium in manifeste klinische Symptomatologie, sowie bei der Beurteilung einer etwaigen symptomatologischen Progression (Brooker et al. 2021).

5.2 Hinführung zu der den Publikationen zugrundeliegenden Fragestellung

Zerebelläre degenerative Erkrankungen sind im quantitativen Vergleich zu denen des Cortex, beispielsweise des gesamten Komplexes dementieller Syndrome, erheblich seltener. Da kausale Therapien für sämtliche Erscheinungsbilder und Subtypen nicht zur Verfügung stehen, sind differentielle Diagnostik und Klassifikation bei der Variabilität von Klinik und Verlauf im Hinblick auf das erforderliche multimodale Vorgehen bei schwerpunktmäßig auf supportive und symptomatische Interventionen beschränkte Therapieoptionen besonders bedeutsam (Ilg et al. 2014; Klockgether et al. 2019). Eine möglichst frühzeitig gestellte Diagnose gerade vor Eintritt irreversibler degenerativer Prozesse bei klinisch manifester Ataxie kann sich auf die Wirksamkeit der verfügbaren Therapieansätze positiv auswirken (Salman 2018).

Neben der molekulargenetischen Diagnostik zur Abgrenzung hereditärer von sporadischen Ataxieformen ist die zerebrale Bildgebung ein weiterer wichtiger diagnostischer Baustein. Mit Hilfe dieser apparativen Methode können sowohl Schwerpunkte struktureller Veränderungen im Zerebellum identifiziert als auch extrazerebelläre, namentlich kortikale degenerative Prozesse, lokalisiert werden, auf die über die zerebelläre Symptomatik hinausgehende Symptome bei den verschiedenen Ataxieformen wie kognitive Einschränkungen oder pyramidale und extrapyramidale Zeichen zurückführbar sind. Insbesondere dem Zusammenhang klinischer Messungen der funktionellen und kognitiven

Beeinträchtigungen bei chronischer Kleinhirndegeneration mit strukturellen Veränderungen des gesamten Gehirns wird in der Publikation „Disability in cerebellar ataxia syndrome is linked to cortical degeneration“ nachgegangen. Eine derartige Fragestellung wurde bisher zwar für einzelne genetisch definierte Ataxieformen evaluiert. Ziel unseres Forschungsvorhabens war es, diese Fragestellung bei weiteren zerebellären degenerativen Prozessen wie DBN-Syndrom, SAOA neben SCA zu untersuchen. Vor dem Hintergrund die rein zerebelläre Lokalisation überschreitender Symptommanifestationen wurde der Frage nachgegangen, inwieweit weitere zerebrale Regionen, insbesondere kortikale, in die Verursachung des klinischen Symptombildes involviert sind.

Dass komplexe Störungen wie Ataxien nicht nur in der klinischen Evaluation messbare Auffälligkeiten aufweisen, sondern auch in ubiquitären Alltagssituationen, die Mobilität erfordern, ist naheliegend. Den Einfluss auf Lebensqualität und Einschränkungen bei Alltagsverrichtungen zu objektivieren und vor dem Hintergrund der limitierten therapeutischen Möglichkeiten Risikopatienten und -konstellationen zu identifizieren, ist für Akzentsetzungen in der Betreuung, unter Umständen auch bei präventiven Rahmeninterventionen, essentiell. Vor diesem Hintergrund sind Stürze für Personen mit Mobilitätseinschränkungen ein generell gefährliches und mit einem hohen Verletzungsrisiko behaftetes Geschehen. Daher ist eine prädiktive Charakterisierung von Patienten, die aufgrund ihrer Symptomkonstellation einem besonders hohen Maß an Risiko zu stürzen ausgesetzt sind, bedeutsam. Mittels einer multimodalen Mobilitätsbewertung, in die Sturzstatus, sowie Häufigkeit und Schweregrad des jeweiligen Sturzgeschehens eingehen, war es das Ziel der Arbeit „Multimodal mobility assessment predicts fall frequency and severity in cerebellar ataxia“, ein Evaluationsinstrument zu entwickeln, mit dem mittels klinischer Bewertung und instrumentengestützter Mobilitätsmessungen eine Risikoprognose und die Implementierung entsprechender Präventionskautelen ermöglicht werden.

6. Zusammenfassung

Im Rahmen des Promotionsvorhabens wurden klinische und morphologische Merkmale bei zerebellären Syndromen mittels MRT-Bildgebung und Mobilitätsparametern untersucht.

In der in Erstautorenschaft verfassten Arbeit „Disability in cerebellar ataxia syndromes is linked to cortical degeneration“ wurde die Fragestellung aufgegriffen, inwieweit sich Symptomatologie und strukturelle Veränderungen des gesamten Zerebrums bei Patienten mit chronischer Kleinhirndegeneration aufeinander beziehen lassen. In die Studie eingeschlossen wurden 30 Patienten mit Kleinhirndegeneration, die aus drei ätiologisch unterschiedlichen Syndromgruppen rekrutiert wurden: Spinozerebelläre Ataxien mit den Subtypen SCA2, SCA3, SCA6 und SCA28 (n=9), Sporadische Ataxien im Erwachsenenalter (n=7), sowie Patienten mit einem DBN-Syndrom (n=14). Ziel der Studie war es zu klären, inwieweit regional differentielle Volumendefizite bei den genannten drei Patientengruppen mittels voxelbasierter und oberflächenbasierter Morphometrie zu identifizieren sind und wie diese mit funktionellen Beeinträchtigungen im motorischen und vestibulären System in Zusammenhang stehen. Damit verbunden war die Frage, wie sich eine Kleinhirndegeneration über Netzwerkveränderungen auf kortikale Strukturen auswirken kann.

Die im Rahmen der Studie untersuchten Patienten und alters- und geschlechtsgleichen Kontrollprobanden wurden in der Ambulanz des Deutschen Schwindel- und Gleichgewichtszentrums der LMU München rekrutiert und klinisch sowie mittels MRT-Bildgebung untersucht.

Die Evaluation des klinischen Status umfasste eine ausführliche krankheitsbezogene Anamnese, die Erhebung etwaiger Komorbiditäten, den retrospektiv ermittelten Sturzstatus, Informationen über die subjektiv bewertete Stabilität und Mobilität im Alltag (FES-I), eine orientierende Objektivierung der kognitiven Leistungsfähigkeit (MoCA), sowie eine Einschätzung des Schweregrades der Ataxiesymptome mit Hilfe des SARA-Scores. Darüber hinaus wurden zur Validierung der in der Selbstbeurteilung gemachten Angaben zur Mobilität im Labor eine quantitative Messung verschiedener Gangparameter und standardisierte neuro-orthoptische Untersuchungen durchgeführt.

Des Weiteren erhielten alle Patienten und Kontrollprobanden eine hochauflösende strukturelle MRT-Bildgebung. Mittels der voxelbasierten Morphometrie konnten graue und weiße Substanz einer volumetrischen Analyse unterzogen werden. Mithilfe oberflächenbasierter Analysen konnte zwischen kortikaler Atrophie und Veränderungen der kortikalen Oberfläche, die auf tiefer liegende degenerative Prozesse der weißen Substanz zurückführbar waren, differenziert werden.

Zur klinischen Charakterisierung wurden verschiedene Variablen wie Krankheitsdauer, SARA-Score, FES-I, MoCA und individuelle Ganggeschwindigkeit miteinander korreliert. Konvergierend mit klinischer Plausibilität ergaben sich negative Korrelationen zwischen

SARA- und MoCA-Score, sowie der individuellen Gehgeschwindigkeit und der FES-I, überdies eine positive Korrelation zwischen MoCA-Score und bevorzugter Ganggeschwindigkeit.

Mittels struktureller MRT-Bildgebung konnte eine Volumenreduktion der grauen Substanz im Kleinhirn bei SCA und SAOA gegenüber gesunden Kontrollen nachgewiesen werden. Die regionale Reduktion zeigte zwischen den Erkrankungsgruppen SCA, SAOA und DBN-Syndrom abweichende Lokalisationsschwerpunkte. Im Hinblick auf den SARA-Score als wesentlichster Parameter für den Schweregrad der Ataxie ergab sich eine negative Korrelation mit Substanzreduktionen im Kleinhirn, den Basalganglien, sowie dem präfrontalen und prämotorischen Kortex, desgleichen zu Clustern in der weißen Substanz von Kleinhirn, Hirnstamm und kortikospinalem Trakt. Auch für die anderen klinischen Parameter ließen sich Assoziationen volumetrischer Reduktion mit dem Ausprägungsgrad der Störung nachweisen.

Der Volumenverlust bei Patienten mit SCA und SAOA war vor allem in den Kleinhirnhemisphären lokalisiert, weniger im Vermis. Darüber hinaus ließen sich auch extrazerebelläre Atrophiemuster bei SCA und SAOA nachweisen, die neben dem Gesamtschweregrad der Ataxie ebenfalls für funktionelle Fertigkeiten wie Ganggeschwindigkeit, Kognition und Vertikalitätswahrnehmung bedeutsam sind. Auch für Patienten mit DBN-Syndrom ließen sich Prädilektionslokalisationen von Volumenverlusten in Flocculus, Nodulus und Uvula nachweisen ohne Beteiligung weiterer Kleinhirnregionen oder extrazerebellärer Strukturen. Das klinisch bedeutsamste Beeinträchtigungsereignis „Sturz“ war mit dem Ausmaß der Volumenreduktion im Hirnstamm korreliert.

In der in Koautorenschaft verfassten Publikation „Multimodal mobility assessment predicts fall frequency and severity in cerebellar ataxia“ wurde die prädiktive Validität der multimodalen klinischen Beurteilung und quantitativer Mobilitätsmessungen in Labor und Alltag zur Einschätzung des Sturzrisikos an 93 Patienten mit sporadischen, erblichen und sekundären Formen von zerebellären Ataxien erhoben. Die Untersuchung umfasste eine multimodale klinische und funktionelle Sturzrisikobewertung, eine Ganguntersuchung im Labor, sowie eine zweiwöchige in vivo Mobilitätsmessung im Lebensumfeld mittels Aktivitätssensoren. Sturzstatus, Sturzhäufigkeit und Sturzschweregrad waren die Ausgangsparameter für die Einschätzung des prädiktiven Potenzials der durchgeführten Mobilitätsmessungen. Circa 2/3 der Patienten berichteten aus dem Untersuchungszeitraum über einen oder mehrere Stürze, ca. 2/3 aus dieser Gruppe über schwere sturzbedingte Verletzungen. Auf der Basis des SARA-Scores und der Bewertung der funktionellen Mobilitätsbeeinträchtigung waren die ataktischen Gangstörungen als leicht bis mittelschwer zu klassifizieren. Im Hinblick auf Prädiktion von Sturzstatus und Sturzhäufigkeit zeigte der retrospektiv erhobene Sturzstatus die höchste Dignität, die Schwere der ataktischen Symptomatik prädizierte vor allem die Sturzschwere. Die Ergebnisse plädieren für ein stufenweises Vorgehen in der Evaluation des Sturzrisikos bei zerebellären

Ataxien. Auf der Grundlage einer sorgfältigen Anamneseerhebung bezüglich der retrospektiven Sturzparameter kann geklärt werden, welche Untergruppe von Patienten besonders sturzgefährdet ist und von weiteren differentiellen Gang- und Mobilitätsuntersuchungen mit der Perspektive zielführender Interventionen profitieren könnte.

