UNIVERSITAT DE BARCELONA

Aplicaciones de telemedicina en el seguimiento clínico de pacientes con enfermedades autoinmunes del sistema nervioso central

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Tesis doctoral

Aplicaciones de telemedicina en el seguimiento clínico de pacientes con enfermedades autoinmunes del sistema nervioso central

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Informe de los directores de la tesis

El Dr. Albert Saiz Hinarejos, Doctor en Medicina y Cirugía, Profesor Agregado de Medicina de la Universidad de Barcelona, y Coordinador de la Unidad de Neuroinmunología y Esclerosis Múltiple del Servicio de Neurología del Hospital Clinic de Barcelona, y la Dra. Yolanda Blanco Morgado, Doctora en Medicina y Cirugía, Profesora Asociada de Medicina de la Universidad de Barcelona, y Especialista Sénior en Neurología del Servicio de Neurología del Hospital Clinic de Barcelona,

Certifican:

Que la memoria titulada "Aplicaciones de la telemedicina en el seguimiento clínico de pacientes con enfermedades autoinmunes del sistema nervioso central", presentada por Nuria Solà Valls para optar al grado de Doctor en Medicina por la Universidad de Barcelona se ha realizado bajo nuestra dirección y cumple todos los requisitos necesarios para ser defendida ante el tribunal correspondiente.

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1. AGRADECIMIENTOS

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2. PRESENTACIÓN

2. Presentación

Esta tesis doctoral se estructura según las directrices de la normativa para la presentación de tesis doctorales como compendio de publicaciones aprobada por la Comisión de Doctorado del Consejo de Gobierno en fecha 24 de Julio de 2008 y modificada el 28 de abril de 2010, al amparo del régimen previsto en el RD 99/2011 del 28 de enero.

La presente memoria se basa en cuatro artículos originales y un articulo de revisión que pertenecen a una misma línea de investigación: la aplicación de herramientas telemáticas para la monitorización clínica de pacientes con enfermedades autoinmunes del sistema nervioso central (SNC).

A modo de resumen, los trabajos presentados en esta tesis han confirmado la viabilidad del uso de herramientas telemáticas para monitorizar el estado neurológico de pacientes con enfermedades autoinmunes del SNC en nuestro medio. Han permitido validar dos de las escalas clínicas más utilizadas en esclerosis múltiple (EM) para su uso remoto y en castellano, un procedimiento necesario para asegurar la fiabilidad de los datos clínicos obtenidos mediante telemedicina. Además, han aportado información relevante sobre el estado funcional de los pacientes en su entorno habitual que complementa la información obtenida en el ámbito hospitalario. Así como ejemplo, hemos visto que la actividad diaria medida por un acelerómetro triaxial es una herramienta más sensible que las medidas convencionales a la hora de monitorizar el estado clínico de los pacientes. Finalmente, hemos demostrado que las herramientas telemáticas son útiles no sólo para evaluar la discapacidad física sino también la cognitiva, y que ayudan a evaluar a pacientes con enfermedades de baja prevalencia, tal como la encefalitis autoinmune mediada por anticuerpos contra la proteína "leucine-rich glioma-inactivated 1" (LGI1), y a analizar qué factores predicen un deterioro cognitivo a largo plazo.

La doctoranda ha recibido financiación del Hospital Clínic de Barcelona a través de un Premio Fin de Residencia Emili Letang, la Fundació Clínic per a la Recerca Biomédica (FCRB) y posteriormente por el Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS) mediante un contrato predoctoral de formación en Investigación en Salud financiado por el Instituto de Salud Carlos III (PFIS; FI16/00251). Además, los coautores de los trabajos aquí presentados han recibido aportaciones del Instituto de Salud Carlos III y Fondo Europeo de Desarrollo Regional (FEDER) a través de los proyectos FIS PI15/00587 (Albert Saiz y Sara Llufriu), FIS 15/00377

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El factor de impacto acumulado de los artículos que componen la presente tesis es de 19,57 según ISI-Web of Knowledge^{SM} – Journal Citation Reports ® de 2019.

3. GLOSARIO ABREVIATURAS

CdV: calidad de vida
EDSS: Expanded Disability Status Scale
EM: esclerosis múltiple
EMPP: esclerosis múltiple primaria progresiva
EMRR: esclerosis múltiple remitente recurrente
EMSP: esclerosis múltiple secundaria progresiva
FAQ: functional activity questionnaire
HADS: hospital anxiety and depression scale
IPAQ: international physical activity questionnaire
LP: liberación prolongada
MCID: Minimal clinically important difference
MET: metabolic equivalent of task
MFIS: escala modificada de fatiga
MHI: escala de salud mental
MMSE: MiniMental State Examination
MSFC: Multiple Sclerosis Functional Composite
MoCA: Montreal Cognitive Assessment
mRS: modified Rankin scale
MSWS-12: Multiple Sclerosis Walking scale 12 items
NARCOMS: North American Research Committee on Multiple Sclerosis
PDDS: Patient Determined Disease Steps
PSQI: Pittsburgh sleep Quality index
SF: sistemas funcionales
SNC: sistema nervioso central
TICs: tecnologías de la información y la comunicación
T25FW: timed 25-foot walk
6MWT: six-minute walk test

4. INTRODUCCIÓN

4.1. Concepto y enfoque actual de la telemedicina

La Telemedicina se define como la prestación de servicios de salud por parte de profesionales sanitarios a través de la utilización de tecnologías de la información y la comunicación (TICs) que permite el intercambio de información válida para la evaluación, el diagnóstico, el tratamiento y la prevención de enfermedades así como para la investigación y la formación continuada de profesionales sanitarios, todo ello con el objetivo final de mejorar la salud de la población y de las comunidades (1). En la era de la medicina súper-especializada, la telemedicina se presenta como un instrumento clave para mejorar la calidad asistencial y hacerla más sostenible, facilitando así la recogida de datos clínicos en un entorno extra-hospitalario.

En los últimos años ha habido un crecimiento progresivo de la utilización de las TICs entre la población española, si bien sigue existiendo una brecha digital que se puede atribuir a la falta de infraestructura (en particular en las zonas rurales), la falta de conocimientos de informática y habilidades necesarias para participar en la sociedad de la información, y/o la falta de interés en lo que la sociedad de la información puede ofrecer. El uso de Internet es máximo en jóvenes de 16 a 24 años y desciende al mínimo (64%) entre las personas de 65 a 74 años (2).

Existen cuatro modelos de prestación de servicios telemáticos (3). El más conocido y utilizado es la teleconsulta, una modalidad de atención a tiempo real entre profesionales de salud o entre profesionales y pacientes. Esta modalidad de telemedicina requiere una planificación como las visitas convencionales. Por el contrario, la "store-and-forward" es una modalidad asíncrona de atención en la que se produce un intercambio de información en diferido y los participantes pueden elegir el momento idóneo para realizarlo. Esta modalidad de tecnología puede representar una solución potencial para los desafíos crecientes creados por la escasez de especialistas y la carencia de recursos suficientes para satisfacer la demanda de atención. Más recientemente, gracias al avance tecnológico en la creación de las TICs, se han establecido dos nuevas modalidades de monitorización remota: la monitorización remota mediante el uso de sensores de almacenamiento de datos en un ambiente extra-hospitalario, y el uso de plataformas de salud que permite obtener información relacionada con el paciente mediante el uso de aplicaciones (3). El teléfono (convencional o inteligente) sigue siendo uno de los métodos de comunicación más utilizados en la práctica asistencial (4, 5).

De cualquier modo, el éxito de una intervención de telemedicina dependerá del impacto que tiene sobre los pacientes y la facilidad que ofrece a los clínicos su implementación en la práctica asistencial (6).

4.2. Aplicaciones de la telemedicina en el ámbito de la Neurología y la Neuroinmunología

Las enfermedades neurológicas son la causa más frecuente de discapacidad global en el mundo y su prevalencia sigue creciendo en paralelo con el incremento de la esperanza de vida de la población (7). Los pacientes con enfermedades neurológicas habitualmente requieren de un seguimiento clínico periódico bien por el curso progresivo que presentan o la presencia de secuelas que requieren de un tratamiento sintomático. Esto puede verse limitado por la carencia de recursos suficientes en ciertas áreas geográficas o la presencia de limitaciones físicas que dificulten los desplazamientos a los centros hospitalarios (8, 9).

La introducción de la telemedicina en la evaluación y el manejo de las enfermedades neurológicas ha sido más lenta que en otras especialidades médicas. En 1999 se observó un cambio de paradigma con la creación del programa de tele-ictus, que permitió la evaluación neurológica remota y el acceso a tratamiento fibrinolítico endovenoso de pacientes con ictus agudo, independientemente de su localización geográfica. Este programa se evaluó en múltiples estudios, incluidos ensayos clínicos y estudios de coste-utilidad demostrando que era una herramienta efectiva, coste-eficiente y segura para recomendar su uso de forma asistencial (10, 11). La monitorización remota de enfermedades neurológicas crónicas, por el contrario, se había mantenido históricamente limitada al soporte telefónico, y no fue hasta 2015 que se incrementó el número de estudios que exploraban su utilidad (12-14).

La Neuroinmunología es la subespecialidad de la Neurología que ha experimentado un crecimiento más rápido, y a la vez ha supuesto un cambio importante en el abordaje clínico de los pacientes en los últimos años (15). La EM es la enfermedad inflamatoria-desmielinizante crónica del SNC de etiología autoinmune más prevalente (50-100 casos por 100.000 habitantes en España) y la primera causa de discapacidad no traumática en el adulto joven (16, 17). La forma clínica remitente recurrente (EMRR) se caracteriza por la presencia de episodios imprevisibles de deterioro clínico agudo (brotes) seguidos por períodos de remisión en los que se produce una recuperación neurológica parcial o completa (18). Los brotes reflejan la aparición de focos agudos de inflamación y/o desmielinización (fenómenos neurodegenerativos) en cualquier zona del SNC. Las formas progresivas (primaria o secundaria progresiva) presentan un deterioro progresivo de la discapacidad en ausencia de brotes, bien desde el diagnóstico (EM primaria progresiva, EMPP) o tras un periodo donde predomina la presencia de brotes (EM secundaria progresiva, EMSP). La EM puede disminuir la calidad de vida (CdV) al interferir con la capacidad de trabajar, realizar actividades de ocio y desempeñar los roles habituales de la vida. Los síntomas que pueden influir

en la CdV suelen estar relacionados con la movilidad, la fatiga y el deterioro cognitivo entre otros (19). Las intervenciones de telemedicina en EM se han centrado en el manejo de los síntomas de la enfermedad y la tele-rehabilitación (20-26). Una revisión sistemática reciente evaluó la efectividad y la seguridad de la tele-rehabilitación en pacientes con EM (9 ensayos clínicos, 531 pacientes) e incluyó intervenciones de fisioterapia, educación y también manejo de los síntomas (24). Los resultados de esta revisión mostraron una reducción de la discapacidad a corto plazo, buen control de los síntomas (como fatiga, dolor, insomnio) y buen efecto sobre el estado funcional, psicológico y la CdV. Su efecto podría ser similar a la terapia presencial y permitir una reducción de los costes sanitarios.

El descubrimiento de auto-anticuerpos neuronales como agentes patogénicos ha sido clave para profundizar en el conocimiento de otras enfermedades autoinmunes, como la encefalitis autoinmune y ha permitido caracterizar el curso clínico y el abordaje terapéutico, así como la búsqueda de factores pronósticos (27). La encefalitis autoinmune mediada por anticuerpos contra la proteína LGI-1 es la segunda causa más frecuente de encefalitis autoinmune y tiene una incidencia de 0,83 casos por 1 millón de personas (28). Se caracteriza por la presencia de síntomas cognitivos y conductuales a los que pueden asociarse crisis epilépticas, crisis distónicas facio-braquiales y/o alteración del nivel de consciencia. La disparidad geográfica de los pacientes y su baja prevalencia dificulta en ocasiones la realización de estudios que permitan profundizar en aspectos fisiopatológicos y/o clínicos de la enfermedad.

En la actualidad, no existen estudios que hayan evaluado el papel y valor de la monitorización remota del estado clínico a corto-medio plazo en pacientes con EM u otras enfermedades autoinmunes del SNC. Y es posible que la elevada heterogeneidad metodológica y la ausencia de análisis robustos de coste-utilidad, hayan limitado la implementación definitiva en la práctica clínica.

4.3. Monitorización clínica remota de los pacientes con enfermedades autoinmunes del sistema nervioso central

Una monitorización clínica estrecha de pacientes con enfermedades autoinmunes del SNC es fundamental para detectar cambios clínicos sugestivos de brotes o progresión clínica que puedan modificar la conducta terapéutica y el pronóstico (29). En los siguientes apartados, se detallará la evidencia existente sobre la utilización de la telemedicina en la evaluación y monitorización clínica de pacientes con EM, y con encefalitis autoinmune anti-LGI1. Ambas enfermedades son autoinmunes y afectan al SNC, pero los pacientes que las padecen tienen diferentes características

sociodemográficas, un hecho que permite explorar la viabilidad y utilidad de la telemedicina en diferentes grupos de población.

4.3.1. Monitorización remota del estado físico y la discapacidad en pacientes con esclerosis múltiple

Para este apartado publicamos el siguiente artículo de revisión "Telemedicine for monitoring MS activity and progression" donde se detalla la evidencia existente sobre el uso de herramientas telemáticas para monitorizar la actividad clínica y la progresión de la discapacidad en pacientes con EM. La escala neurológica más ampliamente utilizada en la práctica clínica es la escala de discapacidad ampliada de Kurtzke (Expanded Disability Status Scale [EDSS, de sus siglas en inglés]) (30). La EDSS es una escala ordinal de 10 puntos (0=normal-10=muerte) que se obtiene a través de la exploración neurológica a partir de la puntuación de 7 sistemas funcionales (SF): piramidal, cerebelo, tronco del encéfalo, sensitivo, esfínteres, visión y estado mental. Desde la publicación del siguiente artículo de revisión, un total de 9 artículos han evaluado la concordancia entre la EDSS convencional y remota mediante el uso de tests auto administrados enviados por correo (31-33), teléfono (34, 35), videoconferencia (36-38) o plataformas digitales (39). En todos los estudios se ha demostrado una concordancia aceptable y similar a la observada entre dos exploradores presenciales (40-43).

No obstante, la discapacidad incluye aspectos de la experiencia de la enfermedad que no pueden ser determinados a través de la exploración neurológica, como las alteraciones emocionales y/o las limitaciones sociales (44, 45). Entre todas las escalas que se comentan en el siguiente trabajo de revisión, hacemos especial mención a la escala "Patient-Determined Disease Steps" (PDDS, de sus siglas en inglés). La PDDS es una escala ordinal que mide la percepción sobre la discapacidad asociada a la EM (46). Consta de nueve ítems que van desde 0 (normal) a 8 (encamado) y el paciente debe puntuar el grado de discapacidad que considera que tiene. Fue creada por la "North American Research Committee on Multiple Sclerosis" (NARCOMS, sus siglas en inglés) y se utiliza en uno de los registros más voluminosos de pacientes con EM de Estados Unidos de América. Tiene una correlación excelente con la EDSS y con medidas de CdV y se utiliza como alternativa a la EDSS cuando ésta no puede realizarse (47).

El uso de dispositivos/sensores de movimiento como los acelerómetros se ha incrementado en la última década para la monitorización clínica de enfermedades crónicas. Estos dispositivos aportan información valiosa sobre el estado funcional de los pacientes que pretenden complementar la monitorización estándar del estado clínico de los pacientes. De hecho, la promoción de una

monitorización estrecha de los pacientes ha demostrado un potencial efecto beneficioso a nivel físico, mental y en la CdV (48, 49).

Trabajo de revisión

Telemedicine for monitoring MS Activity and Progression

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Telemedicine for Monitoring MS Activity and Progression

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Keywords Multiple sclerosis · Telemedicine · Teleneurology · Remote monitoring · Disease progression · Clinical assessment · Adherence · Disease activity · Physical intervention · Remote · Registries and databases · Electronic devices · Daily walking activity

Opinion statement

Telemedicine (TM) is defined as the exchange of medical information between two different physical places. The aims of TM are to provide services that cannot easily be provided face-to-face and improve the efficiency of existing ones. Multiple sclerosis (MS) is a chronic demyelinating disease characterized by a heterogeneous array of symptoms that can lead to severe impairment and may impact on accessibility to medical services, patient's ability to function, and overall health-related quality of life (HRQoL). The use of TM to clinically monitor MS patients has demonstrated benefits by improving HRQoL and reducing associated medical costs. Patient-reported outcome (PRO) measures have been used in TM interventions, registries, and cost-efficiency studies because they offer valuable information about patient's perspective of MS disease burden. Moreover, TM has shown acceptable reliability in the assessment of the neurological impairment by Kurtzke expanded disability status scale (EDSS) and has the potential to develop more sensitive measures, such as average daily walking activity, to closely monitor MS disease progression in real environment. It is likely that the

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use of TM will continue to increase in the following years but larger and controlled studies are necessary to confirm the beneficial effects of TM to deliver an optimal care for patients with MS.

Introduction

Telemedicine (TM) is defined as the exchange of medical information from one site to another via electronic communications to improve the health status of patients [1]. The rationale of TM is to provide services that cannot be easily provided face-to-face and improve the efficiency of existing services. TM can be used as a form of real time communication (e.g., video conference or telephonic conversation) or remote automatic monitoring by store-and-forward technology (e.g., e-mail or devices) in different medical scenarios: acute care, outpatient care, and/or remote monitoring [2]. The most common use of TM is teleconsultation, telediagnosis, and disease monitoring (Fig. 1). In fact, TM has been effective in online psychological interventions and telepsychiatry, computer-based smoking cessation, secondary prevention of chronic diseases, and telerehabilitation (e.g., internet-based physical activity and computer-based cognitive behavioral interventions) [3]. The success of an intervention using TM depends on the positive impact it has on patients and the ease it offers to clinicians for its implementation (see advantages and limitations of TM in Table 1) [4••]. Neurology has adopted TM more slowly in comparison with other specialities, but it has demonstrated benefits in the fields where it has been applied [5, 6], for example in the management of stroke. Telestroke increases the access of specialized physicians to remote areas and improves patients' clinical outcome measures and prognosis. After confirming the benefits of telestroke in large cohorts of patients with a similar methodological approach, the American Heart Association and the American Stroke Association created a statement with evidence-based recommendations for its use worldwide [7, 8].

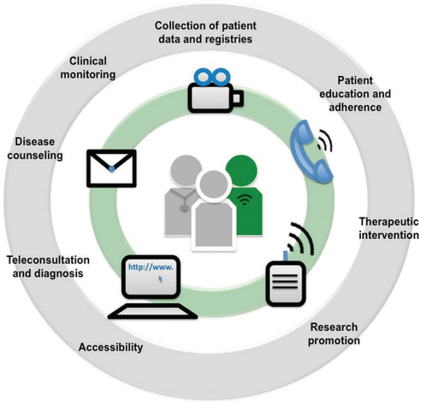

Fig. 1. The rationale for the use of telemedicine. Telemedicine has been applied successfully in almost all aspects of neurological practice. The application of telemedicine may take the form of real-time communication (telephone, videoconference), store-and-forward technology (postal service, web-based systems), or remote monitoring (electronic devices).