7. Abstract (English)

In the dissertation project, clinical and morphological features in cerebellar syndromes were investigated using MRI imaging and mobility parameters.

In the paper "Disability in cerebellar ataxia syndromes is linked to cortical degeneration", which was written in first authorship, the question was addressed how far symptomatology and structural changes of the whole cerebrum can be related to each other in patients with chronic cerebellar degeneration. The study included 30 patients with cerebellar degeneration recruited from three aetiologically distinct syndrome groups: Spinocerebellar ataxias with SCA2, SCA3, SCA6, and SCA28 subtypes (n=9), sporadic adult-onset ataxias (n=7), and patients with downbeat nystagmus syndrome (n=14). The aim of the study was to clarify to what extent regionally differential volume deficits can be identified in the above three patient groups using voxel-based and surface-based morphometry and how these are related to functional impairments in the motor and vestibular systems. A associated question was how cerebellar degeneration may affect cortical structures via network changes.

The patients and age- and sex-matched controls investigated in the study were recruited at the German Center for Vertigo and Balance Disorders of the LMU Munich and examined clinically and by MRI imaging.

The evaluation of the clinical status included a detailed disease-related medical history, the identification of comorbidities, the retrospectively determined fall status, information on the subjectively estimated stability and mobility in everyday life (FES-I), an objective evaluation of the cognitive performance (MoCA), and an assessment of the severity of ataxia symptoms by using the SARA score. In addition, quantitative measurement of various gait parameters and standardized neuroorthoptic examinations were performed in laboratory to validate the mobility information provided in the self-assessment.

Furthermore, all patients and controls underwent high-resolution structural MRI imaging. Using voxel-based morphometry, gray and white matter volume could be analyzed. Using surface-based analyses, it was possible to differentiate between cortical atrophy and cortical surface changes attributed to deeper white matter degenerative processes.

For clinical characterization, several variables such as disease duration, SARA score, FES-I, MoCA, and preferred walking speed were correlated. Converging with clinical plausibility, negative correlations were found between SARA and MoCA score, as well as preferred walking speed and FES-I, and a positive correlation between MoCA score and preferred walking speed.

Structural MRI imaging demonstrated cerebellar gray matter volume reduction in SCA and SAOA compared with healthy controls. The regional reduction showed different localization foci between the disease groups SCA, SAOA and DBN. Regarding the SARA score as the most important parameter for the severity of ataxia, there was a negative correlation with substance reductions in the cerebellum, basal ganglia, and prefrontal

and premotor cortex, as well as with clusters in the white matter of the cerebellum, brainstem, and corticospinal tract. Associations of volumetric reduction with the disease severity could also be detected for the other clinical parameters.

Volume loss in patients with SCA and SAOA was mainly localized in the cerebellar hemispheres, but less in the vermis. In addition, extracerebellar atrophy patterns could also be detected in SCA and SAOA, which are also significant for functional skills such as walking speed, cognition, and vertical perception, besides the overall severity of ataxia. Also for patients with DBN, predilection localizations of volume loss in the flocculus, nodulus, and uvula could be found without involvement of other cerebellar regions or extracerebellar structures. The clinically most significant impairment outcome "fall" was correlated with the extent of volume reduction in the brainstem.

In the co-authored publication "Multimodal mobility assessment predicts fall frequency and severity in cerebellar ataxia" the predictive validity of multimodal clinical assessment and quantitative in- and off-laboratory mobility measurements to evaluate fall risk was assessed in 93 patients with sporadic, hereditary, and secondary forms of cerebellar ataxia. The study included a multimodal clinical and functional fall risk assessment, an in-laboratory gait examination, and a two-week in vivo mobility measurement using activity sensors. Fall status, fall frequency, and fall severity were the outcome parameters to assess the predictive potential of the performed mobility measurements. Approximately 2/3 of the patients reported one or more falls during the study period, and approximately 2/3 of this group reported severe fall-related injuries. Based on the SARA score and the assessment of functional mobility impairment, ataxic gait disorders were classified as mild to moderate. With respect to prediction of fall status and fall frequency, the retrospectively assessed fall status showed the highest dignity, and the severity of ataxic symptoms mainly predicted fall severity. The results argue for a stepwise approach in the evaluation of fall risk in cerebellar ataxias. On the basis of a careful medical history regarding retrospective fall parameters, it can be determined which subgroup of patients is particularly at risk for falls and could benefit from further differential gait and mobility assessments with the perspective of goal-directed interventions.

8. Paper I

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ORIGINAL COMMUNICATION

Disability in cerebellar ataxia syndromes is linked to cortical degeneration

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Abstract

Objective We aimed to relate clinical measures of disability in chronic cerebellar degeneration to structural whole-brain changes using voxel-based and surface-based morphometry (*vbm and sbm*). We were particularly interested in remote effects of cerebellar degeneration in the cerebral cortex.

Methods We recruited 30 patients with cerebellar degeneration of different aetiologies (downbeat nystagmus syndrome, DBN $n=14$, spinocerebellar ataxia, SCA $n=9$, sporadic adult late-onset ataxia, SAOA $n=7$). All patients were thoroughly characterised in the motor, cognitive, vestibular and ocular–motor domains. *Vbm* and *sbm* were used to evaluate structural differences between cerebellar degeneration patients and a group of healthy age- and gender-matched volunteers. Linear regression models were used to correlate functional measures of disease progression and postural stability with whole brain volumetry.

Results Patients with SCA and SAOA showed widespread volume loss in the cerebellar hemispheres and less prominently in the vermis. Patients with DBN showed a distinct pattern of grey matter volume (GMV) loss that was restricted to the vestibular and ocular–motor representations in lobules IX, X and V–VII. Falls were associated with brainstem white matter volume. *VBM* and *SBM* linear regression models revealed associations between severity of ataxic symptoms, cognitive performance and preferred gait velocity. This included extra-cerebellar (sub-)cortical hubs of the motor and locomotion network (putamen, caudate, thalamus, primary motor cortex, prefrontal cortex) and multisensory areas involved in spatial navigation and cognition.

Conclusion Functional disability in multiple domains was associated with structural changes in the cerebral cortex.

Keywords Voxel-based morphometry · Surface-based morphometry · Cerebellar · Downbeat nystagmus · Spinocerebellar ataxia

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Introduction

Patients with chronic cerebellar degeneration typically present with dys-coordinated limb movements, impairments of gait stability, vestibular/ocular–motor symptoms, dysarthria and dysphagia. "Non-cerebellar" symptoms, such as neuropathy, extrapyramidal, pyramidal signs and cognitive impairments, are also present in both hereditary, genetically confirmed ataxias, and sporadic adult-onset ataxias (SAOA) [15, 27, 38]. These phenomenological findings are supported by tracer and neuroimaging studies on the interconnections of cerebellar and cerebral cortices [2, 35, 37, 43]. Dense connections involve the cerebello-thalamo-cortical motor pathways but are also found with prefrontal, cingulate, parietal, temporal and occipital cortex [8, 27, 28, 43]. It is increasingly recognised that most patients with chronic cerebellar degeneration develop neuropsychological symptoms [1, 14, 41]. Functional connectivity MRI (fcMRI) has revealed network alterations, which involve cerebellar and cerebral cortical areas in SCA2 [18, 26]. Also, other SCA subtypes such as SCA3 or SCA6 show patterns of neurodegeneration, which extend beyond the cerebellum and brainstem [16, 29, 32, 40]. The findings of extensive degeneration are also supported by neuropathological post-mortem findings in SCA2 and 6 [5, 7]. Given the strong evidence for intensive cerebello-cerebral interactions, it seems plausible that high-resolution structural imaging in cerebellar ataxia could also detect structural brain changes in distant areas of the cerebral cortex [22, 31]. Using fcMRI, the disruption of cerebello-cerebral networks can be detected. In addition, voxel-based- (vbm) and surface-based morphometry (sbm) could provide direct in vivo evidence for cerebral volume loss in chronic cerebellar degeneration, i.e. a distinction between functional alteration due to cerebellar network dysfunction and manifest cortical structural changes. Compared to SCA and SAOA, the symptomatology is rather restricted in patients with downbeat nystagmus syndrome (DBN) which report mainly oscillopsia and gait unsteadiness [31]. DBN phenomenology and its underlying structural correlates are thus putatively restricted to cerebellar regions of eye movement control and sensory integration [10, 12].

In the current study, we aimed to evaluate (i) a possible differential pattern of volume loss in patients with DBN syndrome, SAOA and SCA, (ii) the extent and pattern of distant volumetric changes in the cerebral cortex and subcortex and (iii) the association of structural degeneration with functional disability in the motor and vestibular system and locomotion.

Methods

Patients

We studied 30 patients with cerebellar degeneration of different aetiologies that were referred to the *German Center for Vertigo and Balance Disorders* of the Munich university hospital, LMU Munich between 2018 and 2020. Of those, 14 patients had downbeat nystagmus syndrome (DBN), seven patients had sporadic adult-onset ataxia (SAOA) and nine patients had spinocerebellar ataxia (SCA2: $n=6$; SCA3, 6, 28: $n=1$ each). Genetic testing was performed in patients with spinocerebellar ataxia to confirm the diagnosis in advance (pathological CAG repeat expansions were found in the ATXN2 gene in SCA2, in the ATXN3 gene in SCA3, in the CACNA1A gene in SCA6, and a pathological variant in the AFG3L2 gene in SCA28). Each patient received a full aetiological workup which included CSF analysis and antibody testing. In the setting of a tertiary specialised centre for vertigo and ocular–motor disorders, most of the time, this workup was completed before patients came to our attention. Patients with cerebellar degeneration with insidious onset and/or additional signs of peripheral neuropathy and vestibulopathy were tested for RFC1 gene mutations. In our sample, none of the patients were GAD-antibody positive and no patients presented with the triad of cerebellar syndrome, peripheral neuropathy and vestibulopathy. There was no case of RFC1 gene mutation. Patients were classified as SAOA or DBN after exclusion of inflammatory, metabolic, vascular, morphological, paraneoplastic, autoimmunological, familial cerebellar ataxia and toxic/pharmacological aetiologies.

Controls

A group of 29 healthy age- and gender-matched healthy controls (HC) with no history of acute or chronic neurological disease received the identical imaging protocol for group comparisons.

Clinical and fall-risk assessment

An assessment of the ambulatory status, disease duration and comorbidities was carried out with all participants in a standardised interview. Falls were assessed retrospectively containing information on fall status (yes or no), and subjective stability was examined by the Falls Efficacy Scale-International (FES-I) [44]. The cognitive performance was measured with an established screening tool (Montreal cognitive assessment, MoCA), the global severity of ataxic symptoms with the scale for the assessment and rating of

ataxia (SARA) [23, 30]. Gait performance was characterised by preferred walking speed assessed on a pressure-sensitive gait carpet (GAITRite, CIR System, Sparta, NJ, USA).

A standardised physical and neurological examination was carried out with each participant. Furthermore, all patients received standardised neuro-orthoptic testing (spontaneous eye position and movements (nystagmus), static otolith function using the subjective visual vertical (SVV), optokinetic nystagmus, vestibulo-ocular reflex (VOR), saccades, smooth pursuit). For the SVV, a mean deviation of> ±2.5° over seven binocular measurements was considered pathological.

Symptomatic medication details were recorded for all cerebellar degeneration patients. In addition to professional physiotherapy (usually one 1-h session per week), all patients were instructed to complete a daily exercise and balance training programme. All patients received identical recommendations for professional and self-supervised physiotherapy.