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease that affects predominantly young adults and is characterized by a heterogeneous array of symptoms that may lead to severe physical disability and impacts on accessibility to medical services, patient's ability to function and overall health-related quality of life (HRQoL). Periodic assessments are fundamental to monitor clinical activity (symptoms, relapses, and disability status) and to prevent disability progression. For these reasons, MS patients may represent an appropriate population for the evaluation of TM as an alternative to traditional hospital-based management. MS patients are good candidates for TM since a high percentage of them perform frequent MS-related searches and are interested in online interaction with specialists and support groups [9]. The majority of studies in MS focus on the effect of remote physical and behavioral interventions to reduce symptoms severity, disease disability, and/or improve HRQoL. However, studies evaluating the effectiveness of monitoring MS symptoms, clinical activity (e.g., relapses), or disease progression are limited.

In this review, we will focus on studies that use TM to monitor MS clinical activity and to detect disease progression.

Table 1. Advantages and limitations of telemedicine interventions

Advantages of telemedicine	Limitations of telemedicine
Accessibility to remote areas	Technical difficulties
Expansion of medical education	Disruption of traditional doctor-patient relationship
Increased efficiency of clinical consultations	Partial loss of information related to physical examination
Improved patients' HRQoL and satisfaction	Reduction of confidentiality
Collection of data for better understanding/monitoring disease course	Difficulty to transfer TM records and documentation to patients' medical records
Reduction of waiting list/medical costs	Not well-established legal issues
Development of tools to measure clinical variables in a real environment	Training on the technologies to use
Promotion of clinical research	Intense and frequent patient and clinician participation

HRQoL health-related quality of life, *TM* telemedicine

Telemedicine for monitoring MS clinical activity

Conventional clinical monitoring includes the evaluation of MS-related symptoms, relapses, and the assessment of neurological impairment using the Kurtzke expanded disability status scale (EDSS). The benefits of a TM intervention can be determined by the clinical effect obtained in patients, the contribution to HRQoL, the cost-efficiency of the process, and patients' satisfaction with the intervention. Brain magnetic resonance imaging characteristics have also been evaluated through TM but will not be discussed in this review [10].

Registry-based TM information systems

Natural history studies have been extremely helpful in understanding the prognostic value of clinical characteristics and comorbidities in large MS populations over time. Since MS is a chronic disease, registries and electronic databases (medical record reviews and administrative data) have been a useful source to assess the impact of environmental factors, comorbidities, and therapies on clinical outcomes, health services, and other population-level outcomes such as mortality [11, 12, 13••]. Almost 20 registries have been identified in Europe [14, 15], most of them completed by clinicians. In 2010, the project "European Register for Multiple Sclerosis (EUReMS)" was created to establish a European-wide platform for systematic analysis and comparison of longitudinally collected MS data in Europe. Regulatory agencies encourage the use of patient-reported outcomes (PRO) in association with clinician-determined measures because they provide different perspectives of the clinical relevance of these objective measures and the impact on HRQoL [16, 17]. The collection of data by MS patients can easily be performed by postal survey, telephone interview, or web-based system. The use of store-and-forward form of TM seems more accurate for collecting data than other systems, probably because patients are able to spend more time considering individual questions. One of the biggest patient-driven MS registries is the North American research committee of MS (NARCOMS) registry (http://narcoms.org/es), created

in 1996 by the researchers of the North American consortium of MS centers. In the last update (August 4, 2015), they collected information of 37,000 MS patients with MS-related medical history, MS relapses, disability status measured by patient-determined disease steps (PDDS), and HRQoL outcome measures [18]. The accuracy of PRO data in comparison with medical records was high for diagnosis date and time to disease progression milestones (measured by an EDSS 3.0 or 6.0), when accepting a variability of 2 years. However, patients tend to overreport other disease characteristics such as the description of neurological symptoms in MS diagnosis, and the number of previous relapses [19]. These differences may not be clinically significant in large epidemiological studies but can be misleading in short-term studies. These registry-based informational systems offer clinicians the possibility to provide individual patients with accurate information about general aspects of MS clinical course, and create evidence-based recommendations, e.g., patients with higher physical activity and active social life show lower deterioration of the disease course over a period of 5 years [20•].

Remote management of MS symptoms

Patients with MS are likely to require long-term provision of care, with fewer requests of acute care and more for social support as disease progresses. Home-based management does not seem to clearly influence the most common outcome measures of neurological impairment (EDSS or multiple sclerosis functional composite [MSFC]), but it ameliorates other aspects of MS that adversely influence functioning and HRQoL such as deconditioning, depression, or fatigue. Self-management programs increase patients' awareness of their situation and enable them to become more confident in coping with the disease. In addition, the external psychosocial and emotional support they receive has also a direct impact on HRQoL. Different TM forms have been used to track disease symptoms over time: two studies assessed symptom intensity during 6 or 12 months [21, 22], one study offered disease counseling by telephone on demand during 12 months [23]; and one study used videoconferencing every week for 6 months [24•]. All studies showed a high rate of participation (81–93 %) and observed a reduction of symptoms severity in the intervention group with an improvement of HRQoL. However, only two studies evaluated changes in disability status and showed controversial results. One of the studies found that there was a lower deterioration of the EDSS in the intervention group after 6 months of TM intervention [24•], but the other one did not observe any significant change using another disability scale, the MSFC after 12 months [21]. This discrepancy is an example of the difficulties that exist when compare these studies because they have important methodological differences and each one has a different standard care system for comparison. Patient's motivation and regular counseling through telephone reminders or text messages can offer beneficial effect on disability status measured by self-reported and objective measures during short periods of time [25]. However, 3- or 6-month periods are too short to indicate a clinically meaningful change in disability, and longer studies are necessary to confirm the real effect of TM on disability status. Medical costs were determined in three studies, significant decrease in hospital admissions and length of stay were found in two studies [23, 24•] and a tendency to reduce the number of home visits in another one [21].

Despite the limitations of these studies that cannot be performed as clinical trials, there is preliminary evidence that TM counseling is effective

to improve the HRQoL of MS patients and it could be a good complement to standard care.

Remote neurological assessment: clinician driven EDSS evaluation

The EDSS is a robust scale considered the gold standard for disability assessment in MS. However, this scale has been extensively criticized because of several shortcomings, including bimodal distribution, major weighting toward ambulation and low reproducibility in the lower range of the scale [26]. The agreement of remote EDSS in comparison with conventional EDSS is not expected to be better than the best physical inter-rater agreement [27]. Remote EDSS has been performed by telephone, videoconference and store-and-forward video (see references in Table 2). All forms of TM have shown similar inter-rater agreements (kappa=0.4–0.5) in comparison to conventional EDSS. In fact, the acceptance of half point of variability between measurements substantially increases the overall agreement (kappa=0.8) [29], with similar figures to those of two physical raters. In a study assessing the EDSS agreement between a hands-on examiner and two observers, one in the room with the patient and another one observing the neurological examination through videoconferencing, the physical distance between the EDSS rater and the patient made no difference (Cronbach's alpha coefficients between 0.96 and 0.99) [30]. Store-and-forward form of TM is a more flexible way to exchange information than real time communication but requires a prior learning process of how to proceed (e.g., to perform the neurological examination) in order to achieve good results.

The EDSS incorporates the neurological examination divided into seven functional systems (FS) with ambulation/mobility index. Changes in FS score may substantially change the overall EDSS score. The agreement observed in each FS by TM depends on which domain is assessed and the form of TM is used. In one study, video recording increased the reproducibility of all FS, especially the main FS (pyramidal, cerebellar, and brainstem FS) with kappa coefficients above 0.7, regardless of the degree of disability [33•]. However, sensory, sphincters and visual FS showed low to moderate agreement, regardless the form of TM that was used.

The impairment of ambulation and/or cognition has a direct impact on patient's autonomy, and it is frequently related to disease progression. Ambulation is the key FS for the EDSS scoring, but its value varies considerably between patients' perception and clinician assessment [34] with an overall moderate agreement between measures. Patient's distance estimation depends on real environmental conditions (e.g., stairs, pavement changes, sidewalks) and MS disease circumstances such as daily fluctuations and the need for an assistive device. Inside the hospital, patient's performance heavily relies on patient's motivation and the persistence of the examining neurologist to perform the test in the best conditions. Despite discrepancies, patients with ambulatory impairment (EDSS≥4.5) showed better agreement between self-reported (SR) and conventional ambulation index than fully ambulatory patients [33•].

Cognitive dysfunction is a prevalent symptom present in up to 65 % of MS patients, and it also shows low reproducibility within studies, probably because patients with neurological impairment frequently have difficulties to evaluate their own everyday competency. TM may offer an alternative approach to assess cognitive impairment in a real environment without using PRO data. One TM study

Table 2. Review of telemedicine studies in multiple sclerosis

Author/year	Geographic area (country)	N	MS subtypes	EDSS score	Type of intervention	Time period (months)	Outcome measure
Goodin et al. 1998 [28]	San Francisco, CA (USA)	30	16 RRMS, 9 SPMS, 5 PPMS	Mean=4.7 Range=1.0–8.0	Computer SR questionnaire	–	Feasibility of SR disability assessment
Pozzilli et al. 2002 [23]	Rome (Italy)	201	40 RRMS, 120 SPMS, 41 PPMS	Intervention group: mean=6.0, SD=2.0 Control group: mean=5.8, SD=2.2	Telephonic counseling on demand	12	Effect on health outcomes and cost-effectiveness
Lechner-Scott et al. 2003 [29]	Basel (Switzerland); Newcastle (Australia); Amsterdam (Netherlands); Barcelona (Spain), Rome and Florence (Italy), and Klinische Entwicklung Schering (Germany)	110	42 RRMS, 13 PRMS, 47 SPMS, 8 PPMS	Mean=4.5 Range=0.0–9.0	Telephonic assessment	–	Feasibility and reliability of telephonic EDSS assessment
Bombardier et al. 2008 [25]	Washington (USA)	130	94 RRMS, 36 SPMS/PPMS	Range=0.0–5.0	Telephone counseling	3	Effect of remote counseling on SR health promoting behaviors and MS symptoms
Kane et al. 2008 [30]	Baltimore and Washington (USA)	20	11 RRMS, 8 SPMS, 1 PPMS	Mean=5.9 SD=1.5	Videoconferencing	–	Reliability of remote EDSS examiner versus hands-on examiner
Ingram et al. 2010 [19]	Wales (UK)	99	20 RRMS, 67 SPMS, 12 PPMS	Mean=6.5 SD=0.8	Postal SR questionnaire or structured telephone interview	–	Validity of SR data collection and comparison between these two forms of TM
Goverover et al. 2010 [31]	New Jersey and New York (USA)	21	19 RRMS, 1 SPMS, 1 PPMS	Range=0.0–6.5	Web-based system	–	Assessment of cognitive deficits while performing an actual daily task by computer
Miller et al. 2011 [21]	Cleveland and surrounding counties (USA)	206	CDMS	–	Web-based system	12	Impact of MS self-management on HRQoL
Zissman et al. 2012 [24•]	Haifa (Israel)	40	40 RRMS	TM group: mean=5.1, SD=0.9 Control group: mean=3.9, SD=1.4	Videoconferencing	6	Effect on clinical status, HRQoL, satisfaction, and costs
		41		Median=6.5	Web-based system	6	

Table 2. (Continued)

Author/year	Geographic area (country)	N	MS subtypes	EDSS score	Type of intervention	Time period (months)	Outcome measure
Turner et al. 2013 [22]	Seattle and Washington (USA)		7 RRMS, 24 SPMS, 10 PPMS	Range=2.0–8.5			Feasibility of using TM monitoring to improve clinical care
Shammas et al. 2014 [32]	Karlsruhe (Germany)	11	8 RRMS, 2 SPMS, 1 PPMS	EDSS group≤2.5: mean=1.8, SD=0.8 EDSS group ≥3.0: Mean=4.4, SD=0.9.	Daily-activity monitoring system	12	Assessment of changes in daily activity and disability measures over time
Sola-Valls et al. 2015 [33•]	Barcelona (Spain)	23	15 RRMS, 8 SPMS	Mean=3.5 Range=1.5–6.5	Web-based SR questionnaires and video recording; accelerometer	24	Feasibility and reliability of remote EDSS assessment and walking activity monitoring

MS multiple sclerosis, *N* number of MS patients, *EDSS* expanded disability status scale, *CDMS* clinically defined MS, *RRMS* relapsing-remitting MS, *SPMS* secondary progressive MS, *PPMS* primary progressive MS, *PRMS* progressive recurrent MS, *SD* standard deviation, *TM* telemedicine, *SR* self-reported, *HRQoL* health-related quality of life

using a web-based system observed that MS patients significantly showed more difficulties than a control group in accurately and independently complete daily tasks with a computer (e.g., purchase of airline tickets for a round trip flight) [31].

Patients' perception of impairment and disability

Disability is defined as a restriction or inability to do an activity in the manner within the range considered normal for a human being, mostly resulting from impairment [35]. Despite impairment and disability are indistinctively used, disability includes aspects of disease experience that cannot be determined in a neurological examination such as emotional and social disturbances [36]. In fact, one study observed that the EDSS had modest correlations with HRQoL measures (R^2=2–22 %) [37], and there were higher differences in HRQoL between patients with EDSS≤4.0 and EDSS≥4.5 than between patients with EDSS 4.5–6.5 and EDSS≥7.0 [38]. Therefore, researchers started to use PRO measures in combination with standard measures to accurately define MS disability in clinical trials. Among these, we are going to focus on the PRO scales that were also used in TM studies.

Studies using the SR-EDSS questionnaire remotely performed by e-mail showed a modest agreement in comparison to conventional EDSS (kappa=0.4) [39, 40]. One study confirmed that its performance in a computer was also feasible and showed good correlation with the conventional EDSS (r=0.98) [28]. However, the agreement between both measures was not reported and its usefulness in comparison with other approaches is unknown.

Besides the EDSS, there are other PRO measures developed to capture domains of disease burden such as fatigue, mood, spasticity, or sexual function. The performance scales (PS) are a group of subscales created by the NARCOMS that assess mobility, bowel/bladder function, fatigue, sensory, vision, cognition, spasticity, and hand function. PS showed a good correlation with the EDSS (r=0.64) and moderate compared to the MSFC (r=−0.58) [41]. Despite this scale has construct validity for overall PS and some subscales (mobility, hand, vision, fatigue, and bladder), the instrument is long (about 2500 words) and difficult to interpret. The patient-determined disease steps (PDDS) is another scale developed by the NARCOMS and has been widely used in research of MS symptoms, sociodemographic characteristics, HRQoL, and physical activity [42, 43]. It has nine ordinal levels ranging between 0 (normal) and 8 (bedridden) and it showed strong correlation with the EDSS (r=0.78), regardless of the degree of disability. PDSS is also biased toward ambulation and shows similar psychometric properties to the EDSS. Researchers and clinicians might consider the PDDS as an alternative assessment of disability, particularly when the EDSS score is not feasible. Caution should be taken when using PDSS in longitudinal studies because there is no reliable data about the responsiveness of this PRO scale.

The Guy's neurologic disability scale (GNDS) is a PRO questionnaire that offers a valuable way to document disease impact in MS. It assesses MS disability into 12 separate subcategories (cognition, mood, vision, speech, swallowing, upper-limb function, lower-limb function, bladder function, bowel function, sexual function, fatigue, and "others") during the previous month [44]. The GNDS showed good correlations with the EDSS (r=0.73) and the MSFC (r=−0.68), and it was similar for all GNDS subscales except for

cognition. The correlation with the EDSS was better for patients with mild disability than for those severely disabled [45]. However, GNDS changes did not always reflect equal changes in EDSS and it showed poor sensitivity to detect acute changes after treatment with corticosteroids [46, 47].

The MS rating scale (MSRS) and the MSRS revised version (MSRS-R) were modified according to the scoring scheme of the GNDS, to use the minimum number of items able to cover the most relevant aspects of MS. It has eight domains: walking, hand function, vision, speaking, swallowing, bowel and bladder, cognition, sensory). These scales were created in a web-based platform for MS patients (www.patientslikeme.com) in 2007. Despite that there are only few studies that evaluated the psychometric properties of MSRS-R, it showed good correlation with the PDSS (r=0.62) and it seems to be more sensitive than PDDS in reflecting cumulative burden of disability resulting from relapses [48].

All previous PRO scales offer different perspectives of impairment and disability, but there are still some aspects of the disease burden that are uncovered, such social and psychological conditions. MSQoL of 54 items (MSQoL-54) is a widely used PRO questionnaire that comprises questions from the Short form 36-item health survey, as a generic measure of HRQoL, and 18 additional MS specific items. In one study with a cohort of 3045 patients, MSQoL-54 was assessed by postal service with a low proportion of missing data [49•]. The international organization of MS nurses in 2007 developed another disability scale, Monitoring my MS (MMMS), a 26-item scale which assesses health conditions of people with MS, the impact of disease on daily activities and interpersonal relationships. Preliminary results demonstrated satisfactory reliability and validity for its use among MS patients [50].

In summary, the introduction of PRO measures that measure MS disease burden and HRQoL is important to determine the impact of interventions in MS and should always complement clinician-assessed measures in clinical practice. Despite the assessment of PRO measures requires time and resources, which sometimes is difficult to combine with clinical practice, the use of TM may overcome these difficulties.

Telemedicine for monitoring MS progression

The sensitivity to detect disease progression should be a key attribute for any assessment tool in MS studies. Based on epidemiological studies, MS patients tend to show a significant worsening of neurological disability and physical status over time in comparison with cognitive or social functioning [51•]. Despite the EDSS demonstrated poor responsiveness to detect changes in disability over time, it is considered one of the standard measures for assessing MS progression in clinical trials. No clear recommendation exists about the interpretation of changes in the EDSS, but it seems that a minimum period of 6 months is necessary to confirm long-term disability [52••]. Worsening of 1.0 point from a baseline EDSS≤5.5 or worsening of 0.5 points from a baseline EDSS ≥/6.0 are commonly recognized as a clinically meaningful change; however, patients with baseline EDSS≤5.5 require an increase ≥2.0 points to equal the impact of disability (measured by the GNDS) of patients with an EDSS≥6.0 who experience an EDSS change of /≥0.5 points [53]. These difficulties have stimulated research into more appropriate and sensitive outcome measures for clinical trials. Walking

impairment is a major feature of progressive forms of MS, and nearly 75 % of MS patients experience some degree of ambulatory disability during the course of the disease [54]. In fact, the EDSS could explain 76 % of the variance observed in daily walking activity [33•]. For these reasons, walking assessments have been used as a common metric for monitoring disease progression in clinical trials. The most frequent assessment tools are the MS walking scale-12 (MSWS-12), the timed 25-foot walk (T25FW) and the 6-min walk test (6MWT). Correlations between objective measures (T25FW and 6MWT) and MSWS-12 are usually poor because they assess different aspects of walking. MSWS-12 is the only one that determines the impact of walking impairment in daily activities during a period of time (2 weeks), but it is less accurate than objective measures to determine changes over time [55, 56••]. In contrast, objective measures may overestimate the real ability to walk of MS patients because they are performed under controlled conditions. Among them, the 6MWT seems to be the most appropriate, since no ceiling effect has been observed in fully ambulatory patients, and it can be performed remotely by using an accelerometer (r=0.76).