Imaging

All patients and HC received high-resolution structural MR-imaging on a clinical 3 T MRI scanner (T1 MPRAGE, 0.75 mm^3 isotropic, 320 slices, TR 2060 ms, TE 2.17 ms, Magnetom Skyra, Siemens Healthcare, Erlangen, Germany).

Voxel-based morphometry (VBM)

We used the CAT12 toolbox version 1739 (Gaser & Dahnke, Department of Psychiatry, University of Jena, Jena, Germany; http://www.neuro.uni-jena.de/cat) within Statistical Parametric Mapping SPM12, version 7771 (https://www.fil.ion.ucl.ac.uk/spm/; Wellcome Department of Cognitive Neurology), using Matlab R2019b (Mathworks) for data quality estimation, preprocessing, and analysis of the data after standard preprocessing, applying a 6 mm Gaussian smoothing kernel. The modulated grey matter (GM) and white matter (WM) images were used for the volumetric analysis.

Surface-based analyses (SBM)

The CAT12 toolbox contains a fully implemented and validated processing pipeline for SBM [13]. We analysed distinct parameters of the cortical geometrical surface, such as cortical thickness (CT), sulcal depth (SD), the fractal dimension (FD) and gyrification indices (GI), to evaluate the complexity of the cortical surface based on the absolute mean curvature approach [17]. This allowed us to differentiate between cortical atrophy and changes of the cortical surface that are due to reshaping of the cortex in response to underlying white matter degeneration or the combination of both. For this purpose, the T1-weighted images underwent tissue segmentation to estimate white matter distance. Local maxima are projected to other grey matter voxels using a neighbour relationship, described by the distance to the white matter which equal cortical thickness. Partial volume correction, sulcal blurring and sulcal asymmetries without reconstruction of the sulci were applied. Topological correction is based on spherical harmonics. For the analysis, spherical mapping of the cortical surface is included [3, 46]. An adapted volume-based diffeomorphic DARTEL algorithm was then applied to the surface for spherical registration. Central cortical surfaces were created for both hemispheres separately. Surface reconstructions of the cortical values for each hemisphere were resampled to the 164 k mesh template space (*Freesurfer*) after merging and then smoothed with a 15 mm (cortical thickness), 20 mm (sulcus depth) and 23 mm (fractal dimension and gyrification index) Gaussian filter respectively.

Statistical analysis

Group comparison and commonalities of cerebellar degeneration

Patients with SCA, SAOA or DBN were compared to the HC in an ANOVA model with group as a factor. Total intracranial volume (TIV) was modelled as a covariate of no interest for the volumetric analyses. Group level *t* statistics were performed for all possible pairs of between-groups comparison.

Association of clinical deficits with chronic cerebellar degeneration

All patients were included in a linear regression model using TIV and age as covariates of no interest. Variables of interest were the SARA, FES-I, MoCA score and the preferred gait velocity.

Specific clinical deficits, such as a history of falls, gaze-evoked nystagmus, and pathological tilts of the SVV (as dichotomous variables), were evaluated using two-sample t tests.

Correction for multiple comparisons

All imaging results from the ANOVA, *t* tests and linear regression models underwent extensive non-parametric permutation testing (*threshold-free cluster enhancement*, *TFCE*) with 10,000 permutations [34]. The results were

corrected for multiple comparisons on the cluster level using family-wise error (FWE) correction. Results below a threshold of $p<0.05$ were considered robust against false positives.

Clinical variables of interest

Distribution, frequency and correlations between the clinical variables of interest were analysed using SPSS (version 26.0.0.1; IBM Corp. 2019, Armonk, NY). Descriptive statistics are reported as mean ± SD or median ± IQR where applicable. First symptoms were recorded as those that led to neurological consultation. If more than one symptom was present, all symptoms at the time of presentation were recorded. Falls were defined as falling to the ground or to a lower level. An analysis of variance (ANOVA) was used to compare mean values of metric and categorial variables between the three patient groups. Tukey post hoc analysis was performed to identify significant differences between the groups.

Patient consent and data availability

The study was performed in accordance with the 1964 Declaration of Helsinki (latest applicable revision Fortaleza 2013) and approved by the institutional review board of LMU, Munich, Germany (no. 333-07). All patients gave informed written consent to participate in the study. The structural imaging patient data is not publicly available due to European Privacy laws and lack of consent for data sharing by the patients.

Results

Demographic and clinical data

Patients with DBN presented with vertigo (79% vs. 29% and 22%) and ocular–motor symptoms (43% vs. 14%, 0%), whereas gait instability was one of the first symptoms (100% vs. 29% in patients with DBN) in SCA and SAOA. A relevant proportion of patients with SAOA and SCA reported falls (71% and 89% respectively). SARA scores were significantly higher in patients with SCA and SAOA compared to patients with DBN (mean 11 points in the

Table 1 Demographic and clinical data

Group	SAOA	SCA	DBN	HC	All	ANOVA $F(3;47)$	p
Demographic							
n (f/m)	7 (3/4)	9 (5/4)	14 (10/4)	21 (13/8)	51 (31/20)		
Age (years; mean ± SD)	59 ± 13	40 ± 17*	65 ± 11*	58 ± 21*,**	57 ± 19	4.3	0.010

Group	SAOA	SCA	DBN	All	ANOVA $F(2;29)$	p
Clinical characteristics						
First symptoms						
Gait disorder (%)	100	100	29	76.3		
Balance disorder (%)	43	11	14	22.7		
Ocular–motor/double vision (%)	14	0	43	19		
Vertigo (%)	29	22	79	43.3		
Speech disorder (%)	14	33	0	15.7		
Ataxia (%)	29	44	0	24.3		
Falls at disease onset (n)	71	89	29	63		
Disease duration (years; median, IQR)	6 ± 6	5 ± 6	6 ± 6	6 ± 5		
MOCA score (median, IQR)	26 ± 4	27 ± 4	27 ± 3	26 ± 3		
SARA score (mean ± SD)	11 ± 4*	10 ± 6*	5 ± 3*	8 ± 5	6.1	0.006
FES-I score (mean ± SD)	37 ± 12	31 ± 10	28 ± 7	31 ± 10	2	n.s
Preferred gait velocity (m/s; mean ± SD)	1.1 ± 0.2	0.9 ± 0.3	1.0 ± 0.3	1.0 ± 0.3	0.8	n.s
SVV tilts (°, mean ± SD)	2.9 ± 2.9	2.2 ± 1.9	1.9 ± 1.4	2.2 ± 2.0	0.6	n.s

*Significant difference in the Tukey post hoc comparison (DBN compared to SAOA and SCA)

**Healthy subjects were age-matched to each cerebellar degeneration group for the imaging analysis

SAOA group and 10 points in the SCA group vs. 5 in the DBN group ($p=0.006$). Balance confidence as assessed by the FES-I was lower in patients with SAOA and SCA compared to those with DBN (mean scores: 37 and 31 vs. 28). Only one patient had clinical signs of corticospinal tract involvement (spasticity, pathological reflexes, aetiology: SCA28). Preferred gait velocity showed no significant differences amongst the three patient groups. Cognitive function and static otolith function (SVV) were similar across all three diagnosis groups and mildly impaired in most patients (Table 1).

Amongst the group of patients with DBN, four patients were already treated with 4-aminopyridine when the study was performed, three of them reported a subjective improvement of symptoms, and one stopped the medication because no improvement was noted. In five other patients, 4-aminopyridine treatment was started during the study period, in two patients we initiated treatment with acetyl-DL-leucine.

From the SAOA patient group, one patient was successfully treated with acetyl-DL-leucine, three patients showed no improvement of symptoms under both acetyl-DL-leucine and 4-aminopyridine therapy.

Of the patients with SCA, four patients with SCA2 and one patient with SCA28 responded well to acetyl-DL-leucine; one patient with SCA 6 did not improve with either acetyl-DL-leucine or 4-aminopyridine therapy.

Partial correlations

We used partial correlations to evaluate associations between the variables of interest (disease duration, SARA score, FES-I score, tilts of the SVV, MoCA scores, gait velocity) using TIV and age as covariates of no interest (Table 2). Here, disease duration as an independent factor was not correlated with any of the variables. We found negative correlations between the variables SARA scores and MoCA scores (degrees of freedom: 26, r: −0.5, p 0.007), the self-determined ambulation speed (df 26, r −0.469, p 0.012), and the subjective fall efficacy (df 26, r 0.646, $p<0.0001$). A positive correlation was found between the MoCA score and the preferred ambulation speed (df 36, r 0.595, p 0.001).

Imaging

Structural whole brain changes in DBN, SCA and SAOA compared toHC

Voxel-based morphometry (VBM) *Grey matter volume (GMV) in the cerebellum* GMV was reduced in the cerebellar cortex in SCA and SAOA compared to the HC. A more prominent GMV reduction in SCA was found in the cerebellar hemispheres (lobules V, VI, Crus I, VII, and VIII) compared to the midline structures (Fig. 1A). In patients with SAOA, GMV reductions were more restricted to the motor (lobule IV-VI) and midline cerebellar structures (lobules IX, vermal V–VII, ocular–motor vermis (OMV)) (Fig. 1C).

Table 2 Partial correlations of the variables of interest using TIV and age as covariates in all cerebellar patients ($n=30$, 26 degrees of freedom)

	Symptom duration	SARA	MoCA	SVV tilt	preferred walking speed	FES-I
Symptom duration						
r	1.000	−0.006	0.086	−0.249	−0.050	0.073
p		0.976	0.664	0.201	0.799	0.711
SARA						
r	−0.006	1.000	**−0.500**	0.335	**−0.469**	**0.646**
p	0.976		**0.007**	0.081	**0.012**	**<0.0001**
MoCA						
r	0.086	**−0.500**	1.000	−0.117	**0.595**	−0.277
p	0.664	**0.007**		0.554	**0.001**	0.154
SVV tilt						
r	−0.249	0.335	−0.117	1.000	0.130	0.311
p	0.201	0.081	0.554		0.510	0.108
Preferred walking speed						
r	−0.050	**−0.469**	**0.595**	0.130	1.000	−0.225
p	0.799	**0.012**	**0.001**	0.510		0.249
FES-I						
r	0.073	**0.646**	−0.277	0.311	−0.225	1.000
p	0.711	**<0.001**	0.154	0.108	0.249	

*$p < 0.05$; two-sided

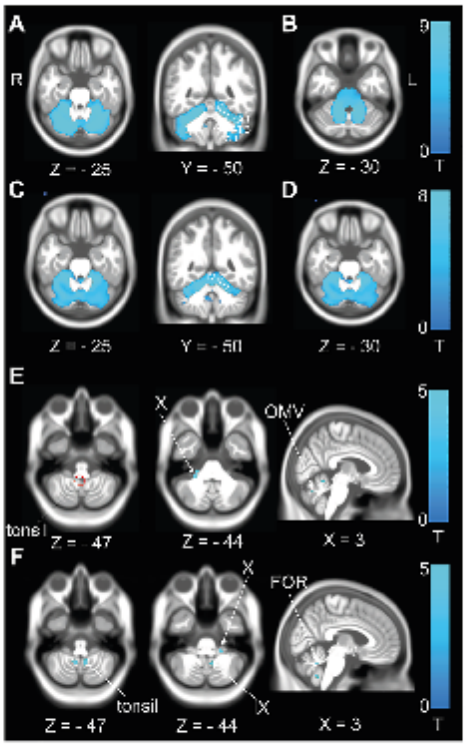

Fig. 1 Differential patterns of volume loss in SCA, SAOA and DBN. **A** GMV reduction in patients with SCA compared to the HC. GMV reduction was detected in the motor cerebellum but extended in the hemispheres towards lobule VIIB, VIII and Crus I **B** WMV reduction in patients with SCA compared to HC. WMV reduction was detected in all three cerebellar peduncles and the adjacent pontine white matter up to the mesencephalon and descending to the medulla oblongata. **C** GMV reduction in patients with SAOA compared to the HC. Patients with SAOA also showed a widely distributed pattern of volume reduction. Compared to the patients with SCA, the pattern was more restricted to the motor lobules (IV–VI) and the vestibular (lobules IX, X) and ocular–motor cerebellar areas (OMV). **D** WMV reduction in patients with SAOA compared to the HC. Like patients with SCA, those with SAOA showed volume loss in the cerebellar peduncles and pontine white matter. All results after permutation testing using TFCE (10,000 permutations), *FWE* corrected $p < 0.05$. **E** GMV reduction in patients with DBN compared to HC. A GMV reduction was present in lobule X, the OMV (vermal lobules V-VII), nodulus and uvula (lobule IX) and the cerebellar tonsils representing the key cerebellar structures for ocular–motor and vestibular processing. An additional cluster was found in hemispheric lobules I–IV. **F** WMV reductions in patients with DBN compared to HC was observed in corresponding parts of the white matter in flocculus, fastigial oculomotor region (FOR), and lobule IX (nodulus/uvula) ($p < 0.001$, uncorrected)

Patients with DBN syndrome showed a GMV reduction restricted to the flocculus (lobule X), OMV (lobules V–VII) and nodulus/uvula (lobule IX) (Fig. 1E).