The importance of collecting ambulation data using electronic devices in real environment has increased in the last few years. This tool provides a behavioral correlate of disability in people with MS and adds value to other measures of walking activity [57]. Pedometers are easy to use and inexpensive but they cannot reflect the intensity of the patients' movements (i.e., the change related to different degree of physical activity) and might suffer from inaccuracy during slow walking speed. Accelerometers have shown good correlation with the EDSS (r=−0.86, p<0.001) and are capable to identify patients with walking impairment (EDSS>4.5, cutoff point of 3279 steps/day) with a high sensitivity and specificity [27]. They have acceptable psychometric properties, and a lower-bound estimate of 800 steps/day seems to represent a clinically meaningful change of free-living walking behavior in MS interventions [58, 59•].

The role of accelerometers in monitoring disease progression is slowly growing. In one study, basal walking activity did not predict a change in disability measured by PDSS over a period of 6 months, but patients with higher disability or those who experienced a relapse had a greater reduction of walking activity over time [60]. Two recent pilot studies observed a decline in walking activity during one [32] and 2 years [33•] of follow-up which exceed the standard error of accelerometer measurement. In one of the studies, the reduction of walking activity after 2 years was mainly observed in patients with ambulatory impairment, despite no evidence of disease progression was observed by EDSS or MSFC. In contrast to accelerometer data, conventional T25FW or 6MWT were not capable to detect this walking reduction over time. Large-scale and prospective studies are needed to validate accelerometry as an adequate instrument to monitor MS disability but these preliminary findings pave the way to include accelerometry in clinical trials, and identify measures for the design and delivery of behavioral interventions in this population.

Conclusions

TM may be a good complement to standard care. Its objective is not certainly to replace a physical visit, but to provide services that cannot be easily done face-to-face, and improve the efficiency of existing ones. The use of TM in MS offers the

opportunity to provide access to remote areas, merge data registries worldwide and improve the way acute and chronic care are delivered. In fact, the promotion of a close self-monitoring of physical, mental, and social functioning has demonstrated beneficial effects in HRQoL. The use of new PRO measures and composite endpoints, in combination with standard disability measures, can be assessed through different forms of TM with acceptable reliability. Moreover, the development of new technologies will allow a closer monitoring of disability status and functioning of MS patients in real environment. However, most of the studies in MS are in an early phase, with low number of participants and important methodological differences. In conclusion, it seems that TM is here to stay and it may offer potential opportunities for overcoming the current deficiencies in MS clinical monitoring. TM promising results will need to encourage randomized controlled trials to confirm the effectiveness and cost-efficiency of this brand-new approach versus conventional modes of practice.

Compliance with Ethics Guidelines

Conflict of Interest

Nuria Sola-Valls, Yolanda Blanco, Maria Sepúlveda, and Eugenia Martinez-Hernandez declare that they have no conflict of interest.

Alberet Saiz has received compensation for consulting services and speaking from Bayer-Schering, Merck-Serono, Biogen-Idec, Sanofi-Aventis, Teva Pharmaceutical Industries Ltd, and Novartis.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors. With regard to the authors' research cited in this paper, all procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2000 and 2008.

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4.3.2. Monitorización remota de la marcha en pacientes con esclerosis múltiple

La alteración de la marcha es el síntoma que más preocupa a los pacientes con EM desde el diagnóstico de la enfermedad, y su aparición tiene un impacto elevado sobre la CdV (50, 51). Habitualmente en la consulta médica, la marcha suele cuantificarse basándose en la percepción del paciente sobre la distancia que puede deambular, lo que se considera una aproximación altamente imprecisa (52, 53). La percepción del paciente se ve influenciada por las barreras físicas del entorno y las limitaciones relacionadas con la EM, que difieren de la evaluación objetiva en un ambiente hospitalario donde las condiciones son ideales y se busca obtener el mejor resultado posible (54). En este sentido, la escala de la marcha de 12 items (MSWS-12, de sus siglas en inglés) si permite puntuar la percepción del paciente sobre diferentes aspectos de la marcha en las últimas 2 semanas, pero no informa sobre la distancia que el paciente puede recorrer (55, 56). La determinación de la distancia que el paciente puede deambular suele cuantificarse mediante tests objetivos que se realizan en un entorno hospitalario. Entre ellos, los más conocidos y utilizados son el test de la marcha de los 25 pies (timed 25 foot walk, T25FW) y el test de los 6 minutos (six minute walk test, 6MWT) (57, 58). El T25FW es un test válido, reproducible y rápido de administrar que mide la velocidad de la marcha y ha demostrado una buena correlación con parámetros funcionales y de CdV (59, 60). El 6MWT cuantifica la distancia en metros recorrida en 6 minutos y permite detectar fluctuaciones en el ritmo de la marcha en comparación con el T25FW pero requiere de una infraestructura y tiempo suficiente para su realización (58, 61-62).

La fampridina de liberación prolongada (LP) (Fampyra®; Biogen Idec, Maidenhead, Berkshire, UK) es el único fármaco aprobado para mejorar aspectos de la marcha en los pacientes con EM que tienen una limitación en la distancia que pueden caminar (EDSS $\geq$ 4.0) y actúa a través del bloqueo de los canales de potasio de los axones desmielinizados. En los estudios pivotales (MS-F203 y MS-F204) se observó una mejoría de un 25% en la velocidad de la marcha mediante el T25FW en 47% de los pacientes respecto a placebo y se relacionó con una mejoría subjetiva de 6 puntos en la MSWS-12 (63, 64) que se mantiene a largo plazo (65). Los estudios que se han realizado de práctica clínica habitual han confirmado la efectividad del fármaco con un porcentaje superior de respondedores (70%). El incremento en este porcentaje puede deberse a diferencias metodológicas entre los estudios y las diferencias en los criterios de respuesta utilizados. En todos, el efecto del tratamiento se ha mantenido a corto-medio plazo especialmente si se usan tests más largos como el 6MWT (66-70). En el momento actual no existe un criterio de respuesta establecido que haya confirmado la efectividad del tratamiento en medidas funcionales, y que permita al clínico

asegurar qué pacientes son respondedores en la vida real.

4.3.3. Utilidad de los acelerómetros para monitorizar la marcha en pacientes con esclerosis múltiple

La marcha es un síntoma clave para determinar la progresión de la discapacidad y las escalas que disponemos en la práctica asistencial, mencionadas previamente, carecen de la sensibilidad necesaria para detectar cambios clínicos de forma precoz (71, 72). Existe controversia, pero se considera por consenso un cambio clínicamente significativo en la escala EDSS de al menos 1.0 punto si la EDSS ≤5.0 o al menos 0.5 puntos si la EDSS ≥5.5 en un período mínimo de 3-6 meses (73), un ≥ 20% en los T25FW o 6MWT o un cambio de ≥6 puntos en la escala MSWS-12 (74-76). Se desconoce si la monitorización clínica más frecuente de la marcha podría ser útil para detectar brotes y/o progresión de la discapacidad.

El uso de herramientas electrónicas como las plataformas de análisis de la marcha han permitido detectar diferencias en el patrón de la marcha de los pacientes con EM con mínima discapacidad asociada (77). De forma paralela, existe un reconocimiento creciente del potencial valor de los acelerómetros para medir la movilidad en pacientes con EM (78). El acelerómetro es un sensor de movimiento que permite detectar cambios de aceleración en el centro de masa corporal durante la actividad y se ha validado como medida de actividad física en personas sanas. La actividad diaria basal (promedio de pasos al día) ha demostrado una buena correlación con la EDSS y los tests de la marcha estándar, siendo capaz de detectar una variabilidad entre pacientes según el grado de discapacidad que no puede detectarse con otras medidas convencionales (79-80). La actividad diaria basal no se ha asociado con un empeoramiento de la discapacidad a 6 meses, pero los pacientes con mayor discapacidad tienen un descenso en la actividad diaria mayor que el resto durante el mismo periodo de tiempo (81, 82). Estudios longitudinales que hayan explorado el papel de los acelerómetros para monitorizar el estado clínico de los pacientes con EM son escasos. Existe un estudio piloto en pacientes con EDSS ≤ 5.0 que mostró una reducción de la actividad diaria a los 12 meses de seguimiento (83). Se desconoce si el acelerómetro podría ser una herramienta más sensible que las herramientas habituales como la EDSS y los tests de la marcha para determinar la progresión de la discapacidad.

4.3.4. Monitorización remota del estado cognitivo en pacientes con encefalitis autoinmune anti-LGI1.

La alteración cognitiva puede ser un síntoma clave en el debut de ciertas enfermedades autoinmunes del SNC, como la encefalitis anti-LGI1 y su progresión también puede plantear cambios en la estrategia terapéutica.

El diagnóstico y tratamiento precoz con inmunoterapia, la buena respuesta al tratamiento y la ausencia de brotes son factores de buen pronóstico funcional en los pacientes con encefalitis autoinmune anti-LGI1 (84, 85). De hecho, un 70% de los pacientes con encefalitis anti-LGI1 son independientes para las actividades cotidianas a los 2 años del diagnóstico, pero solo un tercio vuelven a su estado funcional premórbido (85). La escala más utilizada para medir el estado funcional en estos pacientes ha sido la escala modificada de Rankin (mRS), una escala ampliamente utilizada para evaluar el estado funcional tras un ictus (86, 87). No obstante, no es infrecuente encontrar discrepancias entre los evaluadores para puntuar con esta escala a un mismo paciente. Existen otras escalas como el cuestionario de actividad funcional (FAQ, de sus siglas en inglés) que permiten explorar de manera objetiva la independencia funcional basándose en ítems específicos sobre el estado cognitivo (88, 89) que podrían ser útiles en la evaluación funcional de estos pacientes.

Existen series pequeñas con información adicional de resonancia magnética avanzada, la mayoría con periodos de seguimiento corto, que muestran la presencia de un deterioro cognitivo global que afecta a diferentes dominios como la memoria verbal, las funciones ejecutivas, la velocidad de procesamiento y las funciones visoespaciales. Algunos de estos estudios sugieren que los déficits de memoria verbal pueden persistir en el tiempo (mediana de 2 años), y la existencia de una atrofia hipocampal en un rango variable de pacientes (40-95%) (90-94). La reserva cognitiva premórbida se define como la adaptabilidad de los procesos cognitivos al envejecimiento cerebral o el daño cerebral adquirido (95-97). Está influenciado por diferencias individuales innatas y es dinámica según la exposición a diferentes factores socio-ocupacionales tales como la educación, la profesión, las actividades de ocio y/o el compromiso social. La reserva cognitiva premórbida es un factor protector de deterioro cognitivo y se ha asociado con un menor riesgo de disfunción cognitiva postoperatoria o un mejor estado cognitivo tras una lesión traumática cerebral (98, 99). En el momento actual, se desconoce el estado cognitivo de los pacientes con encefalitis anti-LGI1 a largo plazo y los factores que determinarán qué pacientes tendrán un mayor riesgo de deterioro cognitivo a largo plazo.

La exploración cognitiva remota en pacientes con otras enfermedades neurológicas,

fundamentalmente con demencia y mediante el uso de teléfono, videoconferencia o plataformas específicas ha demostrado su viabilidad (100-104). De ahí que existan validaciones por vía telemática de las principales escalas de cribaje de deterioro cognitivo, como el Mini-Mental State Examination (MMSE) o el Montreal Cognitive Assessment (MoCA) (105-107). Existen estudios de evaluación cognitiva en pacientes con EM (108-110) pero no se dispone de información en otras patologías autoinmunes del SNC.

5. HIPÓTESIS

5. Hipótesis

La telemedicina puede contribuir de manera beneficiosa a la evaluación, monitorización, educación y tratamiento de enfermedades neurológicas crónicas. El diagnóstico precoz y un tratamiento adecuado son factores clave en el manejo de enfermedades autoinmunes del SNC. El uso de herramientas telemáticas puede ayudar a obtener información clínica útil para la toma de decisiones en pacientes con EM y otras enfermedades autoinmunes.

Las hipótesis planteadas son:

1. La mayoría de los pacientes con enfermedades autoinmunes del SNC, y en especial los pacientes con EM, en su mayoría jóvenes, tienen acceso a las tecnologías de la información y la comunicación. Por ello, pensamos que es factible realizar una monitorización de su estado neurológico a distancia mediante herramientas telemáticas/multimedia.
2. Algunas de las escalas utilizadas en la práctica asistencial y en los estudios de investigación, tales como la EDSS y la PDDS, pueden administrase telefónicamente de forma fiable, y con resultados superponibles a los obtenidos de forma presencial convencional.
3. La marcha es el factor que más influye a la hora de determinar que ha progresado la discapacidad en los pacientes con EM. La monitorización continua de la marcha en condiciones reales mediante el uso de un acelerómetro triaxial, puede ser un marcador clínico más sensible que la EDSS y/o los tests de la marcha convencionales para detectar la progresión de la discapacidad.
4. Si la monitorización remota de la marcha mediante un acelerómetro triaxial es más sensible qué los tests de la marcha convencionales, debería ser capaz de identificar mejor a los pacientes que presentan una respuesta clínicamente significativa a fármacos que mejoran la calidad de la marcha tal como fampridina-LP.
5. La evaluación telemática no solo es útil para evaluar la discapacidad física sino también la cognitiva, y esto es importante en enfermedades con baja prevalencia tal como la encefalitis autoinmune mediada por anticuerpos anti-LGI1. Pensamos que la evaluación del estado cognitivo y funcional de estos pacientes mediante escalas específicas telefónicas es viable, y puede ayudar a identificar factores pronósticos de deterioro cognitivo a largo plazo en esta patología.

6. OBJETIVOS

En base a las hipótesis nos planteamos los siguientes objetivos:

1. Traducir al castellano las escalas de EDSS y PDDS, y a) validar su administración por vía telefónica en pacientes con EM; y b) explorar la asociación clínica que existe entre ambas escalas cuando son administradas por vía telefónica.
2. Investigar la viabilidad del uso de una plataforma multimedia en pacientes con EM para determinar: a) la concordancia entre la EDSS obtenida mediante evaluación telemática y la convencional; y b) la utilidad del acelerómetro para caracterizar la marcha, y detectar la progresión de la discapacidad.
3. Determinar la utilidad del acelerómetro como herramienta telemática para definir el efecto clínicamente significativo a fampridina-LP.
4. Investigar en pacientes con encefalitis autoinmune anti-LGI1 la viabilidad de una evaluación cognitiva y funcional remota mediante teléfono, y conocer: a) el estado cognitivo y funcional a largo plazo; y b) los factores predictores de deterioro cognitivo.

7. MATERIAL Y MÉTODOS

7.1. Tipo y diseño de los trabajos

Todos los trabajos que componen esta tesis son observacionales y descriptivos. Dos son de corte transversal (trabajos 1 y 4) y dos longitudinales prospectivos (trabajos 2 y 3).

7.2. Población de estudio - criterios de inclusión y exclusión

Los participantes en los trabajos 1, 2 y 3 fueron pacientes con el diagnóstico de EM definida por los criterios de McDonald 2010 (111) que seguían controles en la Unidad de Neuroinmunología-Esclerosis múltiple del Hospital Clinic de Barcelona. Para su inclusión en el estudio 1 los pacientes debían estar clínicamente estables en los 30 días previos. En el trabajo 2 se propuso la participación a pacientes con EMRR o EMSP que tuvieran una EDSS comprendida entre 1.0 y 6.5 y dispusieran de un dispositivo con conexión a internet. Se excluyeron del estudio los pacientes con la forma EMPP porque se consideró que estos pacientes podían tener un curso evolutivo distinto al resto. En el trabajo 3 se invitaron a participar a todos los pacientes con EM que fueran candidatos al tratamiento con fampridina-LP por presentar una alteración de la marcha y una EDSS comprendida entre 4.0 y 7.0 (112).

Los participantes del trabajo 4 fueron pacientes con encefalitis autoinmune anti-LGI1 diagnosticados en el laboratorio de Neuroinmunología del Institut d'Investigació Biomèdica August Pi i Sunyer (IDIBAPS)- Hospital Clinic entre septiembre de 1998 y junio de 2014. El rango de fechas se estableció para asegurar que todos los participantes tuvieran un tiempo de evolución desde el diagnóstico superior a 4 años. Se seleccionaron solo los pacientes de nacionalidad española para poder realizar la encuesta telefónica en castellano.

Todos los estudios se llevaron a cabo siguiendo las recomendaciones de la declaración de Helsinki y los estudios fueron aprobados por el comité de ética del Hospital Clinic de Barcelona. Los participantes con EM dieron su consentimiento escrito para participar en los estudios y los pacientes con encefalitis anti-LGI1 fueron invitados a participar por su médico tratante y dieron su consentimiento oral al inicio de la entrevista telefónica y junto a un familiar como testigo.

7.3. Intervenciones realizadas

Los trabajos que componen esta tesis tienen en común la evaluación remota de los pacientes mediante diferentes modalidades y métodos de telemedicina. En los trabajos 1, 2 y 3 se realizó una evaluación presencial y otra remota separada un máximo de 15 días, que eran similares y/o complementarias. En el trabajo 4 la evaluación fue telefónica y los resultados se compararon con los

obtenidos por teléfono a un grupo de 23 controles sanos apareados por edad, sexo y nivel educativo.

La evaluación remota del trabajo 1 fue telefónica e incluyó las escalas EDSS y PDDS telefónicas (34, 46). Ambas escalas se compararon con las escalas EDSS (30) y PDDS (47) presenciales y el test de la marcha T25FW (57). En el trabajo 2 se realizó una evaluación remota y presencial periódica durante 2 años (mes 0, 3, 6, 9, 12 y 24). Para la evaluación remota se utilizó una plataforma multimedia que fue creada por Linkcare Health Services SL (http://www.linkcare.es) e incluía una encuesta autoadministrada y la grabación de un video para determinar la EDSS y los SF. La marcha se evaluó a través de un cuestionario autoadministrado (el índice de deambulación) (30) y mediante un acelerómetro triaxial (Actigraph GT3X de Actigraph LLC, Pensacola-FL [EE.UU.]. El acelerómetro es un dispositivo electrónico que se coloca mediante un cinturón elástico en la cadera no dominante y detecta la aceleración del cuerpo en los tres planos del espacio. Mediante un algoritmo interno propio del dispositivo se obtiene información acerca de la aceleración y el promedio de pasos/día y se considera una medida de actividad diaria (113). A todos los pacientes se evaluó la CdV relacionada con la salud (EuroQoL 5D-5L) (114), la fatiga mediante la escala modificada de fatiga (MFIS) (115) y el ánimo a través de la escala de salud mental (MHI) (116). A nivel presencial se realizó la EDSS convencional y se añadieron otros tests con una mayor sensibilidad para detectar progresión de la discapacidad en el tiempo, como la Multiple Sclerosis Functional Composite (MSFC, de sus siglas en inglés) (57) y el 6MWT (58). En el trabajo 3 se evaluó la actividad diaria de los pacientes bajo condiciones habituales mediante un acelerómetro triaxial antes del tratamiento con fampridina-LP y durante el mismo. Los pacientes considerados respondedores a la fampridina-LP continuaron el tratamiento y se realizaron visitas de seguimiento a los 3, 6 y 12 meses. Los pacientes no respondedores detuvieron el tratamiento, como así indica la ficha técnica y fueron reevaluados a los 12 meses. La evaluación presencial incluyó la EDSS, la MSFC, la evaluación de la marcha mediante el T25FW, el 6MWT y la MSWS-12 y de la actividad física mediante el cuestionario internacional de actividad física (IPAQ, de sus siglas en inglés) (117). La CdV relacionada con la salud se midió con el cuestionario EuroQoL-5 (EQ-5D-5L). En el trabajo 4 la evaluación telefónica incluyó la evaluación de la reserva cognitiva por el cuestionario de reserva cognitiva premórbida (118), la evaluación del estado funcional con el cuestionario de actividades funcionales (FAQ, de sus siglas en inglés) (88, 89) y la escala mRS (86, 87) y la evaluación de síntomas asociados como la ansiedad y depresión por la escala de depresión y ansiedad hospitalaria (HADS, de sus siglas en inglés) (119), y el sueño con la escala de calidad del sueño de Pittsburgh (PSQI, de sus siglas en inglés) (120). La evaluación cognitiva remota se

realizó mediante la escala telefónica MMSE (106) y una batería cognitiva breve que incluía el test modificado de aprendizaje verbal de Buschke (memoria verbal) (121), el Trial Making Test en su formato oral (función ejecutiva) (122, 123) y el test de fluencia verbal (lenguaje) usando una categoría semántica.

7.4. Análisis estadístico

Las medidas de tendencia central y de dispersión se proporcionaron según la distribución de la muestra de estudio. La viabilidad de la evaluación remota se determinó por el número medio de llamadas por paciente (trabajo 1) y el número de pacientes que completaron las evaluaciones del total de pacientes candidatos (trabajos 2 y 4). Los pacientes con EM fueron agrupados según su capacidad para deambular (EDSS $\leq$ 4.0 y EDSS >4.0) en los trabajos 1, 2 y 3.

En el trabajo 1, la validez de las escalas EDSS telefónica y PDDS se realizó mediante el análisis de sus propiedades psicométricas y la comparación con las escalas convencionales. Se midió: 1) la consistencia interna, que determina el grado en que los elementos de la escala miden el mismo constructo y fue evaluada mediante el coeficiente alfa de Cronbach; 2) la estabilidad de los test (test-retest), que se mide en un grupo de pacientes seleccionado de forma aleatoria y mediante el coeficiente de correlación intra-clase; 3) la aceptabilidad que mide la calidad en la distribución de los datos (los efectos techo/suelo y la asimetría); 4) la concordancia, que indica la reproducibilidad de los datos recopilados y fue medida por el coeficiente kappa y el porcentaje de evaluaciones con el mismo resultado (número de ocasiones con resultado exacto entre la evaluación convencional y telefónica); 5) la validez de criterio y de constructo que se refiere al grado de eficacia con que se puede predecir una variable de interés a partir de las puntuaciones en un test, y se analizó mediante un análisis de correlación Rho de Spearman entre los tests convencionales y remotos así como su distribución por grupos de pacientes en función de los datos demográficos y clínicos; y 6) la sensibilidad que se define como la capacidad para detectar cambios en las funciones y áreas específicas que se espera que ocurran como consecuencia de la intervención.

En el trabajo 2, se determinó la concordancia mediante el coeficiente kappa y el porcentaje de evaluaciones con el mismo resultado o similares (asumiendo cierta variabilidad como no clínicamente significativa). Se consideró como una diferencia clínica mínimamente significativa (MCID, de sus siglas en inglés) un cambio de la discapacidad medida por la EDSS $\geq$1.0 punto en los pacientes con una EDSS$\leq$ 5.0 o $\geq$0.5 en los pacientes con EDSS >5.0 y/o un empeoramiento de $\geq$20% en al menos un componente de la MSFC (124, 125). Las diferencias grupales de pacientes se

realizaron mediante el test no paramétrico de U de Mann Whitney. Para asegurar la consistencia de los datos obtenidos por el acelerómetro se designó como válido el uso del acelerómetro un mínimo de 3 días con >10h de actividad y sin ningún período de 60 minutos con ausencia de datos (ceros continuos). La actividad diaria medida por el acelerómetro en promedio de pasos/día se utilizó porque este parámetro ha demostrado la mayor correlación entre la EDSS y los tests estándar de la marcha: T25FW (segundos) y 6MWT (metros). La capacidad predictiva del acelerómetro para detectar los pacientes con discapacidad relacionada con la marcha (EDSS >4.0) se realizó con el análisis de la curva ROC. El estudio de regresión lineal generalizada determinó el efecto de la EDSS sobre la actividad diaria ajustando por variables demográficas y clínicas. Las comparaciones a nivel longitudinal se realizaron con la prueba de los rangos con signo de Wilcoxon.

En el trabajo 3 todas las visitas se realizaron a la misma hora del día para disminuir la variabilidad y el posible efecto de otros síntomas como fatiga. La respuesta de fampridina-LP se definió como una mejoría de ≥20% en la velocidad T25FW tras 2 semanas de tratamiento, por ser el criterio más utilizado (125). Los cambios en los tests de la marcha (T25FW y 6MWT) así como en la actividad diaria se expresaron como porcentaje de cambio respecto al basal pretratamiento. Se consideró una MCID como una mejoría del 20% en 6MWT (62). El valor final de MSWS-12 varía de 12 a 60 y se transformó a 0–100 por la siguiente fórmula: [(puntuación observada - 12) / 60 - 12] x100. Se considera un cambio clínico significativo, una diferencia de ≥ 6 puntos menos con respecto al valor basal (63, 64). El cuestionario IPAQ se expresó como MET-min por semana por la siguiente fórmula: [3.3 METs.min.day (caminar) + 4.0 METs.min.day (actividad moderada) + 8.0 METs.min.day (actividad vigorosa)] (117). El índice de CV relacionada por la salud va de 0 (muerte) a 1 (salud completa) y se consideró una MCID de 0.05 (126). EQ-VAS varía de 0 (peor CdV) a 100 (mejor CdV). Las diferencias entre grupos apareados se realizaron con T de Student para muestras apareadas y con la prueba de los rangos con signo de Wilcoxon. Las diferencias entre grupos se analizaron con la T de Student para muestras independientes y la U de Mann-Whitney.

En el trabajo 4, el rendimiento cognitivo de los pacientes con encefalitis autoinmune anti-LGI1 se realizó mediante la versión telefónica de la MMSE (puntuación de 0-26) y se consideró deterioro cognitivo un valor ≤ 21 (127). El rendimiento cognitivo en la batería cognitiva breve se realizó mediante puntuaciones Z calculadas a partir de los valores de referencia obtenidos de controles sanos ajustados por edad, sexo y nivel educativo. Se definió el deterioro cognitivo leve como la afectación de uno o más dominios cognitivos con una puntuación z por debajo de -1.5 desviación estándar de la distribución de controles sanos sin interferencia en las actividades de la

vida diaria. La demencia se consideró cuando los cambios cognitivos tuvieron un impacto negativo en las actividades de la vida diaria (128). Se consideró un mal estado funcional cuando el mRS era ≥ 3 y el FAQ era ≥ 6 (86-89). Las diferencias entre los grupos de deterioro cognitivo leve y demencia fueron estudiadas con el test de $\chi 2$ de Pearson y U de Mann Whitney. La regresión logística binaria se utilizó para identificar los predictores de deterioro cognitivo. La capacidad predictiva de las variables clínicas basales para detectar deterioro cognitivo a largo plazo se realizó con el análisis de curva ROC.

Todos los análisis estadísticos se realizaron con la versión SPSS software (SPSS Inc, Chicago, IL, EE.UU.) y el nivel de significación establecido fue $p< 0.05$.

8. RESULTADOS

Trabajo número 1

Spanish validation of the telephone assessed Expanded Disability Status Scale and Patient Determined Disease Steps in people with multiple sclerosis

Nuria Solà-Valls[1], Mikel Vicente-Pascual[1], Yolanda Blanco[1], Elisabeth Solana[1], Sara Llufriu[1], Eloy Martínez-Heras[1], Elena H. Martínez-Lapiscina[1], María Sepúlveda[1], Irene Pulido-Valdeolivas[1], Irati Zubizarreta[1], Albert Saiz[1]

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En este trabajo se realizó la traducción de la escala EDSS y la PDDS a castellano y se validó su uso por teléfono, así como se determinó el patrón de asociación entre ambos cuestionarios telefónicos.

Para ello se incluyeron 103 pacientes a los que se administró la EDSS y los pacientes completaron el cuestionario de la PDDS convencional. Todos los pacientes fueron evaluados telefónicamente en el plazo de 15 días. La fiabilidad test-retest se evaluó en 36 pacientes.

Como resumen, el estudio muestra que los cuestionarios telefónicos EDSS y PDDS para pacientes españoles son herramientas válidas para evaluar el estado neurológico y la discapacidad relacionada con la EM, y ofrecen información complementaria. Los pacientes con discapacidad relacionada con la marcha (EDSS >4.0) fueron los que obtuvieron una concordancia mayor en las dos escalas. El patrón de asociación entre la EDSS y la PDDS telefónica no fue perfecto, si bien un punto de corte de PDDS de 3 identificó con precisión a los pacientes con una discapacidad relacionada con la marcha.

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Spanish validation of the telephone assessed Expanded Disability Status Scale and Patient Determined Disease Steps in people with multiple sclerosis

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ABSTRACT

Background: The Expanded Disability Status Scale (EDSS) and Patient Determined Disease Steps (PDDS) are two of the most widely disability scales used in multiple sclerosis (MS). When physical visits are unavailable, remote evaluation through telephone interview may be helpful. We aimed to translate both scales into Spanish, and to 1) validate the telephone EDSS and PDDS, and 2) explore the association pattern between both telephone questionnaires.

Methods: 103 patients underwent a neurological examination to generate the EDSS and completed the PDDS questionnaire. Telephone questionnaires (EDSS, PDDS) were performed within 15 days. Feasibility and psychometric properties of both telephone questionnaires included internal consistency, acceptability, inter-rater agreement and validity. Test-retest reliability was evaluated in 36 patients.

Results: Both scales showed excellent internal consistency and test-retest reliability. The agreement between conventional and telephone assessments in ambulatory impaired patients (EDSS > 4.0) was good for EDSS (kappa = 0.72) and excellent for PDDS (kappa = 0.93); fully ambulatory patients (EDSS ≤ 4.0) showed lower values (kappa = 0.24, and 0.54, respectively). Full agreement was higher for telephone PDDS than telephone EDSS (78% vs 44%). Overestimation of disability was more frequent in fully ambulatory patients. Strong correlation was found between telephone questionnaires (rho = 0.88; $p < 0.001$). The pattern of association was not isomorphic, but a PDDS cut-off of 3 identified with high accuracy patients with ambulatory impairment.

Discussion: Telephone EDSS and PDDS questionnaires for Spanish patients are valid tools to assess disability status in MS and offer complementary information. Patients with ambulatory impairment are those who benefit the most from a remote assessment.

1. Introduction

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system that leads to the accumulation of disability over time. The Expanded Disability Status Scale (EDSS) (Kurtzke, 1983) is the standard measurement for assessing neurological impairment and disability in both clinical setting and research studies. However, EDSS assessed by telephone interview may be an appropriate alternative under certain circumstances such as evaluation of patients with restricted mobility or studies looking for long-term EDSS changes in order to avoid loss to follow-up of patients moving to a different MS center. For these reasons, a telephone assessed EDSS was developed and validated for trained physicians more than a decade ago (Lechner-Scott et al, 2003).

In addition to EDSS, patient-reported outcomes (PROs) are becoming increasingly important in order to capture the impact of the disease in patient's lives (Cohen et al., 2012). The Patient Determined Disease Steps (PDDS), a PRO of disability, was developed by researchers associated with the Patient Registry of the North American Research Committee on MS (NARCOMS) which included clinical data of 37.000 MS patients (Hohol et al., 1995, 1999; Schwartz et al., 1999; Marrie and Goldman, 2007; Learmonth et al., 2013). The strong correlation between PDDS and EDSS supported its validity of PDDS as an alternative assessment of disability when the physical EDSS was unfeasible.

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However, little information is available on the reliability of the PDDS scale and the pattern of association between both disability questionnaires, and even less on the telephone assessment. Therefore, we aimed to translate both disability scales into Spanish, and to 1) validate the telephone EDSS and PDDS and, 2) explore the association pattern between both telephone questionnaires.

2. Methods

2.1. Patients

All consecutive MS patients followed at the MS unit of the Hospital Clinic of Barcelona who agreed to participate where included in the study. Patients met the following inclusion criteria: 1) age equal to or greater than eighteen years; 2) clinically definite MS according to 2010 McDonald criteria (Polman et al., 2011) and 3) no relapses within 30 days prior to the inclusion in the study. The study was conducted in accordance with the guidelines of the declaration of Helsinki and the protocol was approved by the Ethical Committee of the Hospital Clinic of Barcelona. All participants signed a written informed consent before enrollment.

2.2. Study design

2.2.1. Translation and adaptation of both questionnaires

An English version of the telephone EDSS was validated in 2003 (Lechner-Scott et al., 2003) and the PDDS questionnaire was obtained directly from http://www.NARCOMS.org/PDDS. Both questionnaires were translated into Spanish (supplementary material 1–2), and evaluated by five MS experts from our center. Feasibility of the telephone EDSS was explored in a pilot study (Sola-Valls et al., 2015).

2.2.2. Conventional assessment

Neurological examination to obtain the EDSS score was performed by one expert in MS with current accreditation of the Neurostatus (Kappos, 2005). Participants also completed the PDDS and performed the timed 25-foot walk (T25FW) test, a validated walking test which measures the time (in seconds) spent in walking as fast as possible a distance of 7.62 m twice (Goldman et al., 2013).

2.2.3. Telephone assessment

Telephone assessment of the EDSS and PDDS was performed by a trained neurologist uninvolved in the conventional assessment, within fifteen days. Telephone EDSS started by ensuring the patient was stable since the last conventional visit. The EDSS questionnaire is a set of questions regarding walking ability and functional systems (FS). There was a strong recommendation to complete all questions regarding FS even though EDSS was based on ambulation. Regarding the PDDS questionnaire, the investigator read all statements and patients selected the option that was closer to his/her disability status at that specific time.

2.2.4. Test-retest of the telephone questionnaires

In order to assess test-retest reliability, 36 random patients repeated the telephone interview within 15 days from the first telephone assessment.

2.3. Statistics

Descriptive statistics were computed as mean (standard deviation) unless otherwise noted. Patients were classified as fully ambulatory (EDSS < 4.0) and ambulatory impaired (EDSS 4.0). Feasibility was measured by the mean number of calls per patient. Internal consistency was assessed by Cronbach's alpha with values of 0.5, 0.6, 0.7, 0.8 and 0.9 interpreted as poor, questionable, acceptable, good and excellent respectively; stability of both tests (test-retest) was measured by the intra-class correlation coefficient (ICC), and acceptability was analyzed by looking for possible floor or ceiling effects (if > 15% scores were in the lowest or highest scores, respectively) and skewness (a substantial departure from normality was considered ≥ 2.1). Inter-rater agreement was measured by 1) kappa coefficient and rated as specified (Landis and Koch, 1977); 2) the percentage of assessments with full agreement (number of occasions with exact result between conventional and telephone assessment); and 3) the percentage of patients with a change of the EDSS lower than what was considered as clinically meaningful in clinical trials (a change of at least 1.0 point at EDSS level ≤5.0 or at least 0.5 point at EDSS level ≥5.5) (Calabresi et al., 2014). Content validity was assessed by a panel of experts using pre-existent validated scales in English and the criterion validity was determined using Spearman rho rank-order correlation coefficients between questionnaires and T25FW test. Values for correlation coefficients of 0.1, 0.3, and 0.5 were interpreted as small, moderate, and large, respectively. Construct validity was assessed by exploring both telephone questionnaires and comparing them by grouping patients based on their demographic and clinical outcomes. Statistical analyses were performed using SPSS version 20.0 (SPSS Inc, Chicago, IL, USA) software.

3. Results

3.1. Patient demographics and feasibility

One hundred and sixteen patients agreed to participate in the study and 103 (89%) completed the conventional and telephone assessments from November 2016 until May 2017. The mean age of the study

Table 1
Demographic and clinical characteristics of the cohort.

	Total sample (*N* = 103) [1]	PwMS and EDSS ≤ 4.0 (*N* = 83)	PwMS and EDSS > 4.0 (*N* = 20)	*Re*-test sample (*N* = 36) [2]	*p* value [1–2]
Age in years, mean (SD)	44.3 (14.7)	44 (10.5)	45.8 (25.9)	39.2 (19.4)	0.2
Sex, n (% female)	69 (67)	54 (65)	15 (75)	23 (65.7)	0.9
MS subtype, n (%)					0.9
Relapsing remitting	87 (84.5)	80 (96.4)	7 (35)	30 (85.7)	
Secondary progressive	7 (6.8)	1 (1.2)	6 (30)	2 (5.7)	
Primary progressive	9 (8.7)	2 (2.4)	7 (35)	3 (8.6)	
Disease duration in years, mean (SD)	12.8 (14.3)	10.6 (9.6)	22.1 (24.3)	15.1 (20.7)	0.9
Conventional EDSS score, median (range)	2.0 (0–6.5)	2.0 (0–4.0)	6.0 (4.5–6.5)	2.0 (0–6.0)	0.8
Conventional PDDS score, median (range)	0.5 (0–7)	0 (0–4)	5 (3–7)	1 (0–6)	0.9
T25FW test in seconds, mean (SD)	5.7 (4.7)	4.3 (1.3)	11.5 (8.1)	5.4 (3.3)	0.9

Abbreviations: PwMS = patients with multiple sclerosis; SD = standard deviation; n = number; MS = multiple sclerosis; EDSS = Expanded Disability Status Scale; PDDS = Patient Determined Disease Steps; T25FW = timed 25-foot walk test.

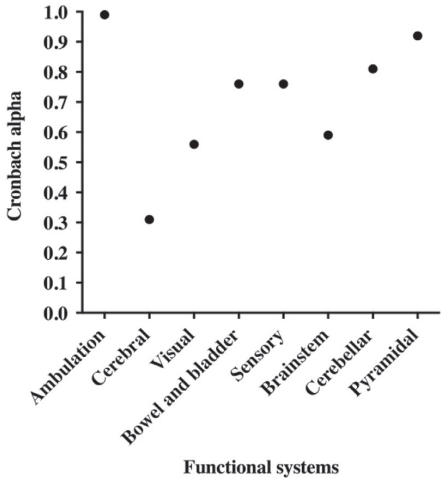

Fig. 1. Cronbach alpha value on functional systems of the telephone Expanded Disability Status Scale.

population was 44 (15) years, and 69 (67%) were women with a median EDSS score of 2.0 (Table 1).

The median number of calls per patient to complete the first telephone interview was 1 (range = 1–9). Thirty-six patients were re-assessed by telephone with a mean time interval of 12 (5) days. No differences in demographic or clinical variables were observed between re-evaluated patients and total sample (Table 1).

3.2. Internal consistency and acceptability

Both telephone assessed EDSS and PDDS showed an excellent internal consistency (Cronbach's alpha: EDSS = 0.99, and PDDS = 0.96). Ambulation and pyramidal FS showed the highest values among all FS (Fig. 1).

Telephone EDSS median score was 2.0 (range, 0–6.5). No floor or ceiling effect was observed (the minimum and maximum scores were 2.9 and 4.9%, respectively). Similarly, telephone PDDS median score was 0.5 (range, 0–7). Half of the patients scored zero suggesting a floor effect of the scale. Skewness statistic in both scales lied within the recommended range. The median value of all FS was 1 except for brainstem, bowel and bladder, visual, and mental FS that was 0. Except for ambulation, all FS showed a floor effect and exceeded the recommended range of skewness.