White matter volume (WMV) in the cerebellum Corresponding to the GMV reductions, patients with SCA and SAOA showed extensive WMV loss in the cerebellar hemispheres and vermis. These WMV reductions extended to the brainstem in the patients with SCA, likely demonstrating volume loss in the cerebellar peduncles up to the midbrain (Fig. 1B, D). We found WMV reductions in the flocculus (lobule X), the fastigial oculomotor region (FOR), nodulus /uvula (lobule IX) and the cerebellar tonsils in patients with DBN compared to HC (Fig. 1F).

Voxel-based morphometry—SARA scores *GMV* The regression model using the total SARA score showed a negative correlation with clusters in the cerebellum (lobules IV–VI, Crus I, II, VIIB, IX), the basal ganglia (putamen and caudate nucleus) and also prefrontal cortex (areas Fp1,2) and (pre-)motor cortex (areas 4,6) (Fig. 2A).

WMV The total SARA score showed a negative correlation with clusters in the cerebellar white matter, brainstem and reached the corticospinal tract (Fig. 2B).

Surface-based morphometry—SARA score *Cortical thickness* In congruence with the volumetric findings, we found a negative correlation of CT with higher SARA scores. This effect was most prominent in the right prefrontal cortex but also included the left prefrontal as well as the temporal and parietal lobes. (Fig. 2C). No changes in SD, GI or FD were observed.

Voxel-based morphometry—Falls efficacy scale (FES-I) *GMV* Balance confidence as assessed by the FES-I was negatively correlated with the integrity of cerebellar lobules Crus I, II and lobule IX. No association with cortical GMV was found for subjective postural stability. (Fig. 3A).

WMV We found a negative correlation of WMV in the middle cerebellar peduncle and around the vestibular nerve root entry zone with the FES-I scores (Fig. 3B).

Voxel-based morphometry—MoCA scores *GMV* The GMV reduction in relation to the MoCA score was remarkably similar compared to those of the SARA score which reflects the correlation between the variables (positive correlation of the MoCA score with brain volume). However, some differences have to be noted. Compared to the SARA score, volumetric changes in the cerebellum were restricted to lobules Crus I, II, lobule IX, dentate nucleus for the MoCA score.

In the (sub-)cortex, volumetric changes associated with the MoCA score involved the thalamus, the hippocampus, prefrontal and orbitofrontal cortex and the inferior parietal lobule as hubs of cognitive/default mode network hubs for

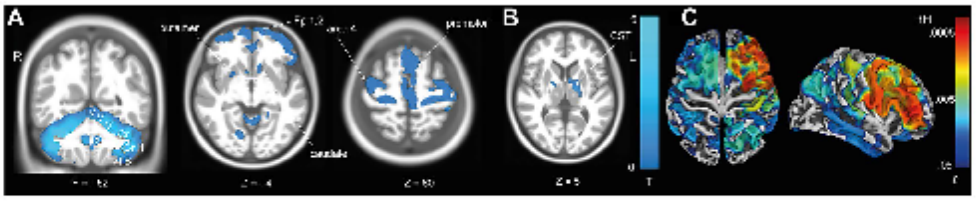

Fig. 2 Volumetric decreases associated with disease severity measured with total SARA score. Linear regression: SARA scores in all cerebellar degeneration patients. **A** Negative correlation of GMV with higher total SARA scores. Significant voxels are located in the cerebellum, basal ganglia (putamen, caudate), primary motor cortex (area 4) and prefrontal cortex (Fp1,2). **B** Negative correlation of WMV with the SARA score reached the corticospinal tract (CST). **C** Negative correlation of cortical thickness with the SARA score were most prominent in the premotor cortex and dorsolateral prefrontal cortex (DLPFC). All vbm results after permutation testing using TFCE (10,000 permutations), *FWE* corrected $p < 0.05$. All sbm results are depicted with logarithmic p value scales FWE corrected after TFCE (10,000 permutations)

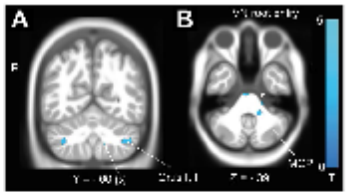

Fig. 3 Volumetric changes associated with subjective postural stability (FES-I). Subjective postural stability was correlated with **A** GMV in cerebellar lobules Crus I, II and **B** WMV in the middle cerebellar peduncle and around the vestibular nerve (VN) root entry zone. All results after permutation testing using TFCE (10,000 permutations), *FWE* corrected $p < 0.05$

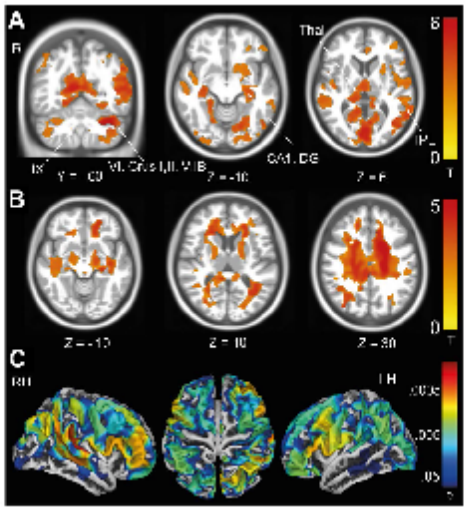

Fig. 4 Volumetric changes associated with cognitive performance (MoCA score). **A** A higher MoCA score was associated with GMV in the cerebellar cognitive lobules Crus (Cr) I, II, lobule IX, the thalamus, the hippocampus (areas CA1,DG (dentate gyrus)), inferior parietal lobule (IPL), but also prefrontal, orbitofrontal and premotor cortex. **B** A correlation of WMV with the MoCA score was detected around the hippocampi, and along the anterior thalamic radiation, but also in the white matter of the premotor cortex. **C** *SBM* showed a correlation of cortical thickness with dorsolateral prefrontal and parietal cortex. *VBM* results are thresholded at $p < 0.05$, *FWE* corrected for multiple comparisons on the cluster levels using *TFCE* (10,000 permutations). *SBM* overlays are depicted with logarithmic p-value scales *FWE* corrected after *TFCE* (10,000 permutations)

the MoCA. Additional correlations were found with visual cortex and the subcortical and cortical motor network (Fig. 4A).

WMV The WMV changes associated with the MoCA score involved cerebello-thalamo-cortical connexions with the prefrontal and motor cortex, the hippocampus and also interhemispheric connections through the posterior segments of the corpus callosum (Fig. 4B).

Surface-based morphometry—MoCA score Similar to the GMV changes, cortical thickness in the prefrontal, and temporo-parietal cortex was positively correlated with higher MoCA scores (Fig. 3C).

Voxel-based morphometry—preferred gait velocity GMV An association of GMV with self-determined gait velocity was observed with multisensory integration centres for spatial orientation, navigation and cognition (PIVC, IPS,

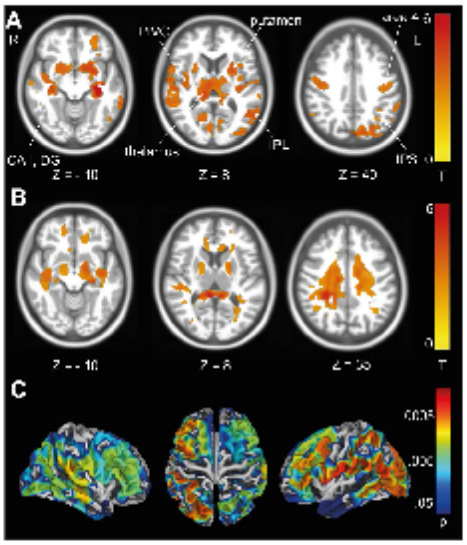

Fig. 5 Volumetric associations with preferred walking speed. **A** An association of *GMV* was observed with multisensory integration centres for spatial orientation, navigation (PIVC, IPS, visual cortex, IPL, hippocampus (subfields CA1,2)) and in the primary motor network (putamen, area 4). **B** An association with white matter volume was observed with white matter tracts around the hippocampus and PIVC, the corticospinal tract and the corpus callosum. **C** *SBM* showed an association of cortical thickness with dorsolateral prefrontal, primary sensory–motor and parietal areas. *VBM* results after permutation testing using *TFCE* (10,000 permutations), *FWE* corrected $p < 0.05$. SBM overlays are depicted with logarithmic p value scales *FWE* corrected after TFCE (10,000 permutations)

visual cortex, IPL, hippocampus (subfields CA1,2)) and in the primary motor network (putamen, area 4) (Fig. 5A).

WMV An association of preferred gait velocity with WMV was observed around the hippocampus and PIVC, the corticospinal tract and the corpus callosum (Fig. 5B).

Surface-based morphometry—preferred gait velocity SBM showed an association of cortical thickness with dorsolateral prefrontal, primary sensory–motor and parietal areas (Fig. 5C).

Clinical deficits Volumetric changes in patients with ocular–motor (gaze-evoked nystagmus) and vestibular perceptual deficits (pathologic tilts of SVV).

GMV Patients with pathological tilts of the SVV compared to those with no tilts (< 2.5°) of the SVV had GMV reduction in the key vestibulo-cerebellar hubs in lobules IX (nodulus, uvula) and X (flocculus) and lobule VIIB (OMV) and in the cerebellar hemispheres (lobules IV–VI, Crus I). Additional clusters of GMV reduction were observed in the cerebral hemispheres in primary motor cortex (area 4) and the frontal pole and orbitofrontal cortex (Fp1, P32, Fo1,2) (Fig. 6A).

Patients with gaze-evoked nystagmus showed volume loss restricted to the cerebellum (lobules X, VIIB) (Fig. 6B).

WMV In both patients with tilts of the SVV and patients with gaze-evoked nystagmus, WMV reduction was limited to the cerebellum and inferior cerebellar peduncle (Fig. 6D, E).