3.3. Reliability between conventional and telephone disability scales

Full agreement between conventional and telephone EDSS scores was modest for fully ambulatory (kappa = 0.24), and good for ambulatory impaired (kappa = 0.72) patients. Regarding conventional and telephone PDDS scores, full agreement was moderate for fully ambulatory (kappa = 0.54) and excellent for ambulatory impaired (kappa = 0.93) patients. FS with best full agreement were ambulation (kappa = 0.87) and pyramidal FS (kappa = 0.61) (Table 2).

Forty-five of the 103 (44%) patients showed full agreement between conventional and telephone EDSS scores and the number of patients increased to 85 (83%) when the change of the EDSS was considered as not clinically meaningful. There was an overestimation of their EDSS score (≥1 point) in 15/18 (83%) patients with EDSS ≤ 5.0 and 2/18 (11%) (≥0.5 point) with EDSS 5.0, and an underestimation in one (6%) patient who had an EDSS score ≤5.0. Regarding PDDS, 80/103 (78%) patients showed full agreement between conventional and telephone PDDS scores. Fourteen of the 23 (61%) patients overestimated and 9 (39%) underestimated their perception of disability (range of 1–3 points for both) (Fig. 2). All but one was fully ambulatory patients.

Test-retest reliability was excellent for both telephone questionnaires (EDSS: rho = 0.88, $p < 0.001$; intra-class correlation [ICC] = 0.96, 95% CI 0.92–0.98; and PDDS: rho = 0.90, $p < 0.001$;

Table 2
Agreement between conventional and telephone EDSS, PDDS and functional systems in the total sample and MS subgroups.

	Total sample (*N* = 103)	PwMS with EDSS ≤ 4.0 (*N* = 83)	PwMS with EDSS > 4.0 (*N* = 20)
EDSS			
Kappa coefficient (95% CI)[a]	0.37 (0.26–0.48)	0.24 (0.12–0.36)	0.72 (0.49–0.95)
Full agreement[b], n %	45 (43.7)	29 (34.9)	16 (80)
Difference "no clinically meaningful"[c], %	85 (83)	67 (80.7)	16 (80)
p value	$p < 0.001$	$p < 0.001$	$p < 0.001$
PDDS			
Kappa coefficient (95% CI)	0.68 (0.57–0.79)	0.54 (0.39–0.69)	0.93 (0.79–1.07)
Full agreement, n %	80 (78)	61 (73.5)	19 (95)
p value	$p < 0.001$	$p < 0.001$	$p < 0.001$
Pyramidal FS			
Kappa coefficient (95% CI)	0.61 (0.50–0.72)	0.59 (0.46–0.72)	0.25 (0.07- 0.57)
Full agreement, n %	73 (70.9)	59 (71.1)	14 (70)
p value	$p < 0.001$	$p < 0.001$	$p = 0.046$
Cerebellar FS			
Kappa coefficient (95% CI)	0.41 (0.28–0.54)	0.44 (0.30–0.58)	−0.005 (−0.37 to 0.36)
Full agreement, n %	59 (59)	52 (62.7)	7 (38.9)
p value	$p < 0.001$	$p < 0.001$	$p = 0.972$
Brainstem FS			
Kappa coefficient (95% CI)	0.48 (0.31-0.65)	0.57 (0.39–0.75)	0.20 (−0.13 to 0.33)
Full agreement, n %	81 (79.4)	70 (84.3)	11 (57.9)
p value	$p < 0.001$	$p < 0.001$	$p = 0.16$
Sensory FS			
Kappa coefficient (95% CI)	0.43 (0.29–0.57)	0.46 (0.30–0.62)	0.26 (0.04–0.48)
Full agreement, n %	62 (60.2)	54 (65.1)	8 (40)
p value	$p < 0.001$	$p < 0.001$	$p = 0.003$
Bowel and bladder FS			
Kappa coefficient (95% CI)	0.43 (0.31–0.55)	0.35 (0.20–0.50)	0.40 (0.13–0.67)
Full agreement, n %	71 (68.9)	60 (72.3)	11 (55)
p value	$p < 0.001$	$p < 0.001$	$p = 0.001$
Visual FS			
Kappa coefficient (95% CI)	0.22 (0.07–0.37)	0.33 (0.15–0.51)	−0.05 (−0.24 to 0.14)
Full agreement, n %	64 (62.7)	58 (69.9)	6 (31.6)
p value	$p = 0.002$	$p < 0.001$	$p = 0.625$
Mental FS			
Kappa coefficient (95% CI)	0.16 (0.02–0.3)	0.18 (0.03–0.33)	0.01 (−0.25 to 0.27)
Full agreement, n %	64 (62.1)	56 (67.5)	8 (40)
p value	$p = 0.007$	0.003	$p = 0.902$
Ambulation FS			
Kappa coefficient (95% CI)	0.87 (0.79–0.95)	0.88 (0.78–0.98)	0.75 (0.55–0.95)
Full agreement, n %	94 (91.3)	78 (94)	16 (80)
p value	$p < 0.001$	$p < 0.001$	$p < 0.001$

Abbreviations: PwMS = patients with multiple sclerosis; CI = confidence interval; n = number; MS = multiple sclerosis; EDSS = Expanded Disability Status Scale; PDDS = Patient Determined Disease Steps; FS = functional system.

[a] Kappa coefficient (95% CI) refers to a pooled kappa of full agreement considering conventional and telephone assessments;

[b] Full agreement refers to the number of occasions with exact result between conventional and telephone assessment;

[c] Difference "no clinically meaningful" represents a change of 0.5 points in patients with EDSS level ≤5.0.

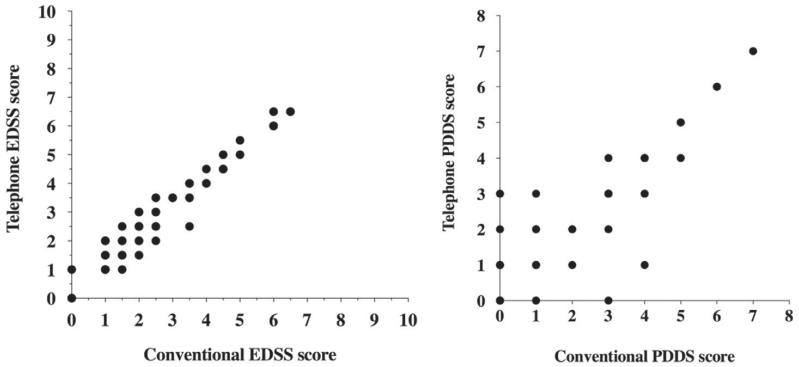

Fig. 2. Scatterplot of correlation between conventional and telephone EDSS and PDDS scores.

ICC = 0.97, 95% CI 0.94–0.99). The percentage of patients with equal score in both telephone EDSS questionnaires was 48%, while that of PDDS was 81%.

3.4. Criterion validity: correlations between conventional and telephone disability scales and between FS scores

Correlation between conventional and telephone EDSS was good for the overall sample and for each disability subgroup (Fig. 2 and Table 3). Overall, good correlations were observed in all FS except for visual and mental FS. Fully ambulatory patients showed better association between conventional and telephone FS than ambulatory impaired patients. The correlation between conventional and telephone PDDS was good for the overall sample and for each disability subgroup (Table 3). Telephone EDSS and PDDS questionnaires showed a good correlation (rho = 0.88, $p < 0.001$), similar to the correlation observed between conventional EDSS and PDDS (rho = 0.79, $p < 0.001$). Both telephone disability scales correlated strongly with telephone pyramidal, cerebellar and ambulation FS. No significant differences were observed in the magnitude of correlations between each telephone disability scale and FS scores (data not shown).

3.5. Construct validity: correlations between telephone disability scales and clinical features

Telephone EDSS, telephone PDDS and telephone assessed pyramidal, cerebellar and ambulation FS showed a moderate correlation with demographic and clinical measures (Table 4).

There were differences in telephone EDSS or PDDS among disease subtypes but not with gender (data not shown). T25FW test showed a good correlation with both telephone questionnaires for the overall sample (Fig. 3), and the association was strong with ambulation, pyramidal and cerebellar FS.

Table 3
Correlations between conventional and telephone EDSS, PDDS and functional systems.

Conventional and telephone	Total sample (N = 103)	PwMS with EDSS ≤ 4.0 (N = 83)	PwMS with EDSS > 4.0 (N = 20)
EDSS	0.94 (<0.001)	0.89 (<0.001)	0.93 (0.001)
PDDS	0.88 (<0.001)	0.75 (<0.001)	0.96 (0.001)
Pyramidal FS	0.85 (<0.001)	0.81 (<0.001)	0.61 (0.004)
Cerebellar FS	0.71 (<0.001)	0.64 (<0.001)	0.12 (0.6)
Brainstem FS	0.53 (<0.001)	0.66 (<0.001)	0.27 (0.3)
Sensory FS	0.56 (<0.001)	0.69 (<0.001)	0.47 (0.04)
Bowel and bladder FS	0.67 (<0.001)	0.53 (<0.001)	0.55 (0.01)
Visual FS	0.35 ($p < 0.001$)	0.50 (<0.001)	−0.11 (0.7)
Mental FS	0.21 (0.04)	0.26 (0.18)	−0.07 (0.8)
Ambulation FS	0.96 (<0.001)	0.90 (<0.001)	0.99 (<0.001)

All values are Spearman rho (p value). Abbreviations: PwMS = patient with multiple sclerosis; EDSS = Expanded Disability Status Scale; PDDS = Patient Determined Disease Steps; FS = functional system.

Table 4
Correlations of telephone EDSS, PDDS and functional systems with demographic and clinical outcomes.

	Outcome measures T25FW score, seconds	Age, years	Disease duration, years
Telephone EDSS score	0.68 (<0.001)	0.39 (<0.001)	0.45 ($p < 0.001$)
Telephone PDDS score	0.62 (<0.001)	0.37 ($p < 0.001$)	0.45 ($p < 0.001$)
Pyramidal FS	0.62 (<0.001)	0.44 (<0.001)	0.55 (<0.001)
Cerebellar FS	0.61 (<0.001)	0.33 (0.001)	0.43 (<0.001)
Brainstem FS	0.22 (0.03)	0.13 (0.21)	0.05 (0.60)
Sensory FS	0.12 (0.3)	0.01 (0.92)	0.14 (0.18)
Bowel and bladder FS	0.41 (<0.001)	0.13 (0.19)	0.30 (0.002)
Visual FS	0.1 (0.35)	0.19 (0.05)	0.09 (0.40)
Mental FS	0.31 (0.001)	0.11 (0.26)	0.20 (0.04)
Ambulation FS	0.68 (<0.001)	0.40 (<0.001)	0.44 (<0.001)

Abbreviations: EDSS = Expanded Disability Disease Steps; PDDS = Patient Disability Disease Steps; FS = functional system; T25FW = timed-25foot walk.

3.6. Pattern of association between telephone EDSS and PDDS

We found a strong linear association between telephone EDSS and PDDS questionnaires (rho = 0.88, $p < 0.001$), and the result remained significant within disability subgroups (fully ambulatory: rho = 0.76, $p < 0.001$; ambulatory impaired: rho = 0.85, $p < 0.001$). We further regressed telephone EDSS scores on telephone PDDS score ($R^2 = 0.83$, $p < 0.001$), resulting in the regression equation, telephone PDDS score = - 1.4 + 1.02*(telephone EDSS score). When we defined a conversion range of EDSS scores for each PDDS score, based on the results of the regression equation and previous work (Kobelt et al., 2006) we found that full agreement between telephone questionnaires ranged from 27% to 100%. The percentage of variability was higher for fully ambulatory compared to ambulatory disabled patients. A PDDS ≥ 3 identified patients with EDSS > 4.0 with a high sensitivity and specificity (area under the curve = 0.97; 95% CI 0.94–0.99; $p < 0.001$) (Table 5). The magnitude and pattern of correlation between telephone EDSS and PDDS did not differ significantly from the observed by conventional assessments (data not shown).

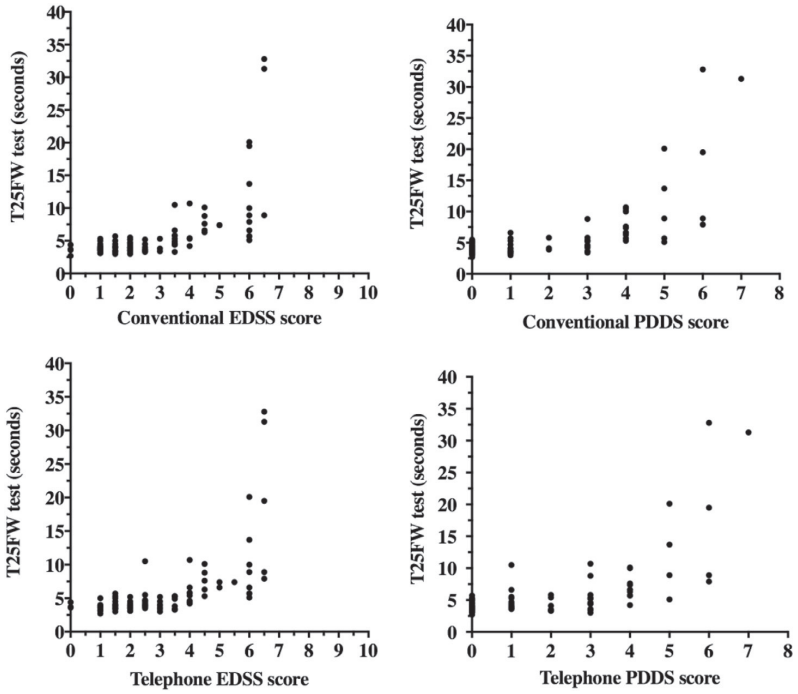

Fig. 3. Correlation between T25FW and both conventional and telephone EDSS and PDDS questionnaires.

Table 5
Pattern of association between telephone EDSS and PDDS questionnaires.

Telephone PDDS score (N patients)	Telephone EDSS, median (range)	Suggested EDSS score related to PDDS[a]	Full agreement[b], %	Difference "no clinically meaningful[c], %
0 (N = 46)	1.5 (0–3.5)	≤1.5	56.5	84.8
1 (N = 17)	2.5 (1.5–4.0)	2.0–2.5	64.7	82.4
2 (N = 7)	3.5 (2.0–4.0)	3.0–3.5	42.9	85.7
3 (N = 13)	4.0 (2.5–4.5)	4.0–4.5	53.9	69.3
4 (N = 11)	5.0 (4.0–6.0)	5.0–5.5	27.3	54.6
5 (N = 4)	6.0 (6.0–6.0)	6.0	100	100
6 (N = 4)	6.5 (6.5–6.5)	6.5	100	100
7 (N = 1)	6.5 (6.5–6.5)	7.0–7.5	0	0
8 (N = 0)	–	8.0–9.5	–	–

Abbreviations: PDDS = Patient Disability Disease Steps; EDSS = Expanded Disability Disease Steps; N = number.

[a] Recommended EDSS score predefined by a regression equation and previous work (Kobelt et al., 2006);

[b] Full agreement refers to the number of occasions with exact result between conventional and telephone assessments;

[c] Difference "no clinically meaningful" represents a change of 0.5 points in patients with EDSS level ≤5.0).

4. Discussion

Telephone assessed EDSS was validated as a useful alternative to conventional EDSS for clinical studies with long-term follow-up or with patients unable to attend the visits, and more recently PDDS, a patient-reported outcome of disability, was proposed as an alternative to the EDSS. Considering their value in some circumstances, we aimed to adapt and validate both questionnaires for their use in Spanish subjects with MS. Our study shows an excellent internal consistency and acceptability of both telephone EDSS and PDDS questionnaires, with results comparable to the original English versions.

Only few studies have addressed the reliability of remote EDSS assessment, most of them using paper (Bowen et al., 2001; Cheng et al., 2001; Goodin, 1998), few of them using multimedia (Leddy et al., 2013; Bove et al., 2018; Sola-Valls et al., 2015), and only one of them using telephone as a form of administration (Lechner-Scott et al., 2003). One important aspect which is consistent with most of these studies is a good agreement between conventional and telephone EDSS scores in ambulatory impaired patients (Amato et al., 1988; Noseworthy et al., 1990; Lechner-Scott et al., 2003). However, the overall full agreement of 44% increased to 83%, regardless of the EDSS score, when we considered that the change in the EDSS score was not clinically meaningful (a change of at least 1.0 point at EDSS level ≤5.0 or at least 0.5 point at EDSS level ≥5.5) (Calabresi et al., 2014).

Moreover, similar to the study that validated the telephone EDSS assessment, we found higher values for pyramidal and lowest for mental FS, reinforcing that motor involvement and ambulation are primary contributors to EDSS (Lechner-Scott et al., 2003). This information is important at the time of scoring the EDSS, because fully ambulatory patients are mainly those who overestimate their disability by telephone EDSS interview. Disagreement at lower EDSS might be explained by the lack of detailed questions in telephone EDSS questionnaire to assess each functional system and the inability to score zero value for the assessment of functional system.

Despite no previous report of telephone PDDS assessment was found, this PRO scale was equal to the conventional one, written on paper. Regarding conventional and telephone PDDS scores, there was an overall full agreement in 78% of the patients, and it was excellent for ambulatory impaired patients. The disagreement was mostly observed in fully ambulatory patients that tended to overestimate (61%) and less frequently underestimate (39%) their disability. Of note, the test-retest of the telephone PDDS showed a higher reliability than the telephone EDSS (81% vs 48%, respectively). The observed differences in reliability between the two telephone questionnaires is likely due to the fact that conventional and telephone EDSS are essentially different since

conventional EDSS is based on a full neurological examination in contrast to telephone EDSS which is a questionnaire based on patient's perception. In this case, an inter-rater variability should also be considered. Conventional and telephone PDDS are the same patient-reported outcome and patient's perception may remain more stable for shorts period of time. Regardless of the scale applied, patients tend to perceive their disability worse than what physicians observe by physical examination, especially in fully ambulatory patients, suggesting that other factors may contribute to this dissociation.

Our study confirms the good correlation observed previously between the EDSS and the PDDS, and the pattern of association with FS, clinical and demographic features, and extends the information to that obtained by telephone interview. The magnitude and pattern of correlation between telephone did not differ from the observed by conventional assessment. It is important to note that most of our participants showed mild disability (median EDSS = 2.0) compared to the previous study (median EDSS = 4.5), and this may explain the differences in the magnitude of the correlations. Regardless of the type of assessment, we observed better correlations in the EDSS and PDDS scores for ambulatory impaired patients. The observation of a good correlation of both telephone EDSS and PDDS with T25FW test reinforced that these scales are focused towards ambulation.

Despite both telephone questionnaires strongly correlated with each other and showed similar methodological properties to be validated as a patient-reported outcome of disability in MS, their use indistinctly would not be recommended. Telephone-assessed EDSS, similar to conventional EDSS, offers enough information about certain aspects of the neurological status, but there is a need of trained physicians to reduce inter-rater variability and it is time-consuming. In contrast, telephone PDDS offers a general and simple view of disability status but it relies exclusively on patient's perception. For this, the pattern of conversion between these two scales is far from perfect, being fully ambulatory patients those with a higher percentage of variability in scoring their disability. In this sense, a cut-off of PDDS ≥ 3 accurately included all patients who had walking disability (EDSS > 4.0).

As a limitation, this validation study was obtained from a single MS center, and we did not cover the full disability range present in MS population. Despite this, it can be confidently assumed that the current study population represents the normal variation of the disease, and the patients included share the clinical characteristics of previous cohort involved in telephone interview (Lechner-Scott et al., 2003).