Volumetric changes in patients with falls at disease onset *GMV*GMV reductions in patients with a history of falls was more extensive compared to those with ocular–motor or vestibular perceptual deficits. GMV reductions were restricted to the cerebellum (vermis and hemispheres) (Fig. 6C).

WMV In contrast to the patients with ocular–motor and vestibular perceptual deficits, WMV reduction in patients with a history of falls extended to the brainstem, likely by means of volume loss in the cerebellar peduncles (Fig. 6E).

Discussion

In the current study, we found that: (I) Both SCA and SAOA led to widely distributed GMV and WMV loss in the cerebellar hemispheres. The WMV reduction extended to the brainstem and seems to be related to volume loss in the cerebellar peduncles. (II) In patients with DBN syndrome, volumetric changes follow the presumed pathophysiology with volume loss in the flocculus, nodulus, uvula and related white matter, not affecting other cerebellar functional modules or extra-cerebellar structures. (III) Falls are associated with volume loss in the brainstem. (IV) Functional disability is associated with distant volume loss in the cerebral cortex and sub-cortex.

Imaging data

The current study extends previous findings of structural degeneration in different types of ataxias. In general, patients with SCA and with SAOA showed a wide distribution of cerebellar volume loss. In contrast, volume loss in DBN followed a more restricted pattern [12, 42]. Besides the GMV reduction in the main hubs for vestibular processing in the cerebellum, an additional GMV and WMV reduction was found in the OMV and FOR [12]. The specialisation of the OMV and FOR for horizontal saccade generation, adaptation and accuracy is well established [6, 24, 39, 45]. In lesions of the FOR or OMV, saccades are mainly reported to be horizontally deviated [36, 39]. Based on the volumetric findings,

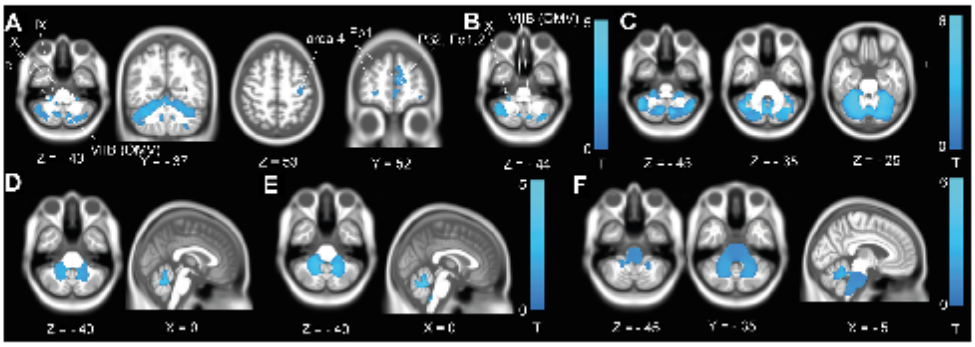

Fig. 6 Volume loss in cerebellar degeneration related to ocular–motor deficits, vestibular perceptual deficits and the history of falls. **A** GMV reduction in patients with tilts of the SVV compared to the HC. Volume reductions were found in vestibular and ocular–motor cerebellar lobules (IX, X, VIIB, corresponding to nodulus, uvula, flocculus and ocular–motor vermis (OMV). Additional GMV loss was detected in the cerebellar hemispheres. Remote volume loss was also observed in primary motor (area 4) and rostral frontal cortex (frontal pole Fp1, orbitofrontal cortex Fo 1,2 and rostral cingulate cortex p32). **B** GMV reduction in patients with gaze-evoked nystagmus compared to the HC were also located in lobules X, OMV and the cerebellar hemispheres. **C** GMV reduction in patients with falls at disease onset was observed in all cerebellar lobules. WMV loss in patients with SVV tilts (**D**) and gaze-evoked nystagmus (**E**) compared to the HC was restricted to the cerebellum around the vestibular and ocular–motor regions. In contrast, patients with a history of falling (**F**) had additional WMV loss in the brainstem, likely reflecting volume loss in the cerebellar peduncles. All results after permutation testing using TFCE (10,000 permutations), *FWE* corrected $p < 0.05$

the OMV and FOR might also be involved in the vertical resetting after the involuntary upward drift in DBN.

Structure–function association for ocular–motor/vestibular domain and falls

Both static otolith dysfunction (pathologic SVV tilts) and gaze-evoked nystagmus were associated with GMV and WMV reductions in the motor (lobules IV-VI) and vestibular/ocular–motor representations (lobules IX, X, OMV). SVV tilts were additionally associated with a GMV reduction in the primary motor cortex and prefrontal cortex, supporting the integrated nature of verticality processing [4].

Falls, as a hallmark of patients with cerebellar ataxia, were prevalent in our cohort. We found a widespread distribution of volume loss in the cerebellum and brainstem of fallers. Similarly, the regression models for balance confidence and fear of falling (i.e. FES-I) point towards a reduction of white matter connexions to the brainstem. Thus, falls would be the consequence of impaired structural connexions from the cerebellum to the brainstem for postural control, locomotion execution and vestibulo-spinal reflex functioning [11, 19].

Structure–function association for walking speed and cognitive functions

The pattern of volumetric changes in the cerebral cortex and sub-cortex for these variables involved mainly sensorimotor integration centres for spatial orientation, navigation and cognition (PIVC, IPL, IPS, hippocampus), thus indicating an interrelationship of overall cognitive and locomotor functions to non-cerebellar integration sites of motion perception and sensorimotor processes.

Structural correlates of ataxia severity

Using *VBM*, we found negative correlations between the SARA score and the cerebellum, brainstem, but also for multiple areas in the cortex and sub-cortex, such as the (pre-) motor cortex and frontal pole. Additionally, *SBM* revealed a negative correlation of cortical thickness with the SARA score, most strikingly in the premotor cortex and posterior parietal areas. Interestingly, these cerebral volumetric findings were also associated with preferred gait velocity and cognitive performance. The partial correlation analysis revealed relevant correlations between these measures. This suggests that the volumetric cerebello-cortical correlations may reflect overall functional disability in chronic cerebellar degeneration with respect to higher order processing (i.e. gait speed, cognitive processing capacity). Since these

measures were not correlated with disease duration, longitudinal data might help to further investigate the effect of disease progression on structural brain findings. It is our interpretation that the atrophy patterns above reflect the network structure of cerebello-cortical processing.

Atrophy patterns in SCA are grossly classified as involving the cerebellum only (i.e. in our cohort SCA6), pontocerebellar atrophy (SCA3) or even the cortex (SCA2) [20–22]. Widely distributed neurodegeneration has also been reported in other types of SCA including SCA3 and SCA6 [7, 32]. Given the preponderance of patients with SCA2 and SAOA in our sample, the *VBM* and *SBM* findings are likely driven by these patients.

On the other hand, DBN seems to be a very confined ocular–motor/vestibulo-cerebellar system degeneration.

In summary, the current findings indicate a phenomenology-dependent structural degeneration of different types of cerebellar disorders. Most strikingly, DBN appears to be a degeneration of mainly midline, vestibular– and ocular–motor cerebellar hubs. The challenging health problem of falls in cerebellar ataxia seems to be related to impaired connexions to the brainstem. Moreover, extra-cerebellar degeneration is present in SCA and SAOA and associated with verticality perception, global functional (dis-)ability, such as gait speed and cognitive functioning, as well as the overall severity of ataxia.

Limitations

Our patient sample includes a variety of causes of cerebellar degeneration with a moderate overall sample size. The latter is due to the rarity of cerebellar degeneration patients even in the setting of a tertiary, research-oriented facility. Furthermore, we refrained to test correlations of ataxia subtypes with whole brain imaging, given the sample size. Therefore, with the current data, functional disability in distinct subtypes of cerebellar degeneration cannot be correlated with whole brain volumetry.

However, as neurodegeneration has been shown to extend beyond the boundaries of the historical descriptions of these entities, the aim of this study was to establish common principles of structural brain changes in relation to clinical deficits in cerebellar degeneration in general. We were particularly interested in cerebello-cortical interactions.

Differential changes in functional connectivity have been established for different SCA subtypes based on resting-state fMRI [25, 26, 40]. We did not deem it appropriate to discuss the differential pattern of volumetric changes in comparison to fMRI findings in distinct SCA aetiologies due to the differences in the group composition and the methodological differences.

More recently, standardised evaluation tools have been presented to grasp differential aspects of cerebellar dysfunction, including the cognitive (CCAS scale) and ocular–motor domains (SODA score) [9, 33]. In the current study, we were particularly interested in the effects of cerebellar degeneration on cortical structure and function. Therefore, we used the Montreal Cognitive assessment as a tool to screen for cognitive dysfunction which is validated for extra-cerebellar neurodegeneration. It should be noted in addition that the CCAS scale and the MoCA cover similar functional domains.

To thoroughly characterise the ocular–motor profiles of our sample, all patients received a dedicated neuro-orthoptic and video-oculographic evaluation which also included the estimation of the SVV and fundus photography. The use of an extensive quantitative ocular–motor examination paradigm likely sufficiently covers all aspects of the standardised SODA score.

We used meticulous clinical testing with an established quantitative evaluation of ataxia, subjective stability, vestibular–/ocular–motor function and walking performance to evaluate common and distinct patterns of volume loss in cerebellar degeneration. Extensive permutation testing and conservative *FWE* correction for multiple testing (robust against false-positive) were applied to account for the above-mentioned limitations.

Conclusions

This study shows distinct volumetric changes in different types of cerebellar degeneration. Volumetric changes in cortical and subcortical hubs for motor performance, locomotion, navigation and cognition reflect functional disability in chronic cerebellar degeneration.

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Declarations

Conflicts of interest Julian Conrad reports no conflicts of interest relevant to the manuscript. Anna Huppert reports no conflicts of interest relevant to the manuscript. Ria Maxine Ruehl reports no conflicts of interest relevant to the manuscript. Max Wuehr reports no conflicts of interest relevant to the manuscript. Roman Schniepp reports no conflicts of interest relevant to the manuscript. Peter zu Eulenburg reports no conflicts of interest relevant to the manuscript.

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9. Paper II

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ORIGINAL ARTICLE

Multimodal Mobility Assessment Predicts Fall Frequency and Severity in Cerebellar Ataxia

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Abstract
This cohort study aims to evaluate the predictive validity of multimodal clinical assessment and quantitative measures of in- and off-laboratory mobility for fall-risk estimation in patients with cerebellar ataxia (CA).
Occurrence, severity, and consequences of falling were prospectively assessed for 6 months in 93 patients with hereditary ($N = 36$) and sporadic or secondary ($N = 57$) forms of CA and 63 healthy controls. Participants completed a multimodal clinical and functional fall risk assessment, in-laboratory gait examination, and a 2-week inertial sensor-based daily mobility monitoring. Multivariate logistic regression analyses were performed to evaluate the predictive capacity of all clinical and in- and off-laboratory mobility measures with respect to fall (1) status (non-faller vs. faller), (2) frequency (occasional vs. frequent falls), and (3) severity (benign vs. injurious fall) of patients.
64% of patients experienced one or recurrent falls and 65% of these severe fall-related injuries during prospective assessment. Mobility impairments in patients corresponded to a mild-to-moderate ataxic gait disorder. Patients' fall status and frequency could be reliably predicted (78% and 81% accuracy, respectively), primarily based on their retrospective fall status. Clinical scoring of ataxic symptoms and in- and off-laboratory gait and mobility measures improved classification and provided unique information for the prediction of fall severity (84% accuracy).
These results encourage a stepwise approach for fall risk assessment in patients with CA: fall history-taking readily and reliably informs the clinician about patients' general fall risk. Clinical scoring and instrument-based mobility measures provide further in-depth information on the risk of recurrent and injurious falling.

Keywords Cerebellar ataxia · Falls · Fall prediction · Gait analysis · Mobility monitoring

Introduction

Gait disturbances are a common and disabling complication in patients with cerebellar ataxia (CA) with significant implications for patients' capacity for independent living and quality of life [1, 2]. Walking impairments in CA are linked to a considerable risk of recurrent falling, which frequently results in severe secondary comorbidities and a loss of functional independence. Retrospective and prospective fall surveys in CA indicate that 74–93% of patients experience at least one fall per year [3–5]. Many of these patients suffer from fall-related injuries (74–85%), which potentially (23–31%) result in a fracture or joint dislocation [3, 4]. Since causal therapeutic approaches are currently not available [6, 7], a primary treatment objective in CA is an effective prevention of falling and fall-related injuries.

Fall prevention in CA requires reliable screening and classification procedures to assess and identify individuals at particular risk of falling and severe fall-related complications. Distinct risk factors including symptom severity, the number of non-ataxic symptoms, and the duration and etiology of disease were associated to higher fall rates in CA patients [3–5, 8]. However, the predictive validity of these factors considerably differed between studies. Complementary approaches aim to identify fall risk-related features

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linked to balance and gait impairments in CA. Accordingly, variability in the movement pattern, a defining feature of gait ataxia [9, 10] that increases with disease severity [11], was shown to be associated with patients' general fall status and risk of recurrent falling [2, 11, 12]. Subsequent analyses, however, indicated that gait variability markers may be only predictive for a specific subclass of falls (falls resulting from tripping or stumbling) [13]. Furthermore, quantitative gait assessment is currently mostly restricted to in-laboratory settings and thus potentially underestimates the challenges of everyday-life mobility during which patients actually fall.

Recent advances in off-laboratory mobility assessment using body-worn inertial sensors promise a more specific characterization of patients' balance impairments and fall risk in environmentally valid settings [14]. Inertial sensor-based mobility assessment has been shown to consistently capture central features of ataxic gait impairments under real-life conditions [15]. In contrast to in-laboratory gait assessment approaches that primarily focus on a detailed characterization of spatiotemporal features of walking impairments, body-worn sensors may further provide important complementary insights into patients' overall mobility status and balance capabilities from a macroscopic perspective [14, 16–19]. This information could supplement and overcome limitations of currently available screening tools for fall risk assessment in CA.

The aim of this study was to evaluate and compare the predictive validity of currently available and recently established screening tools for fall risk identification in patients with CA. To this end, we prospectively assessed the occurrence, frequency, and consequences of falling in a comprehensive cohort of patients with CA of different etiologies. Subsequently, multimodal score-based and clinical fall risk assessment outcomes as well as measures from instrument-based in-laboratory gait examination and long-term off-laboratory mobility monitoring were evaluated with respect to their relevance for forecasting the occurrence, frequency, and severity of falls.

Methods

Participants

Longitudinal cohort study with 93 patients with CA and 63 healthy controls recruited (study ID: DRKS00007762) from 06/2015 to 02/2018 at the University Hospital Munich. Patients were included based on the following criteria: (1) presence of clinical ataxia [20] due to sporadic, secondary, or hereditary forms of CA, (2) age between 18 and 80, and (3) ability to ambulate independently without walking aids. Inclusion criteria for controls were (1) no history of neurological or psychiatric disease, (2) age between 18 and 80, and (3) no other diseases with manifest ambulation problems.

Clinical Work-Up and Fall Assessment at Inclusion

All patients and controls underwent a standardized physical examination, which included a survey of the following information: ambulatory status, functional status, medication, and falls within the preceding 6 months. According to the WHO criteria, a fall was defined as an event which results in a person coming to rest inadvertently on the ground or floor or other lower level [21]. A near-fall was defined as an event that results in a marked postural instability requiring a supporting step and/or balance adjustment. Retrospective fall assessment included information on fall status (faller vs. non-faller), fall frequency (no, occasional, frequent falls (≥ two falls)), and fall severity (1: near-fall; 2: no or mild injury; 3: injury requiring medical attention; 4: injury requiring hospital admission) according to the Hopkins Falls Grading Scale (HFGS) [22]. The subjective level of stability was assessed by the Falls Efficacy Scale-International (FES-I) and the Activities-specific Balance Confidence Scale (ABC-d) [23, 24]. Health-related quality of life was assessed by the Short-Form Health Survey (SF-12) [25]. Cognitive function was screened with the Montreal Cognitive Assessment (MOCA) [26]. Each participant underwent a complete neurological and physical examination including the assessment of functional mobility by the Timed up and Go Test (TUG) and the Functional Gait Assessment Score (FGA) [27, 28]. Severity of ataxia symptoms in patients was rated using the Scale for the Assessment and Rating of Ataxia (SARA) with a maximum of 40 points (indicating most severe form of ataxia) [29].

Prospective Fall Assessment

Each participant was provided with a fall diary covering a 6-month follow-up period. Participants were asked to document near-fall and fall events on a daily basis with information on the time, the environmental circumstances, the fall mechanism (e.g., tripping, vertigo/dizziness, impaired consciousness, others), the duration of the post-fall lying phase, and the related HFGS of each event. Participants were additionally contacted by phone monthly to cross-check and validate the documented information. Based on the prospective fall assessment, participants were categorized with respect to fall status, frequency, and severity.

In-laboratory Gait Examination

In-laboratory gait assessment was performed on a 6.7 m-long pressure-sensitive carpet (GAITRite®, CIR System, Sparta, NJ, USA) at 120 Hz. Participants walked over the carpet at

their self-chosen (PWS), slow (SWS), and maximum walking speed (MWS). Each condition was recorded 4 times. Gait assessment was conducted without additional ambulatory aids. For each walking condition, the following spatiotemporal gait parameters were analyzed: gait velocity, base of support, stride length, stride time, swing phase percentage, double support percentage, coefficient of variation (CV) of the base of support, CV of stride time, CV of stride length, gait asymmetry index, and phase synchronization index [30].

Off-laboratory Mobility Assessment

Following the initial visit, monitoring of daily mobility was undertaken for 14 days. Participants wore an inertial sensor-based activity monitor (ActivPAL®, PAL Technologies, Glasgow), which recorded the sequence and period of individual bouts of ambulatory, sedentary, and sleeping behavior at 10 Hz. The inertial sensor was placed on the thigh of the dominant leg approximately 0.1 m cranially and 0.05 m laterally to the patella. Participants were advised to continue their daily activities as usual and not to change their routine. Upon completion of the recording period, participants removed the sensor by themselves and send it back by mail.

The following parameters (expressed as average daily estimates) were computed from the ActivPAL data [31, 32]: daily intensity (amount of daily energy expenditure expressed as the total metabolic equivalents (METS)), daily volume (percentage of ambulatory, sedentary, or sleeping time), daily step count, daily number of sit-to-stance transitions, daily pattern of ambulatory behavior (computed as the exponent alpha that quantifies the distribution of bouts, with lower alpha values indicating a greater contribution of long bouts).

Data Analysis Procedures

Descriptive statistics are reported as mean ± SD. In a first step, analysis of variance (ANOVA) and chi-squared tests were used to test for differences of metric and categorical parameters from clinical assessment, in-laboratory gait examination, off-laboratory mobility assessment, and retro- and prospective fall assessment between patients and controls. The subsequent statistical analyses focused solely on patient data: multivariate backward logistic regression analyses (controlled for age, gender, and leg length) were performed to identify independent predictors associated with the three dependent prospectively assessed fall measures of interest: (I) non-faller vs. faller, (II) occasional vs. frequent faller, and (III) non-severe vs. severe falling (defined as HFGS 3 or 4). For each regression model sensitivity, specificity and correct classification are reported as quality parameter derived by the classification matrix. Initially, all potential predictor parameters from clinical and mobility assessment were subjected to an ANOVA (including post hoc comparison via Sheffé procedures) with respect to the three above-mentioned fall categories. Subsequently, only those parameters that yielded a significance level of their F value ≤ 0.05 were considered in the respective regression model. To avoid collinearity, relationships among parameters were examined using Pearson's correlations. If parameters were strongly correlated ($r > 0.7$), only the one most strongly associated with the dependent measure was retained. This statistical approach is based on [33]. Statistical analysis was performed using SPSS (Version 25.0; IBM Corp., Armonk, NY).

Results

Characteristics of the Study Cohort

Demographic information and clinical characteristics of patients and controls are summarized in Table 1. The patient cohort included hereditary degenerative forms of ataxia ($N = 36$), sporadic degenerative forms of ataxia (sporadic adult-onset ataxia, $N = 36$), ataxia due to focal vascular or neo-plastic cerebellar lesions ($N = 3$), and downbeat nystagmus syndrome ($N = 18$). Patients had a mean SARA score of 10.2 (range: [3;24]), indicating an on average moderate severity of ataxic symptoms. Accordingly, assessment of functional mobility revealed mildly impaired balance and gait capacity of patients compared to controls (FGA: $F_{1,153} = 91.4$, $p < 0.001$) despite normal performance in the TUG. Patients reported increased fear of falling (FES-I: $F_{1,153} = 78.5$, $p < 0.001$), decreased balance confidence (ABC-d: $F_{1,153} = 114.8$, $p < 0.001$), and showed moderately reduced cognitive function (MoCA: $F_{1,153} = 16.3$, $p < 0.001$). Health-related quality of life scores did not differ between patients and controls.

In- and Off-laboratory Mobility Assessment

Descriptive information on outcomes from in- and off-laboratory mobility assessment is summarized in Table 2. During in-laboratory gait assessment, patients showed walking impairments corresponding to an ataxic gait disorder with reduced walking speed ($F_{1,153} = 39.9$, $p < 0.001$), prolonged double support phases ($F_{1,153} = 22.6$, $p < 0.001$), increased base of support ($F_{1,153} = 65.7$, $p < 0.001$), spatiotemporal variability (stride length CV: $F_{1,153} = 21.3$, $p < 0.001$; stride time CV: $F_{1,153} = 28.1$, $p < 0.001$), and asymmetry within their stride-to-stride pattern (gait asymmetry: $F_{1,153} = 24.5$, $p < 0.001$; phase synchronization: $F_{1,153} = 17.3$, $p < 0.001$). Off-laboratory monitoring of daily life mobility revealed a general reduction of energy expenditure ($F_{1,153} = 48.7$, $p < 0.001$) with a reduced daily amount of time spent during

Table 1 Characteristics of the study cohort

	Healthy subjects	Cerebellar disorders	$F_{1,153}$		p
Demographical characteristics					
N (f/m)	63 (31/32)	93 (35/58)			
Age [y]	49 ± 14	57 ± 18	2.4		n.s
Diagnoses		14 SCA 11 FRDA 11 EA2 18 DBN 35 SAOA 1 ARAC 1 ACM 1 post stroke			
Clinical performance scales					
SARA score [points]	–	10.2 ± 2.6			
FGA [points]	29 ± 3	21 ± 6	91.4		< 0.001
TUG [s]	8.8 ± 3.2	11.2 ± 7.1	0.7		n.s
MOCA [points]	29 ± 3	24 ± 6	16.5		< 0.001
Subjective symptome scales					
ABC-d [%]	95 ± 9	63 ± 22	114.8		< 0.001
FES-I [points]	17 ± 2	31 ± 13	78.5		< 0.001
SF-12 [points]	31 ± 3	30 ± 4	1.15		< 0.001
			df	c^2	p
Retrospective falls status					
No falls [n, %]	57, 90	32, 34	2	37.2	< 0.001
Occasional fall [n, %]	4, 7	21, 23			
Frequent falls [n, %]	2, 3	40, 43			
Retrospective falls severity					
Hopkins grade I [%]	28, 45	22, 24	3	46.8	< 0.001
II [%]	17, 27	46, 49			
III [%]	17, 27	14, 15			
IV [%]	0, 0	11, 12			

f, female; *m*, male; *FGA*, functional gait assessment; *FES-I*, falls efficacy scale – international; *TUG*, timed-up-and-go test; *MOCA*, montreal cognitive assessment; *SF-12*, short form 12; *BVP*, bilateral vestibular failure; *UVP*, unilateral vestibular failure; *SCA*, spinocerebellar ataxia; *FRDA*, friedreich ataxia; *EA2*, episodic ataxia type 2; *DBN*, downbeat nystagmus syndrome; *SAOA*, sporadic adult onset ataxia; *ARAC*, autosomal recessive cerebellar ataxia; *ACM*, tumor cerebellar; C^2, chi-square test

ambulation ($F_{1,153} = 45.2$, $p < 0.001$) and a smaller step count ($F_{1,153} = 45.1$, $p < 0.001$) in patients compared to controls.