To conclude, this study provides evidence supporting the validity of both telephone EDSS and PDDS questionnaires translated into Spanish. Both telephone questionnaires are reliable resources for obtaining information about the neurological status in MS, and they are complementary. Patients with higher EDSS scores are those who may benefit the most from these types of interventions. Despite a telephone interview will never replace a face to face visit, if needed, the election of one specific disability scale must be considered carefully based on the study needs and goals.

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Declaration of interest

NSV received reimbursement from Genzyme and Bayer-Schering. MVP, ES and EMH declare no conflict of interest. YB received reimbursement from Biogen, Novartis and Genzyme. SL received reimbursement from Biogen, Novartis, Teva, Genzyme and Merck. EHMLP received reimbursement from Biogen, Genzyme, Novartis and Roche. MS received reimbursement from Genzyme and Biogen. IPV received reimbursement from Roche and Genzyme and holds stock options in Aura Innovative Robotics. IZ received reimbursement from Genzyme, Biogen, Merck and Bayer-Schering. AS received reimbursement from Bayer-Schering, Merck, Biogen, Genzyme, TEVA, Novartis, and Roche.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2018.11.018.

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Trabajo número 2

Walking function in clinical monitoring of multiple sclerosis by telemedicine

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En este trabajo se investigó la viabilidad de la evaluación telemática mediante el uso de herramientas multimedia en pacientes con EM, así como la concordancia entre la EDSS evaluada por vía convencional y remota, y la utilidad del acelerómetro para caracterizar mejor la discapacidad de los pacientes.

Para ello, 25 pacientes con una discapacidad medida por la EDSS entre 1.0–6.5 fueron evaluados cada 3 meses durante el primer año, y en el año 2. Las visitas remotas incluyeron la grabación de un video con un examen neurológico autoevaluado, y cuestionarios multimedia específicos. La marcha se cuantificó mediante un cuestionario autoadministrado, la realización del test de los 6 minutos y la monitorización de la actividad diaria por un acelerómetro triaxial.

Como resumen, este estudio muestra que la monitorización clínica por telemedicina es factible en los pacientes con EM, y que la concordancia entre evaluación remota y presencial es similar a la observada entre dos evaluadores presenciales. La mejor concordancia se obtuvo para pacientes con discapacidad relacionada con la marcha (EDSS>4.0). Los acelerómetros capturaron cambios en la actividad diaria (promedio de pasos/día) que no fueron detectados en otras medidas clínicas evaluadas a los 2 años.

J Neurol
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ORIGINAL COMMUNICATION

Walking function in clinical monitoring of multiple sclerosis by telemedicine

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Abstract Walking limitation is a key component of disability in patients with multiple sclerosis (MS), but the information on daily walking activity and disability over time is limited. To determine, (1) the agreement between the standard measurements of MS-related disability [expanded disability status scale (EDSS), functional systems (FS) and ambulation index (AI)] obtained by conventional and remote evaluation using a multimedia platform; (2) the usefulness of monitoring 6-min walk test (6MWT) and average daily walking activity (aDWA) to better characterize patients disability. Twenty-five patients (EDSS score 1.0–6.5) were evaluated every 3 months for the first year, and aDWA repeated at year 2. Remote visits included the recording of a video with self-performed neurological examination and specific multimedia questionnaires. aDWA was measured by a triaxial accelerometer. All but two patients completed the study. Modest agreement between conventional and multimedia EDSS was found for EDSS ≤ 4.0 (kappa $= 0.2$) and good for EDSS ≥ 4.5 (kappa $= 0.6$). For the overall sample, pyramidal, cerebellar and brainstem FS showed the greatest agreement (kappa $= 0.7$). SR-AI showed a modest agreement for EDSS ≤ 4.0 and good for EDSS ≥ 4.5 (kappa $= 0.3$ and 0.6, respectively). There was a strong correlation between conventional and 6MWT measured by accelerometer ($r = 0.76$). The aDWA correlated strongly with the EDSS ($r = -0.86$) and a cut-off point of 3279.3 steps/day discriminated patients with ambulatory impairment. There was a significant decline in aDWA over 2 years in patients with ambulatory impairment that were not observed by standard measurements of disability. MS clinical monitoring by telemedicine is feasible, but the observed lower agreement in less disabled patients emphasizes the need to optimize the assessment methodology. Accelerometers capture changes that may indicate deterioration over time.

Keywords Multiple sclerosis · Telemedicine · Disability progression · Accelerometer · Daily walking activity

Introduction

Telemedicine, described as the "use of communication technologies to assist in the diagnosis and treatment of medical conditions through the transmission of data between two different physical places", offers the potential of improving accessibility to health services [1] but reports on using this potentially promising technology with reliable markers of disability and walking activity are limited. Presently, the expanded disability status scale (EDSS) is the standard measurement of disability and disease progression in multiple sclerosis (MS), but it has several limitations. At the lower end of the scale (EDSS score ≤ 4.0), the score is influenced by signs detected in the neurological examination, while higher EDSS scores (EDSS ≥ 4.5) is mainly based on walking ability [2–4]. In addition, the EDSS is less responsive to changes in patients with greater disability [3, 4]. Gait impairment is a frequent finding over the course of MS, but there appears to be a reduction of speed and stride length during walking in people with mild MS compared with age- and sex-matched control subjects [5, 6]. The usual tools to measure walking function are short lasting standard

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tests such as the timed 25-foot walk (T25FW) and the longer 2 or 6-min walk test (2MWT or 6MWT). Recently, accelerometers have been introduced to measure continuous ambulation in real life conditions [7]. The aims of this longitudinal pilot study were: (1) to examine the feasibility of using a multimedia platform and determine the reliability of the obtained EDSS (multimedia EDSS) in comparison with the conventional EDSS (standard physical neurological examination), and (2) to explore the usefulness of monitoring continuous ambulation (daily walking activity measured by an accelerometer) to better characterize the patient's disability status and its potential use for detecting disease progression over time in a cohort of MS patients.

Methods

Patients

Twenty-five consecutive MS patients were prospectively selected from the MS Unit of the Hospital Clinic of Barcelona. The inclusion criteria were: (1) clinically definite MS according to 2010 McDonald criteria [8]; (2) relapsing-remitting or secondary progressive forms; (3) EDSS score between 1.0 and 6.5; and (4) availability of a home computer with internet connection.

Study schedule and procedures

This longitudinal study included six visits, one every 3 months (month 0, 3, 6, 9 and 12) for 1 year, and one additional visit after 2 years of follow-up (Fig. 1). The first year, each visit included a double evaluation, first at the Hospital (conventional visit) and the following day at home (remote visit). Conventional and remote visits were evaluated by two independent and blinded raters. The conventional visit included a neurological examination, recording of the EDSS [2], the multiple sclerosis functional composite (MSFC) [9], and the performance of the 6MWT [10]. The following day after each conventional visit, patients were remotely evaluated by a multimedia system: a health management platform created by Linkcare Health

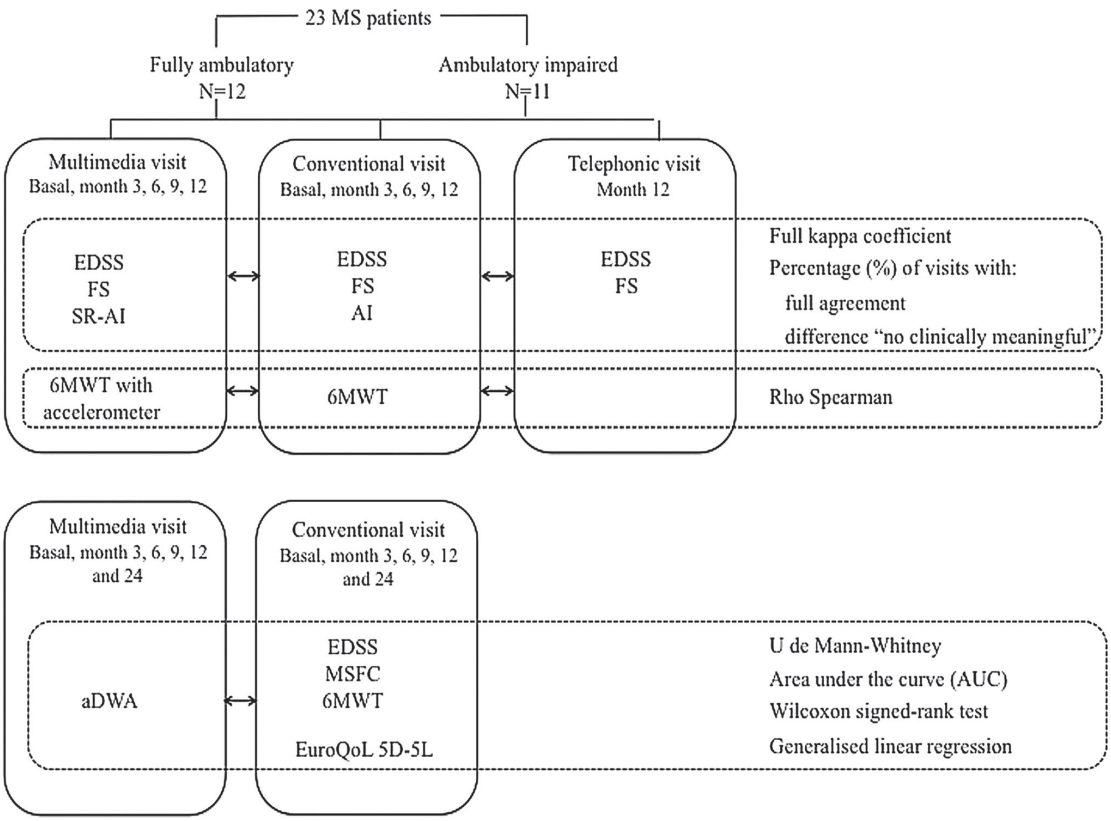

Fig. 1 Study procedures and assessments. *EDSS* expanded disability status scale, *FS* functional systems, *AI* ambulation index, *SR-AI* self-reported ambulation index, *MSFC* multiple sclerosis functional composite, *6MWT* 6-min walk test, *aDWA* average daily walking activity

Services SL (http://www.linkcare.es). This remote visit included recording a video of a self-performed neurological examination (patients were previously trained) to evaluate pyramidal, cerebellar and brainstem functional systems (FS); visual FS was measured by an electronic Snellen eye chart; sensory, bowel and bladder FS were evaluated by a set of electronic questions [11] and cognitive FS by the questionnaire of the multiple sclerosis quality of life (MSQoL) inventory [12]. Walking distance was graded from 0 to 12 according to ambulation index (AI) score by neurostatus definitions [using the measured distance in the conventional visit, and the estimated by the patient in the self-reported AI (SR-AI)] [11]. Every 6 months, this remote visit also included an evaluation of fatigue and depression [12]; fatigue was determined by the modified fatigue impact scale (MFIS), which scores range from 0 to 84, with higher scores indicating a greater impact of fatigue on a patient's activities, and depression was determined by the mental health inventory (MHI) which scores range from 0 to 100, with higher scores indicating better mental health. At the end of the first year, the assessment of the EDSS by a telephone questionnaire [13] and the quality of life by the EuroQoL 5D-5L [14] instrument were administered to all patients. The additional visit at year 2 included the conventional visit with the recording of the EDSS, the MSFC and the performance of the 6MWT (Fig. 1).

Remote walking assessment

The following day after each conventional visit, patients performed the 6MWT test at home with a portable triaxial accelerometer (Actigraph GT3X) and subsequently wore the accelerometer for a period of 7 consecutive days. The accelerometer was worn on an elastic belt around the non-dominant hip determined by the Edinburgh handedness inventory [15]. Patients were asked to wear it the entire day, except while sleeping, and were instructed to do their usual routine. To ensure the consistency of accelerometer data, we designated a valid measurement as $\geq$3 days of accelerometer activity with $\geq$10 h without any period of $\geq$60 min of no accelerometer data (continuous zeros). Average daily walking activity (aDWA) was measured in steps during the day (steps/day) because this parameter has shown the highest correlation between the EDSS and standardized walking tests: T25FW (seconds) and 6MWT (meters) [16].

Statistical analysis

In this pilot study, we calculated a sample size of 25 participants according to previous research that suggest that it should be 10 % of the sample projected for the larger study in the field with an α and β error of 0.05 and 0.80, respectively, and a small effect size (0.10). Full agreements measured by kappa coefficients and values of Pearson's correlation coefficients were rated as previously reported [17, 18]. Moreover, we evaluated the percentage of visits with full agreement, and the percentage of visits that had a change of the EDSS lower than what was considered as clinically meaningful in clinical trials (a change of at least 1.0 point at EDSS level $\leq$ 5.0 or at least 0.5 point at EDSS level $\geq$ 5.5) [19]. Disease progression was defined as: a change of at least 1.0 point at EDSS level $\leq$ 5.0 or at least 0.5 point at EDSS level $\geq$ 5.5 [19] and/or a worsening from baseline on scores of at least one MSFC component by 20 % [20]. Patients were grouped by their EDSS score in fully ambulatory patients (EDSS $\leq$ 4.0) and patients with ambulatory impairment (EDSS $\geq$ 4.5). Differences across ambulation subgroups were performed by Mann–Whitney U test. Accuracy of the potential predictive value of an accelerometer to detect patients with EDSS $\geq$ 4.5 was analyzed by the area under the curve (AUC). Generalized linear regression analysis was conducted by regressing aDWA and EDSS, and included age, body mass index, fatigue and mood score as confounding variables. Longitudinal data was analyzed by Wilcoxon signed-rank test for paired nonparametric comparisons. All p values were two tailed and they were considered significant at $p \leq 0.05$. Statistical analyses were performed using SPSS version 20.0 (SPSS Inc, Chicago, IL, USA) software.

Results

Patients' characteristics and feasibility of remote monitoring

Twenty-three of the 25 (92 %) patients completed the study. One patient withdrew from the study after the first visit because she was unable to attend the physical visits, and the second after having a heart attack. Demographic and clinical characteristics of the 23 patients who completed the study are shown in Table 1. Eleven of the 23 (48 %) patients had an EDSS score $\geq$ 4.5. Nearly half of the patients (42 %) had minor technical problems during the study (i.e., problems in sending the video or answering the questionnaires) but these problems were solved easily. Nineteen (85 %) participants reported telemedicine monitoring as a positive experience and eight (35 %) found it highly suitable.

Agreement between conventional and remote measurements

Overall full agreement between conventional and multimedia EDSS measures was modest for fully ambulatory patients [EDSS $\leq$ 4.0; kappa = 0.20, 95 % confidence interval (CI) 0.1–0.3, $p < 0.01$] and good for patients with ambulatory

Table 1 Demographic and clinical characteristics of the study sample

	MS patients ($N = 23$)
Sex, female:male	12:11
Age, years; mean (SD)	46.7 (10.0)
MS type, RR:SP	15:8
BMI, kg/m^2; mean (SD)	24.4 (4.0)
Smoking (%)	21.7
MFIS score; mean (SD)	55.3 (17.1)
MHI score; mean (SD)	57 (8.2)
Disease duration, years; mean (SD)	14.2 (9.9)
EDSS; median (range)	3.5 (1.5–6.5)
ARR; mean (SD)	0.5 (0.4)
MSSS; mean (SD)	4.8 (8.9)
Time to EDSS 4.0, years, mean (SD)	9.6 (3.6)
Time to progressive phase, years; mean (SD)	14.1 (13.0)

MS multiple sclerosis, *SD* standard deviation, *RR* relapsing-remitting, *SP* secondary progressive, *BMI* body mass index, *MFIS* modified fatigue impact scale, *MHI* mental health inventory, *EDSS* expanded disability status scale, *ARR* annualized relapse rate, *MSSS* multiple sclerosis severity score

impairment (EDSS $\geq$ 4.5; kappa = 0.60, 95 % CI 0.4–0.8, $p < 0.01$) (Table 2). Conventional and multimedia agreement in FS was good for pyramidal (kappa = 0.70, 95 % CI 0.6–0.8, $p < 0.01$), cerebellar (kappa = 0.71, 95 % CI 0.6–0.8, $p < 0.01$) and brainstem (kappa = 0.70, 95 % CI 0.6–0.8, $p < 0.01$), and low to moderate for the other FS (Fig. 2). Full agreement between both EDSS measures was observed in 45 % of visits, and increased to 82 % when the change in the EDSS was not considered clinically meaningful (a change of 0.5 points in patients with EDSS level $\leq$ 5.0). Multimedia EDSS showed better agreement than telephonic EDSS when compared with conventional EDSS measures. Full agreement between conventional and telephonic EDSS was poor for fully ambulatory patients (kappa = 0.05, 95 % CI −0.1 to 0.3, $p = 0.6$) and moderate for patients with ambulatory impairment (kappa = 0.50, 95 % CI 0.1–0.9, $p = 0.25$) (Table 2). Full agreement was observed in 36 % of the visits, and increased to 72 % when the change in the EDSS was not considered clinically meaningful. The agreement between conventional and telephonic FS ranged from poor to modest, but the kappa values were always lower than the observed between the conventional and multimedia FS (data not shown). A moderate agreement was observed between the conventional and SR-AI for the entire sample (kappa = 0.52, 95 % CI 0.3–0.7, $p < 0.01$) but full agreement was observed in 68.2 % of visits; patients with ambulatory impairment showed good agreement (kappa = 0.60, 95 % CI 0.2–1, $p < 0.01$) in contrast with fully ambulatory patients (kappa = 0.30, 95 % CI −0.2 to 0.6, $p = 0.2$) (Table 2).

Remote monitoring of continuous ambulation by accelerometer

The 6MWT evaluated by accelerometer correlated strongly with conventional 6MWT ($r = 0.76$, $p < 0.01$). A robust correlation was also found between aDWA and the EDSS score ($r = -0.86$, $p < 0.01$). In the generalized linear regression model, disability status (EDSS score) was the single significant predictor that accounted for 76 % of the variance in aDWA (adjusted $R^2 = 0.76$, $p < 0.01$). When the model was applied to patients with an EDSS score $\geq$ 4.5, the result remained similar ($R^2 = 0.77$, $p < 0.01$), but it decreased to 22 % in patients with an EDSS score $\leq$ 4.0 ($R^2 = 0.22$, $p = 0.21$). The mean $\pm$ SD aDWA of the total sample was 5597.3 $\pm$ 3751.7 steps/day. There were significant differences between fully ambulatory patients (7283.4 $\pm$ 3141.6 steps/day) and those with ambulatory impairment (1550.9 $\pm$ 943.1 steps/day) ($p < 0.01$), and these differences were maintained throughout the study (Fig. 3). A cut-off point of 3279.3 steps/day was able to discriminate patients with ambulatory impairment from fully ambulatory patients with a high sensitivity (0.9), specificity (1.0) and accuracy (AUC = 0.99, 95 % CI 0.97–1.0, $p < 0.01$). Using this cut-off point, a significant difference in the EuroQoL 5D-5L index value was observed between fully ambulatory patients and those with ambulatory impairment (0.8 vs. 0.6, respectively, $p < 0.01$). The linear regression equation indicated that every 1-point increase in the EDSS score yielded a reduction of 1198.2 steps/day (95 % CI 2079–317.4, $p = 0.09$) in fully ambulatory patients, and a reduction of 1340.4 steps/day (95 % CI 2134.3–546.5, $p < 0.02$) in patients with ambulatory impairment.