Fall Assessment

Fall epidemiology in patients and controls is summarized in Tables 1 and 3. Both retrospective and prospective assessments revealed a considerably higher incidence of fallers, recurrent fallers, and severe fall-related injuries in patients compared to controls. According to the retrospective fall assessment, 66% of patients had experienced at least one fall within the last 6 months and 66% of those reported recurrent falling. Thirty-six percent of patients that fell reported fall-related injuries that required medical attention.

In the 6-month follow-up period, all participants registered fall information in their falls diary that was counter-checked by structured monthly telephone interviews. Falls diary information from 13 patients and 7 controls was considered invalid and excluded from further analysis due to missing telephone contact data or discrepancies between the falls information documented in the diary and surveyed during monthly phone interviews. The total numbers of near-fall and fall events in patients registered during prospective assessment were 313 and 612, respectively. A majority of falls in patients with CA occurred indoors (75%) in domestic environments (71%), primarily on even surface (71%). Most falls were linked to walking or turning (71%) and 74% occurred either forwards or backwards. The most frequent causes of falling in patients were tripping (33%) and imbalance (23%). The most commonly reported associated symptoms with falling were dizziness and vertigo (20%) (Tables 3 and 4). A

Table 2 In- and off-laboratory gait and mobility assessment

	Healthy subjects	Cerebellar disorders	$F_{1,153}$	p
In-laboratory gait measures				
Gait velocity [m/s]	1.2 ± 0.2	0.9 ± 0.2*	39.9	< 0.001
Stride length [m]	1.3 ± 0.2	1.1 ± 0.3	34.5	< 0.001
Stride time [s]	1.1 ± 0.1	1.3 ± 0.1*	9.0	0.003
Swing phase [%]	38 ± 2	37 ± 2	63.4	< 0.001
Double support phase [%]	24 ± 4	30 ± 9*	22.6	< 0.001
Base of support [m]	0.08 ± 0.03	0.15 ± 0.06*	65.7	< 0.001
Base of support CV [%]	24 ± 15	24 ± 12	0.7	n.s
Stride length CV [%]	2.2 ± 1.1	5.6 ± 4.6*	21.3	< 0.001
Stride time CV [%]	2.3 ± 1.9	5.2 ± 1.2*	28.1	< 0.001
Gait asymmetry index [%]	2.5 ± 1.5	6.8 ± 3.7*	24.5	< 0.001
Phase synchronization [%]	4.1 ± 1.4	9.9 ± 5.3*	17.3	< 0.001
Mobility				
Adherence				
Days recorded [d]	12.3 ± 1.9	12.4 ± 1.2	0.2	n.s
Time sensor worn [%]	96 ± 12	99 ± 6	0.8	n.s
Volume				
Median step count ± SD [#]	10,208 ± 3,299	6305 ± 3,302*	45.1	< 0.001
Mean ambulation % ± SD [%]	8.7 ± 2.6	5.7 ± 2.5*	45.2	< 0.001
Mean sedentary % ± SD [%]	27.8 ± 7.7	34.5 ± 10.2*	39.2	< 0.001
Median sleep % ± SD [%]	40.8 ± 6.7	42.3 ± 9.9	0.9	n.s
Activity				
Median ambulation bout # ± SD [#]	456 ± 134	338 ± 139*	23.8	< 0.001
Ambulatory bout duration ± SD [s]	17 ± 5	15 ± 4	9.8	.002
Mean daily intensity ± SD [MET]	35 ± 1	33 ± 1*	48.7	< 0.001
Pattern				
Mean ambulation alpha ± SD	1.42 ± 0.04	1.43 ± 0.04	1.5	n.s
Median sit-walk transitions ± SD	40 ± 16	36 ± 13	2.7	n.s

*indicates significant difference in the Sheffé posthoc comparison (to healthy subjects)

CV, coefficient of variation; *SD*, standard deviation

Table 3 Outcomes form prospective fall assessment

	Proportion of fallers				Fall events			
	Healthy subjects $N = 56$		Cerebellar disorders $N = 80$		Healthy subjects $N = 9$ falls		Cerebellar disorders $N = 313$	
	N	%	*N*	%	*N*	%	*N*	%
Fall epidemiology								
No falls	47	**84**	28	**36**	–	–	–	–
Occasional fall	9	**16**	18	**23**	9	**100**	18	**6**
Frequent falls	0	**0**	34	**41**	0	**0**	295	**94**
	$Chi^2 < 0.001$				**$Chi^2 < 0.001$**			
Fall severity (HFGS)					$N = 18$		$N = 925$	
1	4	**31**	10	**14**	9	**50**	612	**66**
2	5	**38**	44	**63**	5	**20**	293	**32**
3	4	**31**	14	**18**	4	**22**	16	**2**
4	0	**0**	4	**5**	0	**0**	4	**0**
	$Chi^2 < 0.001$				**$Chi^2 < 0.001$**			

Information on falls epidemiology on considers actual fall events (excluding near-fall events). Information on falls severity considers both fall and near-fall events

HFGS, Hopkins falls grading scale

total of 5% of falls resulted in injuries which required outpatient medical treatment and 1% necessitated inpatient medical treatment. Overall, outcomes from prospective assessment revealed that 64% of the patients experienced falls within the 6-month follow-up period and 65% of these patients reported recurrent falling. Severe fall-related injuries that required medical attention occurred in 29% of patients that fell (Table 3).

Multivariate Fall Classification Models

The predictive model for fall status (non-faller vs. faller) was obtained after 10 iteration steps and yielded a correct prediction of 78% (sensitivity: 70%; specificity: 86%). The model included 5 predictive factors from socio-demographic and in-laboratory mobility assessment, with the most important being retrospective fall status and CV of stride time during slow walking (Table 5, Section A). Accordingly, a positive history of falls and impaired dynamic walking stability were the most important risk factors for experiencing falls during follow-up. No parameter of the mobility assessment was significantly represented in this model (Fig. 1).

The predictive model for fall frequency (occasional vs. frequent faller) was obtained after 13 iteration steps and achieved a correct prediction of 81% (sensitivity: 77%; specificity: 86%). The model included 3 predictive variables from socio-demographic and off-laboratory mobility assessment, with the most influential being retrospective fall status and intensity of daily mobility (Table 5, Section B). Thus, besides a positive history of falls, high daily activity levels were an independent risk factor for frequent falling during follow-up assessment (Fig. 1).

The predictive model for fall severity (falls that do vs. do not necessitate medical attention) was obtained after 12 iteration steps and yielded a correct prediction of 84% (sensitivity: 75%; specificity: 89%). The model only considered 2 parameters from clinical and off-laboratory mobility assessment, namely the subscore "heel-shin-test" of the SARA and ambulatory bout alpha (Table 5, Section C) (Fig. 1).

Discussion

In this study, we prospectively assessed the occurrence, circumstances, and consequences of falling in patients with CA and evaluated the predictive validity of a comprehensive set of clinical and instrument-based health and mobility screening tools for identifying patients at particular risk of falling. Prospective fall assessment revealed that recurrent and injurious falling is a severe complication already in mild-to-moderate stages of cerebellar disease. Multimodal measures from clinical and

Table 4 Prospective fall assessment. Fall event details

	fall events			
	Healthy subjects $n=9$ falls		Cerebellar disorders $n=313$	
	n	%	*n*	%
Environment				
At home	2	**22**	207	**71**
Public area	7	**78**	83	**29**
Indoor	2	**22**	218	**75**
Outdoor	7	**78**	72	**25**
	xx			
Even underground	0	**0**	210	**71**
Uneven underground	1	**11**	10	**3**
Stairs	1	**11**	28	**9**
Incline/decline	2	**22**	4	**1**
Slippery underground	3	**33**	22	**7**
Obstacle	2	**22**	21	**7**
Circumstances				
Morning	0	**0**	84	**28**
Noon/afternoon	4	**44**	144	**48**
Evening	5	**56**	68	**23**
Night	0	**0**	16	**5**
Symptoms				
Dizziness/ vertigo	0	**0**	60	**20**
Pain	2	**22**	5	**2**
Weakness	0	**0**	6	**2**
Collapse	0	**0**	14	**4**
Not specified	7	**78**	228	**73**
Sequence				
Anterior	5	**56**	101	**35**
Posterior	1	**11**	114	**39**
Lateral	3	**33**	69	**24**
Vertical	0	**0**	5	**2**
Tripping	2	**22**	104	**38**
Slipping	3	**33**	22	**8**
Weakness	0	**0**	46	**17**
Instability/ imbalance	0	**0**	88	**32**
Inattentive	0	**0**	9	**3**
Contact/ collision	4	**44**	3	**1**
Behavior				
Locomotion	4	**44**	203	**66**
Transition	0	**0**	42	**14**
Turning	2	**22**	16	**5**
Reaching/leaning	0	**0**	26	**9**
Standing	0	**0**	19	**6**
Sitting	0	**0**	1	**0**
Doing sports/ activities	3	**33**	2	**0**

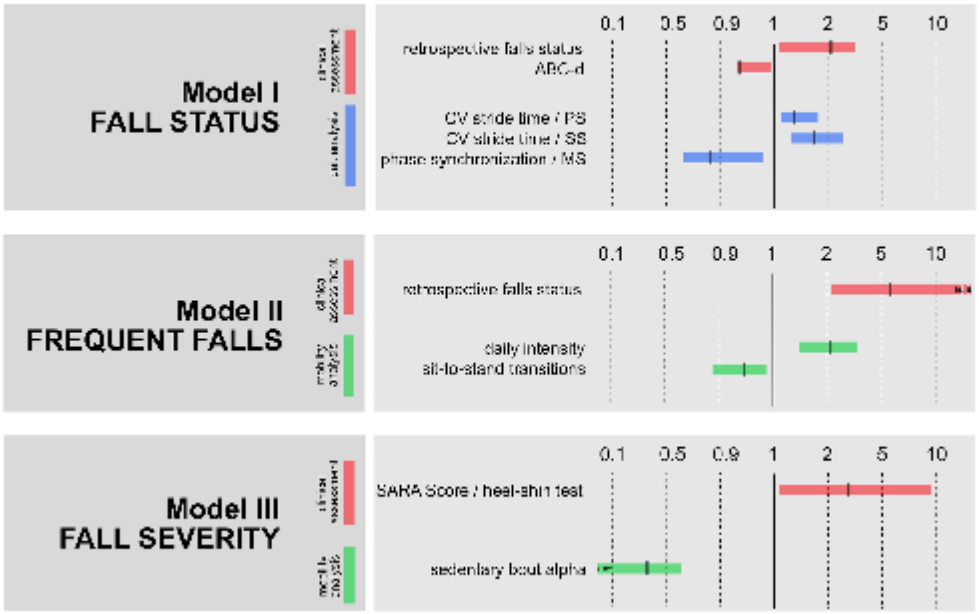

Fig. 1 Overview of predictive factors for fall events in CA. Figure 1 represents the relevant factors for predicting fall events (model 1-3). Paramters were derived from clinical assessment (red), in-laboratory gait assessment (green), and off-laboratory mobility assessment (blue). Bars represent the limits of Exp(beta) of the regression models

in- and off-laboratory assessment not only allowed us to characterize complementary aspects of the health and mobility status in CA, but were differentially associated with distinct aspects of fall events in patients with CA. Consequently, multivariate fall risk classification models built on these measures yielded a high accuracy that outperforms previous models that only considered a limited set of explanatory characteristics. In the following, we will discuss the differential relationships between health status, mobility impairments, and risk of falling in CA and propose a guideline for a multi-level, stepwise approach for fall risk assessment in these patients.