Longitudinal walking assessment

After 2 years of follow-up, four patients (17.4 %) had a relapse but no progression of the disease was observed in any patient included in the study. Indeed, no evidence of disability progression was observed by the EDSS score (mean difference = −0.04, $p = 0.65$) or the MSFC z-score (mean difference = 0.1, $p = 0.14$) in the overall sample. Focusing on walking assessments, we observed a significant decline in aDWA over time (mean difference = 1717.7 steps/day, $p = 0.01$), mainly explained by a significant decrease in patients with ambulatory impairment (mean difference = 1279 steps/day, $p = 0.02$), and a trend in fully ambulatory patients (mean difference = −2119.9 steps/day, $p = 0.08$). By contrast, fully ambulatory patients showed a mild improvement in the 6MWT (mean difference = 47.2 m, $p = 0.04$), whereas the changes were not significant in patients with

Table 2 Inter-rater agreement between conventional and remote measurements

		Total sample	Fully ambulatory (EDSS ≤ 4.0)	Ambulatory impaired (EDSS ≥ 4.5)
Conventional vs. multimedia EDSS	Kappa coefficient (95 % CI)[a]	0.4 (0.3–0.5)	0.2 (0.1–0.3)	0.6 (0.4–0.8)
	Percentage (%) of visits with:			
	Full agreement[b]	44.8	33.8	44.8
	Difference "no clinically meaningful"[c]	81.9	81.1	86.7
Conventional vs. telephonic EDSS	Kappa coefficient (95 % CI)[a]	0.3 (0.1–0.5)	0.05 (−0.1 to 0.3)	0.5 (0.1–0.9)
	Percentage (%) of visits with:			
	Full agreement[b]	36.4	20	62.5
	Difference "no clinically meaningful"[c]	72.2	73.3	75
Self-reported ambulation score vs. measured at hospital	Kappa coefficient (95 % CI)[a]	0.5 (0.3–0.7)	0.3 (−0.2 to 0.6)	0.6 (0.2–1)
	Percentage (%) of visits with:			
	Full agreement[b]	68.2	73.3	62.5

EDSS expanded disability status scale, *CI* confidence interval

[a] Kappa coefficient (95 % CI) refers to a pooled kappa of full agreement considering all visits

[b] Full agreement refers to the number of visits with exact result between conventional and remote measurement

[c] Difference "no clinically meaningful" represents a change of 0.5 points in patients with EDSS level ≤ 5.0

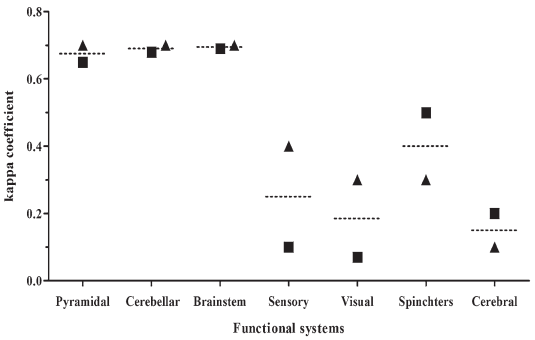

Fig. 2 Full agreement on functional systems of the EDSS between conventional and multimedia measurements. Kappa coefficient was measured according to ambulation subgroups: fully ambulatory patients (■) and patients with ambulatory impairment (▲). *EDSS* expanded disability status scale

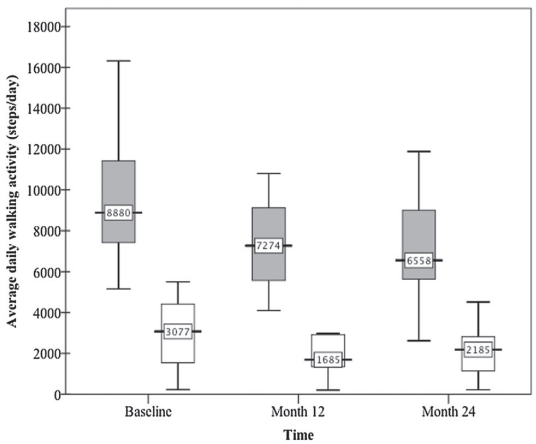

Fig. 3 *Box-plot* of average daily walking activity in ambulation subgroups during the study (*box* 25–75 % percentile range; *central horizontal bar* mean; *whiskers* from minimum to maximum). Average daily walking activity from fully ambulatory patients and patients with ambulatory impairment are plotted in *dark grey* and *white*, respectively

ambulatory impairment. Regarding T25FW, no significant change was observed in any group (Table 3).

Discussion

This study provides several findings that may be relevant at the time of adopting telemedicine as a tool for clinical monitoring or a therapeutic intervention in MS: (1) the implementation of a program by telemedicine is feasible; (2) good agreement between conventional and remote EDSS is only found in more disabled patients (EDSS score ≥ 4.5); (3) pyramidal, cerebellar and brainstem FS are the more reliable measures of impairment regardless of the degree of disability; (4) SR-AI shows modest agreement for fully ambulatory patients (EDSS score ≤ 4.0); (5) strong correlation is found between conventional 6MWT and the one measured by accelerometer; (6) aDWA correlates strongly with the EDSS score, and can discriminate patients with or without ambulatory impairment; and (7) aDWA can detect changes that are not observed by the standard measurements of disability over time. Taking into account the low reproducibility of the EDSS, especially at the lower end of the scale [3, 4], the finding of a modest

Table 3 Changes in walking measures at 2 years from baseline

		Total sample	*p*	Fully ambulatory (EDSS $\leq$ 4.0)	*p*	Ambulatory impaired (EDSS $\geq$ 4.5)	*p*
No. of patients		23		12		11	
aDWA by accelerometer (steps/day)	Mean difference (SD)	−1717.7 (2912.8)	0.01	−2119.9 (3798.4)	0.08	−1279 (1545.4)	0.02
	Mean % of change (SD)	−18.7 (36.8)	na	−19.2 (33.9)	na	−18 (41.3)	na
6MWT (m)	Mean difference (SD)	19.4 (72)	0.21	47.2 (71.3)	0.04	−10.9 (62.3)	0.57
	Mean % of change (SD)	3.1 (22.3)	na	13.1 (20.4)	na	−7.8 (19.6)	na
T25FW (s)	Mean difference (SD)	0.8 (3)	0.23	−0.3 (1)	0.30	2 (4)	0.14
	Mean % of change (SD)	3.6 (23.2)	na	−4.6 (18.1)	na	12.6 (25.5)	na
	Difference of z-score	0.1	0.21	0.1	0.45	0.1	0.31

Mean difference is expressed as 2 years value minus baseline value

EDSS expanded disability status scale, *p p* value, *aDWA* average daily walking activity, *6MWT* 6 min walk test, *T25FW* timed 25-foot walk, *SD* standard deviation, *na* no applicable

agreement between conventional and remote EDSS score was not unexpected. In fact, we found similar agreement in the range of inter-rater agreement reported between two physical examiners (kappa of 0.45–0.50) [21–23]. Similarly, we observed a better agreement for those patients more disabled in whom the EDSS score is weighted heavily toward ambulatory disability [24]. However, when we considered that a variation of the EDSS score was not clinically meaningful, the agreement was 82 % regardless of the EDSS score. It is likely that the reduction of the FS scoring variability by the use of a video in the multimedia EDSS assessment has contributed to these results [25, 26]. These results compare favorably with the ones observed by the telephonic interview in terms of better agreement with the EDSS and the FS scores, with a higher percentage of full agreement between conventional and remote assessment. Similar to a previous report with an equivalent kappa coefficient [13], a better reliability was found in patients with higher EDSS scores, indicating that in more disabled patients (EDSS $\geq$ 4.5), the telephonic interview could be useful when they are unable to attend a visit. The finding of a low agreement between self- and measured-ambulation has been noted previously [27, 28]. In our study, fully ambulatory patients tended to underestimate their walking distances (30 %), whereas in patients with ambulatory impairment, the frequency of under- or over estimation was more variable (12 and 25 %, respectively). This information is not only important at the time of scoring the EDSS but also when interpreting disease progression. Thus, in more disabled patients, a full agreement was only seen in 63 % of the visits, reinforcing the importance of including objective measures of ambulation in clinical monitoring by telemedicine.

In the last decade, accelerometer-based technology has been evaluated for objectively monitoring the total amount of daily activity as a clinical mobility measure of MS patients under real-world conditions [29]. In this sense, we found that the 6MWT, a reliable and valid tool for measuring walking ability, can be monitored remotely by using an accelerometer ($r = 0.76$). Moreover, the strong correlation between aDWA and the EDSS ($r = -0.86$) indicates a commonality between these two measures. Using a cut-off point of 3279.3 steps/day, we were able to identify patients with walking impairment with a high sensitivity and specificity, and these patients showed lower quality of life scores. Although in the whole sample we found that disability status (EDSS score) may explain approximately 76 % of the variance of aDWA, this was true for patients with ambulatory impairment but not for fully ambulatory patients, in whom the EDSS only contributed to 23 % of the variability in aDWA [30]. Altogether, these data would suggest that aDWA could be a good measure of disability in more disabled patients, and perhaps more responsive to changes of disability in this subgroup of patients than clinical measures. We detected a significant decline of the aDWA in patients with ambulatory impairment (EDSS $\geq$ 4.5), which exceed the standard error of accelerometer measurement [31, 32]. Despite the limitation of our small sample size, this is the first study that documents longitudinal changes in aDWA in comparison with other standardized walking tests. Although standard walking tests are reliable for assessing ambulation under controlled conditions, they may not reflect the real-life circumstances involved in walking impairment, and perhaps may overestimate real ambulation and physical activity. Therefore, the inclusion of new, more sensitive instruments to measure walking function may help to better monitor the disease and identify the rate and predictors of change for the design and delivery of behavioral interventions in this population.

In conclusion, MS clinical monitoring by telemedicine is feasible, but carries several limitations such as the lower reliability of the assessment in less disabled patients. Despite the use of a video-recording that seems to improve the

agreement for the most valuable functional systems (pyramidal, cerebellar, and brainstem), our results emphasize the need to optimize the assessment methodology. Although the remote evaluation does not substitute a physical visit, the results support the multimedia EDSS assessment as a reliable tool to monitor especially disabled MS patients at distance. Indeed, changes in ambulatory physical parameters recorded by accelerometers can be used as an objective measurement of clinical monitoring and treatment intervention in MS patients. Large-scale prospective studies are needed to validate aDWA as an adequate instrument for detecting MS disability over time.

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Conflicts of interest Núria Sola-Valls, Yolanda Blanco, Maria Sepúlveda, Sara Llufriu, Elena H Martínez-Lapiscina, Delon La Puma and Francesc Graus declare that there is no conflict of interest. Pablo Villoslada has received consultation fees from Roche, Novartis, Neurotech Pharma and is founder and hold stocks of Bionure Farma. Albert Saiz has received compensation for consulting services and speaking from Bayer-Schering, Merck-Serono, Biogen-Idec, Sanofi-Aventis, Teva Pharmaceutical Industries Ltd and Novartis.

Ethical standards All participants provided their written informed consent prior to their inclusion in the study. This clinical study was approved by the ethical committee of the Hospital Clinic of Barcelona and therefore performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

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Trabajo número 3

Combined walking outcome measures identify clinically meaningful response to prolonged-release fampridine

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Este trabajo evaluó el potencial beneficio del acelerómetro para determinar la respuesta terapéutica a fampridina de liberación prolongada (fampridina-LP) a corto y medio plazo.

Para ello, se realizó un estudio prospectivo en 32 pacientes con EM tratados con fampridina-LP y se utilizó el T25FW, el 6MWT, la MSWS-12, la EuroQoL-5 y un acelerómetro para cuantificar la actividad diaria durante 7 días. Todos los tests se repitieron cada 3 meses hasta completar un año de seguimiento en los pacientes respondedores. Los no respondedores fueron reevaluados al año.

Como resumen, 25 pacientes (78%) se consideraron respondedores con una mejoría del T25FW $\geq$ 20% después de 2 semanas de tratamiento, una cifra superior a la observada en los ensayos clínicos pivotales. La combinación de T25FW y MSWS-12 identificó mejor a aquellos pacientes que presentarán un beneficio clínicamente significativo de fampridina-LP mediante herramientas funcionales, y su persistencia en el tiempo.

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Original Research

Combined walking outcome measures identify clinically meaningful response to prolonged-release fampridine

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Abstract

Background: Gait impairment is common in multiple sclerosis (MS) and negatively impacts patients' health-related quality of life (HRQoL). Prolonged-release fampridine (PR-fam) improves walking speed, but it is unclear which walking measures are the most suitable for identifying treatment response. Our aim was to assess the effect of PR-fam and the outcome measures that best identify short- and long-term clinically meaningful response.

Methods: We conducted a prospective study in 32 MS patients treated with PR-fam for a year. The assessments at 2 weeks, 3, 6 and 12 months included: timed 25-foot walk (T25FW), 6-minute walk test (6MWT), MS Walking Scale-12 (MSWS-12), a five-level version of the EuroQoL-5 dimensions, and accelerometry. PR-fam response was defined as an improvement in T25FW $\geqslant$20%.

Results: Twenty-five (78%) patients were considered responders after 2 weeks of PR-fam and improved significantly in all measures. Responders to T25FW and MSWS-12 ($n = 19$) showed a significant improvement in HRQoL and accelerometer data compared with responders only to T25FW ($n = 6$). At 1 year, 15/20 (75%) patients remained responders, but only those with permanent response to T25FW and MSWS-12 ($n = 8$; 53%) showed a significant improvement in 6MWT and HRQoL.

Conclusion: The combination of T25FW and MSWS-12 identify better those patients with a clinically significant benefit of PR-fam.

Keywords: accelerometer, minimal clinical difference, multiple sclerosis, patient-reported outcome, PR-fampridine, quality of life

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Introduction

Gait impairment is a frequent manifestation along the course of multiple sclerosis (MS) and has a negative impact on patients' health-related quality of life (HRQoL).[1,2] Prolonged-release fampridine (PR-fam) (Fampyra®; Biogen Idec, Maidenhead, Berkshire, UK) is a voltage-dependent potassium channel blocker that improves conduction in demyelinated nerves.[3] In two phase III double-blind clinical trials (MS-F203 and MS-F204) PR-fam improved the timed 25-foot walk (T25FW) walking speed and this change was associated with patient-rated walking perception.[4,5] Previous reports support an increase of $\geqslant$20% of T25FW as a minimal clinically important difference (MCID),[6–8] but it is unclear if this outcome best identifies short- and long-term clinically meaningful response to PR-fam in the setting of real clinical practice. Moreover, extension studies from clinical trials suggested that longer walking tests might be more relevant for assessing the clinical benefit of PR-fam.[9,10] Free-living accelerometry, especially three-dimensional accelerometers, provides information about walking behavior in the real environment, and daily walking activity (DWA) correlates with disability measures.[11,12] Hence, DWA could be a suitable outcome measure for pharmacological and rehabilitation intervention. Although multiple

outcomes exist for measuring walking in MS,[13] there is no consensus on which tests are more suitable for identifying those patients who actually benefit from therapy.

To address the question of which assessment best identifies patients benefiting from PR-fam, in this study, we aimed to (a) assess the effect of PR-fam using different walking tests and functional measures, and (b) determine the outcome measures that best identify short- and long-term clinically meaningful response to PR-fam.

Methods

Patients

We conducted this prospective study by including all consecutive MS patients with walking impairment followed at the MS unit of the Hospital Clinic of Barcelona that met the approved criteria to be treated with PR-fam:[3] (a) clinically definite MS according to the 2010 McDonald criteria;[14] (b) Expanded Disability Status Scale (EDSS) score between 4.0 and 7.0;[15] (c) no relapses within 60 days; and (d) adequate renal function and no previous history of seizures or cardiac arrhythmia. Patients meeting these criteria were invited to participate in the study. The study was conducted in accordance with the guidelines of the Declaration of Helsinki and the protocol approved by the Ethical Committee of the Hospital Clinic of Barcelona (HCB/2015/0045). All subjects had voluntarily given written informed consent prior to their participation.

Study design

Patients were assessed according to the approval of the European Medicines Agency that includes the evaluation of PR-fam response 15 days after treatment initiation.[16] An extra visit was performed one week before to PR-fam initiation to confirm that patients met the inclusion criteria and to register DWA measured through a commercial accelerometer (Actigraph GT3X from Actigraph LLC, Pensacola-FL (USA)) in basal conditions. All clinical visits were performed at the same time of day to minimize variability and the possible effect of other symptoms such as fatigue. PR-fam response was defined as $\geqslant$20% improvement of T25FW speed after 2 weeks of PR-fam treatment.[6] PR-fam responder patients continued treatment if they agreed and were further assessed at 3 and 6 months, and 1 year. Patients who did not meet the defined response criteria stopped the treatment and were reevaluated at 1 year.

Measures and procedures

Disability was evaluated by scores on the EDSS[15] and the Multiple Sclerosis Functional Composite (MSFC).[17] Three walking measures were obtained: the T25FW test, the 6-min walk test (6MWT),[18] and the 12-item MS Walking Scale (MSWS-12) questionnaire.[19] Two functional measures were also evaluated: the International Physical Activity Questionnaire (IPAQ),[20] and DWA assessed by a portable triaxial accelerometer (Actigraph GT3X, steps/day) for 7 days during waking hours (excluding bathing or swimming) doing their usual routine.[21] Accelerometer data (steps/day and counts/day) were averaged if 3 or more days out of the 7-day period showed $\geqslant$10 h of accelerometer wearing without any period of $\geqslant$60 min of no accelerometer data (continuous zeros). HRQoL was measured with the five-level version of the EuroQoL-5 dimensions (EQ-5D-5L) instrument. The EQ index value is divided into five dimensions (mobility, self-care, usual activities, pain/complaints, and anxiety/depression) and the visual analog score (EQ-VAS) estimates the overall health state.[22]

Statistics

Changes in average walking tests (T25FW, 6MWT) and DWA on treatment were reported as percentage of change from average pretreatment value. We considered the MCID change as an improvement of 20% in T25FW test and 6MWT.[6,8,23] The MSWS-12 total score ranges from 12 to 60 and it was transformed to 0–100 by the following formula: [(observed score − 12)/60 − 12] × 100. Negative MSWS-12 change scores imply subject-perceived improvement in walking ability during treatment, and we considered a meaningful clinical change a difference of $\geqslant$6 points from baseline.[4,5,24] IPAQ questionnaire was expressed as MET-min per week by the following formula: [3.3 METs·min·day (walking) + 4.0 METs·min·day (moderate activity) + 8.0 METs·min·day (vigorous activity)]. EQ index value ranged from 0 (death) to 1 (full health) and we considered a MCID a difference of 0.05.[25] EQ-VAS ranges from 0 (worst quality of life) to 100 (best quality of life). Descriptive analyses (means, ranges, and standard deviations) and the significance of group differences (p values, 95% confidence intervals) from baseline to on-treatment visit

Table 1. Demographic and disease characteristics of the multiple sclerosis population at baseline.