Balance and Mobility Impairments

Patients in our study cohort had different etiologies of CA at rather early stages of disease with mild-to-moderate symptom severity indicated by an average SARA score of 10 points. Clinical scoring of functional mobility in these patients demonstrated moderate impairments of balance and gait regulation. In-laboratory gait assessment showed corresponding walking characteristic of the staggering, broad-based phenotype of ataxic gait disorders [9, 10, 34, 35]. Balance and gait impairments both correlated with disease severity and were linked to reduced subjective balance confidence and increased fear of falling [11].

Off-laboratory measures of daily activity indicated only mildly affected everyday mobility behavior in patients with moderate reductions in the total volume and intensity of ambulatory activity. Patients performed less and shorter periods of walking and spent more time with sedentary behavior. In contrast to gait impairments, alterations of patients' daily mobility were mainly independent of ataxia severity. Correspondingly, patients reported near-to-normal health-related quality of life scores (SF-12). In contrast, two previous studies on patients with hereditary CA at more advanced disease stages observed considerable impairments of daily activities that correlated with the severity of ataxic symptoms [18, 19]. Our findings thus suggest that despite apparent balance and gait impairments, patients at early stages of CA are more or less able to manage and retain near-to-normal daily life activity. However, impairments of daily mobility become increasingly relevant and disabling for patients at later stages of disease.

Table 5 Multivariate fall classification models

	Model information	Parameter information						
	Correct prediction	Coefficient	SE	df	*p*	Exp(b)	Low	High
A)**Model fall status**	0.78							
Retrospective fall status		0.73	0.32	1	0.024	**2.076**	1.101	3.913
ABC-d		−0.03	0.02	1	0.037	**0.936**	0.940	0.998
Preferred walking—CV of stride time		0.25	0.16	1	0.045	**1.289**	1.102	1.761
Slow walking—CV of stride time		0.65	0.21	1	0.031	**1.757**	1.251	2.321
Maximally fast walking—phase synchronization index		−0.22	0.10	1	0.022	**0.806**	0.670	0.971
B)**Model fall frequency**	0.81							
Retrospective fall status		1.92	0.53	1	0.001	**6.850**	2.445	19.193
Daily intensity		0.83	0.12	1	0.004	**2.382**	1.309	4.333
Sit-to-stand transitions		−0.059	0.03	1	0.033	**0.943**	0.893	0.995
C)**Model fall severity**	0.84							
SARA subscore heel-shin test		1.16	0.56	1	0.037	**3.201**	1.075	9.534
Sedentary bout alpha		−1.45	0.95	1	0.044	**0.467**	0.002	0.621

ABC-d, activity-specific balance confidence scale; *CV*, coefficient of variation; *SARA*, scale for the assessment and rating of ataxia

Fall Epidemiology and Fall Risk Prediction in Patients with CA

Our 6-month prospective fall assessment in patients with CA revealed a fall incidence of 64%, which lies within the range of previous reports (50% in a 3-month assessment period [3], 84% in a 1-year assessment period [5]). Two third of patients that fell experienced recurrent falling and one third suffered from severe fall-related injuries requiring medical attention or even inpatient treatment. Furthermore, direct comparison of retrospective and prospective fall assessment outcomes revealed a high agreement with respect to fall status, frequency, and severity. Overall, retrospective and prospective fall assessment outcomes both emphasize that recurrent and injurious falling are frequent already in early stages of CA despite the relatively preserved ability for independent ambulation in these patients.

The relative distribution of circumstances and mechanisms of falling reported during prospective assessment largely confirm previous reports [3, 5, 36]. Most falls of patients occurred indoors on even ground and were linked to activities of walking or turning. The predominant causes of falling were tripping and postural instability. This suggests that most falls in CA are intrinsically generated in situations where the center of mass moves outside the base of support and dynamic balance cannot be adequately recovered. Furthermore, the high rate of sensations of vertigo and dizziness associated with falling in patients supports previous reports on the prevalence of persistent or episodic symptoms of vertigo and dizziness in CA ("cerebellar vertigo and dizziness") [37, 38].

To identify explanatory variables that may predict patients' fall status, frequency, and severity, we performed multiple regression analyses considering a wide range of sociodemographic characteristics and outcomes from clinical, self-report-based, and in- and off-laboratory gait and mobility assessments. Predictive models for each of the three fall categories yielded good-to-excellent classificatory performance (78–84%) with respect to previously established criteria for fall risk assessment approaches [39, 40]. Accurate prediction of both patients' general fall status and fall frequency primarily relied on information from retrospective fall assessment. Accordingly, the presence of previous falls was the single most influential predictor for experiencing one or more falls in the 6-month follow-up assessment. Analogous to fall risk assessment guidelines in geriatric populations [41, 42], this finding suggests that patients' fall history should be routinely surveyed during general medical history taking in order to readily identify those patients with particular risk of falling.

Prediction of patients' general fall status further relied on parameters from in-laboratory gait assessment. In particular, increased levels of gait variability were identified as an independent risk factor for experiencing falls during the follow-up period. Irregularity of movement is a defining characteristic of cerebellar disease [9, 10] and scales with the severity of symptoms [11]. A close link between increased gait variability and the risk of falling in CA has been previously reported based on retrospective fall information [2, 11]. This relationship has been shown most prominent for slow walking modes. The current findings further complement this hypothesis by giving evidence for a relationship between gait variability at preferred speed

walking and prospective fall risk in patients with CA. Gait irregularities have been particularly linked to the risk of falling due to tripping during undisturbed walking [36] — the most prevalent fall mechanism in our cohort. Thus, instrument-based measures of gait instability appear to be a suitable tool to improve the baseline fall risk estimation in patients with CA.

Interestingly, off-laboratory mobility measures did not contribute to basic fall risk estimation, but only became relevant for identifying patients at particular risk of frequent and injurious falling. Accordingly, prolonged periods of sedentary activity were predictive for injurious falling and a higher intensity of daily-life activity for experiencing recurrent falls. At first glance, the latter observation appears to be counterintuitive, since the level of daily physical activity is considered a global health marker [43] and training-induced increases in physical activity were found to not affect the risk of falling in an elderly population [44]. However, previous reports correspondingly observed that higher amounts of physical activity are associated to an increased fall risk in the elderly population [45] and patients with early Parkinson's disease [17]. This suggests that especially patients with early-stage gait impairments who still maintain near-to-normal levels of daily activity are at particular risk of experiencing recurrent falls during ambulation. It is reasonable that a higher exposure to gait instability during preserved daily activity behavior might influence the risk for frequent falling in a supraordinate way. This risk presumably not decreases before advanced disease stages that are linked to considerably reduced levels of daily activity [17]. However, a clinical advice to reduce ambulatory activity to protect patients from recurrent falling would not be appropriate due to the apparent neuroprotective effects of activity in these patients [46, 47]. Rather, a balance must be found between maintaining activity and applying protective measures that specifically minimize the risk of severe fall-related injuries in these patients.

Whether the severity of ataxic symptoms directly influences fall risk in patients with CA is still controversial. A retrospective study in patients with spinocerebellar ataxias found that fall frequency was associated with the severity of ataxia assessed by the SARA score [4]. However, this association failed to persist in a subsequent prospective follow-up study on the same cohort [5]. A more recent study including patients with sporadic and hereditary forms of CA found no evidence for an association between the SARA score and patients' fall risk [11]. Our findings support the latter observations but further indicated that the severity of ataxic symptoms becomes relevant for estimating patients' risk of injurious falling. Accordingly, an increase in the SARA score (subscore for limb ataxia) more than doubled the risk of experiencing fall-related injuries that necessitated medical attention. This association presumably points to a link between the severity of ataxic symptoms (particularly limb dysmetria) and the patients' capacity for protective postural coping strategies to counterbalance falls. A severe discoordination of limb movements might thus interfere with and hinder the execution of protective postural adjustments while falling.

Taken together, the differential contributions from clinical and instrument-based measures for predicting fall risk in CA encourage and provide guidelines for a multi-level, stepwise fall risk assessment approach in these patients: Accordingly, basic index information that is readily available from medical history taking allows a good estimation of the general fall risk and may promptly inform the clinician which patient would or would not benefit from a more in-depth examination. For those patients at risk of falling, a more elaborate disease severity rating and measures from instrument-based gait and mobility examination provide additional, unique information with respect to the severity of their fall susceptibility and the likelihood for the occurrence of severe fall-related injuries.

Study Limitations

The cross-sectional study design yielded a heterogenous sample of patients including hereditary, sporadic, and secondary forms of CA which comfounds a direct comparison to previous reports that only considered hereditary forms of CA [4, 5, 18]. However, despite this heterogeneity and the preponderance of earlier disease stages in our cohort, we found a good agreement with existing literature regarding the epidemiology, circumstances, and mechanism of falling in CA. Furthermore, we did not analyze effects of medications on fall risk in our patients with CA. Medication status, in particular, the commonly described "fall risk increasing drugs" such as hypnotics, antipsychotics, antidepressants have been shown relevant risk factors for fall occurrence in geriatric populations [48] and should be considered in follow-up studies. Finally, we are aware that the applied technology for in- and off-laboratory assessment of gait and mobility function is elaborate and currently restricted to specialized clinical centers. However, relevant outcome measures of these assessments (e.g., gait variability or intensity of daily activities) have been shown to be reliably transferable to low-cost wearable technology [15, 49] that could in future facilitate a broad application of a multimodal fall risk screening in patients with CA.

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Data Availability Data reported in this article will be shared with any appropriately qualified investigator on request after pseudonymization.

Declarations

Ethics Approval The study protocol was approved by the local Ethics Committee of the Ludwig-Maximilians University of Munich, (Nr. 421–13) and was conducted according to the Declaration of Helsinki.

Consent to Participate All participants gave their informed written consent prior to the experiments.

Conflict of Interest The authors declare no competing interests.

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