	MS patients ($n = 35$)
Age in years, mean (SD)	50 (20.8)
Sex, women *n* (%)	22 (62.9)
CMI in kg/m^2, mean (SD)	24.8 (4.2)
MS subtype, *n* (%)	
Relapsing–remitting MS	9 (25.7)
Secondary–progressive MS	14 (40)
Primary–progressive MS	12 (34.3)
Disease duration from onset in years, mean (SD)	19 (10)
EDSS score, median (range)	5.5 (4.0–6.5)
T25FW speed in m/s; *n* (%)	
<6 s	3 (8.6)
6–7.99 s	8 (22.9)
⩾8 s	24 (68.6)
MSWS-12 score in %, mean (SD)	81.2 (20)
MS symptoms, *n* (%)	
Fatigue	5 (14.3)
Imbalance	7 (20)
Lower-limb weakness	10 (28.6)
Lower-limb spasticity	11 (31.4)
Lower-limb loss of sensation	2 (5.7)

CMI, corporal mass index; EDSS, Expanded Disability Status Scale; MS, multiple sclerosis; MSWS-12, Multiple Sclerosis Walking Scale; SD, standard deviation; T25FW, timed 25-foot walk test.

were evaluated using a Student's paired t test and nonparametric Wilcoxon signed rank, otherwise. t test and Mann–Whitney U test were applied for group comparison. Statistical significance was defined as $p \leqslant 0.05$ and all analyses were performed using SPSS version 20.0 (SPSS Inc, Chicago, IL, USA) software.

Results

Patient demographics and clinical characteristics

A total of 35 consecutive MS patients were included in the study from June 2014 to January 2017. Most of them (74%) had a progressive form of MS and a median EDSS score of 5.5 (range, 4.0–6.5). The demographic and clinical characteristics are shown in Table 1. Patients' major complaint about walking was lower-limb spasticity (31%), lower-limb weakness (29%) and imbalance (20%).

Baseline prolonged-release fampridine safety

Three female patients withdrew from the study before completing baseline evaluation due to adverse events: a syncope that required hospitalization, persistent nausea, and severe dizziness, respectively. Finally, 32 patients completed the baseline evaluation, and 14 (44%) experienced

Table 2. Response to prolonged-release fampridine for the different outcomes categorized by response to the timed 25-foot walk test.

	Responders ($n = 25$)	**Non-responders ($n = 7$)**
Response to different walking tests, *n* (%)		
T25FW, 6MWT and MSWS-12	15 (46.9)	–
T25FWT and 6MWT	6 (18.8)	–
T25FWT and MSWS-12	4 (12.5)	–
MSWS-12	–	3 (9.4)
None	–	4 (12.5)
% of change in T25FW, mean (SD)	51.2 (21.6)**	4.5 (15.1)
% of change in MSWS-12, mean (SD)	–26.2 (16.3)**	–6.6 (16.2)
% of change in 6MWT, mean (SD)	44.5 (58.1)**	5.2 (11.8)
% of change in DWA steps/day, mean (SD)	7 (14.6)*	3.6 (14.4)
IPAQ score in MET-min/week, mean (SD)		
EQ-5D-5L, mean (SD)	1034.2 (3430.1)*	–673.6 (1855.9)
EQ index value	0.1 (0.2)*	0.1 (0.1)*
EQ-VAS	12.1 (13)**	0.8 (19.6)
EDSS score, median (range)		
MSFC, mean (SD)	0 (–0.5–0.0)*	0 (0)
Total *Z* score	0.3 (0.2)**	0.1 (0.2)
9HPT *Z* score	0.3 (0.4)*	0.2 (0.3)
PASAT *Z* score	0.2 (0.7)	0.04 (0.4)

PR-fampridine response was defined as the improvement in speed of ⩾20% in the T25FW. Comparisons were assessed with paired *t* test;
*$p < 0.05$, **$p < 0.01$.
6MWT, 6-minute walk test; 9HPT, nine-hole peg test; DWA, daily walking activity; EDSS, Expanded Disability Status Scale; EQ-5D-5L, five-level version of the EuroQoL-5 dimensions; IPAQ, International Physical Activity Questionnaire; MET, metabolic equivalent of task; MSFC, Multiple Sclerosis Functional Composite; MSWS-12, Multiple Sclerosis Walking Scale; PASAT, Paced Auditory Serial Addition Test; PR-fampridine, prolonged-release fampridine; SD, standard deviation; T25FW, timed 25-foot walk test; VAS, Visual Analog Scale.

mild and transitory adverse events, the most frequent being: dizziness (18.8%), insomnia (12.5%), and headache (12.5%).

Baseline prolonged-release fampridine response

Twenty-five (78%) patients were considered PR-fam responders. No baseline differences were observed between responder patients and nonresponder patients in walking measures, and global IPAQ (data not shown). PR-fam responder patients had a significant improvement in all walking outcomes (T25FW, 6MWT, MSWS-12), and functional measures (IPAQ, DWA) (Table 2). Responder patients also showed a statistically significant improvement in HRQoL (EQ index value and EQ-VAS), while nonresponder patients only improved in EQ index value (Table 2). Significant changes were found in MSFC *Z* score (mean

Table 3. Response to prolonged-release fampridine for the clinical outcomes categorized by response to timed 25-foot walk test (T25FW) test and Multiple Sclerosis Walking Scale-12 items or T25FW only.

	Responders ($n = 25$)	
	Response to T25FW and MSWS-12 ($n = 19$)	**Response to T25FW only ($n = 6$)**
% of change in T25FW, mean (SD)	51 (21–4)**	51.7 (24.2)*
% of change in MSWS-12, mean (SD)	–33.7 (10.2)**	–2.4 (1.6)*
% of change in 6MWT, mean (SD)	47.4 (66.6)**	35.2 (8.1)*
% of change in DWA steps/day, mean (SD)	11.1 (13.5)*	–6.1 (9.8)
IPAQ score in MET-min/week, mean (SD)	921.5 (3698.6)	1391.3 (2651.3)
EQ-5D-5L, mean (SD)		
EQ index value	0.2 (0.1)*	0.01 (0.2)
EQ-VAS	16.5 (11.1)**	–1.7 (8.2)
EDSS score, median (range)	0 (–0.5–0.5)*	0 (–0.5–0.0)
MSFC, mean (SD)		
Total *Z* score	0.3 (0.2)**	0.4 (0.3)*
9HPT *Z* score	0.4 (0.4)*	0.05 (0.3)
PASAT *Z* score	–0.01 (0.6)	0.7 (0.8)

PR-fampridine response to T25FW was defined as an improvement in speed of ⩾20% in the T25FW and response to the Multiple Sclerosis Walking Scale (MSWS-12) as an improvement of ⩾6 points. Comparisons were assessed with paired *t* test;
*$p < 0.05$, **$p < 0.01$.
6MWT, 6-minute walk test; 9HPT, nine-hole peg test; DWA, daily walking activity; EDSS, Expanded Disability Status Scale; EQ-5D-5L, five-level version of the EuroQoL-5 dimensions; IPAQ, International Physical Activity Questionnaire; MET, metabolic equivalent of task; MSFC, Multiple Sclerosis Functional Composite; PASAT, Paced Auditory Serial Addition Test; PR-fampridine, prolonged-release fampridine; SD, standard deviation; T25FW, timed 25-foot walk test; VAS, Visual Analog Scale.

difference = 0.3; $p < 0.001$) and hand dexterity in nine-hole peg test (9HPT) *Z* score (mean difference = 0.3; $p = 0.002$) in responder patients (Table 2).

Among responder patients to T25FW test, 15 (60%) patients also improved the 6MWT and MSWS-12; 6 (24%) in the 6MWT only, and 4 (16%) in the MSWS-12 only. The mean improvement in the T25FW test was similar among the three groups of patients (50.3 ± 23.9, 51.7 ± 24.2 and 53.7 ± 7.9, respectively, $p = 0.99$). Patients with response to T25FW test and MSWS-12 ($n = 19$) showed a significant improvement in the percentage of change in DWA, HRQoL (EQ index value and EQ-VAS) and 9HPT *Z* score (Table 3) in contrast to patients who only responded to T25FW test ($n = 6$).

In correlation analysis, the percentage of change in DWA correlated with global MSWS-12 score ($r = -0.49$, $p = 0.01$), and individual aspects of the scale such as the ability to climb up and down stairs ($r = -0.4$, $p = 0.03$), to standing when doing things ($r = -0.4$, $p = 0.03$), balance ($r = -0.5$, $p = 0.02$), the need to use support when walking outdoors ($r = -0.5$, $p = 0.02$) and walking smoothly ($r = -0.4$; $p = 0.04$). The percentage of change in MSWS-12 also correlated with the mean difference of HRQoL (EQ-VAS, $r = -0.4$; $p = 0.03$).

Long-term prolonged-release fampridine response

A total of 20 (80%) of the 25 responder patients were available for longitudinal evaluation (4

Table 4. Longitudinal changes based on the permanent response to T25FW test and MSWS-12.

	Permanent response to T25FW and MSWS-12 ($n = 8$)	Permanent response to T25FW ($n = 7$)
3 months		
% of change in T25FW, mean (SD)	55 (16.8)*	61.2 (26.5)*
% of change in MSWS-12, mean (SD)	−34.4 (14.9)*	−14 (23.7)
% of change in 6MWT, mean (SD)	29.3 (23.6)	39.7 (18)*
% of change in DWA steps/day, mean (SD)	12.5 (25)	−1.3 (6.4)
EQ-5D-5L, mean (SD)		
EQ index value	0.2 (0.2)*	0 (0.2)
EQ-VAS	25 (14.9)*	1.4 (3.8)
EDSS score, median (range)	0 (−0.5–0.0)	0 (−0.5–0.0)
MSFC, mean (SD)		
Total *Z* score	0.3 (0.2)*	0.4 (0.5)
9HPT *Z* score	0.3 (0.5)	0.3 (0.2)*
PASAT *Z* score	0.3 (0.5)	0.3 (1.2)
6 months		
% of change in T25FW, mean (SD)	58.8 (24)*	56.4 (23.4)*
% of change in MSWS-12, mean (SD)	−27.6 (8)*	−0.3 (12.8)
% of change in 6MWT, mean (SD)	31.8 (23.4)*	17.9 (25)
% of change in DWA steps/day, mean (SD)	27.6 (65.4)	−13.6 (51.7)
EQ-5D-5L, mean (SD)		
EQ index value	0.2 (0.1)*	0.1 (0.1)
EQ-VAS	21.9 (16.2)*	−2.5 (4.2)
EDSS score, median (range)	0 (−0.5–0.0)	0 (−0.5–0.0)
MSFC, mean (SD)		
Total *Z* score	0.2 (0.2)	0.4 (0.4)*
9HPT *Z* score	0.2 (0.5)	0.2 (0.4)
PASAT *Z* score	0 (0.4)	0.3 (0.7)
12 months		
% of change in T25FW, mean (SD)	57.5 (26.2)*	43.6 (26)*
% of change in MSWS-12, mean (SD)	−28.4 (11.9)*	8.9 (10.5)*
% of change in 6MWT, mean (SD)	28.2 (11.9)*	1.9 (15.5)

Table 4. (Continued)

	Permanent response to T25FW and MSWS-12 ($n = 8$)	Permanent response to T25FW ($n = 7$)
% of change in DWA steps/day, mean (SD)	19.4 (43.5)	−14.2 (37.1)
EQ-5D-5L, mean (SD)		
EQ index value	0.2 (0.1)*	0 (0.1)
EQ-VAS	21.3 (16.6)*	−7.9 (10.8)
EDSS score, median (range)	0 (−0.5–0.5)	0 (−0.5–0.0)
MSFC, mean (SD)		
Total *Z* score	0.3 (0.2)*	0.3 (0.4)
9HPT *Z* score	0.3 (0.4)	0.04 (0.5)
PASAT *Z* score	0.2 (0.3)	0.5 (0.7)

Permanent response was defined as an improvement in speed of ⩾20% in timed 25-foot walk (T25FW) and an improvement of ⩾6 points in multiple sclerosis walking scale (MSWS-12) in all visits. Comparisons were assessed with paired *t* test;
*$p < 0.05$, **$p < 0.01$.
6MWT, 6-minute walk test; 9HPT, nine-hole peg test; DWA, daily walking activity; EDSS, Expanded Disability Status Scale; EQ-5D-5L, five-level version of the EuroQoL-5 dimensions; IPAQ, International Physical Activity Questionnaire; MET, metabolic equivalent of task; MSFC, Multiple Sclerosis Functional Composite; MSWS-12, Multiple Sclerosis Walking Scale; PASAT, Paced Auditory Serial Addition Test; SD, standard deviation; VAS, visual analog scale.

patients were excluded because they did not return for all visits, and one decided to discontinue PR-fam because lack of perceived effectiveness). No patient had relapses or changed the disease-modifying therapies or the symptomatic treatment during the study. Eighteen (90%) patients remained as responder patients at 3 months, 17 (85 %) at 6 months and 15 (75%) at 12 months. The longitudinal changes in PR-fam responder patients and nonresponder patients at each timepoint are shown in Supplementary Table 1. At 1 year, 8 out of 15 (53%) responder patients showed permanent response to T25FW test and MSWS-12 during all timepoints of evaluation. This subgroup of patients had a significant improvement in the 6MWT and HRQoL (EQ index value and EQ-VAS) considered clinically meaningful that was not observed in patients with permanent response only to T25FW test (Table 4). Responder patients to both tests had an improvement in DWA that ranged from 12.5% to 27.6%, while responder patients to T25FW test alone had a worsening from −1.3 to −14.2%, despite the difference not reaching statistical significance.

In correlation analysis, changes in HRQoL correlated with changes in MSWS-12 over time (3 months: EQ index value, $r = -0.6$, $p = 0.007$ and EQ-VAS, $r = -0.4$, $p = 0.09$; 6 months: EQ index value, $r = -0.6$, $p = 0.007$ and EQ-VAS, $r = -0.8$, $p < 0.001$; 1 year: EQ index value, $r = -0.8$, $p < 0.001$ and EQ-VAS, $r = -0.7$, $p = 0.002$).

Reevaluation of nonresponder patients at long term

Four out of five patients lost their response to PR-fam and they were retested. Two of them were considered responders, one patient to T25FW test and one to T25FW and MSW-12. The responder to both tests clinically improved in 6MWT (35%), walking mobility (steps/day = 27.6%) and HRQoL (EQ index value = 0.4 and EQ-VAS = 20%) in contrast to the responder to the T25FW test only (6MWT = 0%, DWA = 0.3, EQ index value = 0.03, EQ-VAS = −4).

Evolution of baseline nonresponder patients

Baseline nonresponder patients ($n = 5$) were assessed 1 year after baseline PR-fam evaluation. No significant changes were observed in disability measures (EDSS score and MSFC *Z* score) but they showed a decrease in speed (T25FW test,

mean % of change = −4.4, $p = 0.9$), endurance (6MWT, mean % of change = −13.5, $p = 0.1$), and self-perception (MSWS-12, mean difference = 5.4, $p = 0.7$). Patients also had a decrease in DWA measured by steps (% of change, mean = −12.8, $p = 0.04$) and HRQoL (EQ index value, mean difference = −0.2, $p = 0.04$).

Discussion

The objective of this study was to assess PR-fam response by using different walking tests and functional measures, and determine the most suitable outcome measures to identify short- and long-term clinically meaningful response to PR-fam in the setting of real clinical practice. Our study shows that at 2 weeks after therapy initiation, most patients (78%) are PR-fam responder patients but only those with a combined response to T25FW test and MSWS-12 had a significant and clinically meaningful improvement in HRQoL and DWA. Moreover, this study provides new information on the usefulness of combined outcomes measures, suggesting that patients with permanent response to both tests at 1 year were those who remained with a clinically significant effect in endurance and HRQoL. The observed strong correlation between the change in measures of HRQoL and patient-reported outcome (MSWS-12) emphasizes the clinical relevance of the results and contributes to build on the existing real-world experience with this drug.

In this study, we used as criteria of PR-fam response the most accepted MCID of ⩾20% in the T25FW test because this threshold represents a clinically meaningful change in walking performance.[6,26,27] Using this definition, up to 75% of the PR-fam responder patients at short term remained as responder patients at 1 year. However, a significant persistent efficacy over a period of 2 years using other established criteria of response has also been reported.[28] The study showed that 80% of the patients with ⩾10% of improvement (T25FW test) at short term maintained a similar degree of responsiveness after long-term therapy. Moreover, more than one third of patients with none or poor initial response improved their walking function when they were tested again after 2 years.[28] Our results agree with previous results because two out of the four patients who lost the criteria of response over the period of study exhibited responsiveness once again. Overall, these data reinforce the importance of a further reevaluation of the efficacy in patients with poor initial response but also in those who lose the efficacy over time. Conversely, monitoring the efficacy on a regular basis is important because its loss may be related to progression of the disease not revealed by a change in the EDSS score, such as we observed in the evolution of our cohort of nonresponder patients at baseline.

Our study has several limitations. We do not know whether the clinically meaningful outcome observed in our study could have been reached with lower thresholds of T25FW test or using other response criteria defined in previous clinical trials. In fact, it has been suggested that the use of a different anchor might result in a different threshold for a clinically meaningful change in the T25FW test.[7] Moreover, the T25FW test has a ceiling effect in patients with mild disability.[13] In our study, for example, responder patients who scored the T25FW test in less than 6 sec had a mean percentage of change of 21%, but it rose to 55% in those who scored in more than 8 sec. Another limitation of the study was the small sample size that might have influenced the statistical significance of some outcomes. For example, the significant improvement in DWA at short term was lost at long term; however, at 1 year, we found a DWA increase in responder patients to the T25FW test and MSWS-12 (12.5–27.6%), whereas those responder patients to T25FW only had a decrease DWA (−1.3 to −14.2%). The fact that we observed a good correlation between improvement of DWA and MSWS-12 suggests an additional benefit effect may be clinically meaningful in the real-life setting. Additional studies, however, are needed to confirm these data. Finally, safety findings were according to pivotal studies, and no new adverse events were observed with PR-fam long-term therapy.

In conclusion, our study confirms long-term beneficial effect of PR-fam on walking function in real clinical practice, and suggests that the combination of objective measures (T25FW test) and patient-reported outcomes (MSWS-12) in the definition of PR-fam responder patients best identifies those patients with clinically meaningful improvement.

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Conflict of interest statement

NSV received compensation for consulting services and speaker honoraria from Genzyme and Bayer-Schering.
YB received speaker honoraria from Biogen, Novartis and Genzyme.
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SL received speaker honoraria from Biogen Idec, Novartis, Teva, Genzyme and Merck.
EHM-L is a researcher in the OCTIMS Study, an observational study (which involves no specific drugs) to validate SD-OCT as a biomarker for multiple sclerosis, sponsored by Novartis. She has received speaking honoraria from Biogen and Genzyme and travel reimbursement from Genzyme, Roche, for international and national meetings over the last 3 years. She is a member of the working committee of the International Multiple Sclerosis Visual System (IMSVISUAL) Consortium.
IZ has received travel reimbursement from Genzyme, Biogen, Merck for national and international meetings over the last 3 years.
IP received travel funding from Roche Spain and Sanofi-Aventis, European Academy of Neurology, and European Committee for Treatment and Research in Multiple Sclerosis; holds a patent for an affordable eye tracking system to measure eye movement in neurologic diseases; and holds stock options in Aura Innovative Robotics.
CM declared no conflicts of interest.
PV received consultation fees from Roche, Novartis, Neurotech Pharma and hold stocks of Bionure Farma, Mint-Labs, Spire Bioventures and Health Engineering. He is currently an employee of Genentech, but this work was done before joining the company as part of his academic activities.
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Trabajo número 4

Telemedicine assessment of long-term cognitive and functional status in anti-leucine-rich, glioma- inactivated 1 encephalitis

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En este trabajo se evaluó la viabilidad de una entrevista telefónica estructurada para determinar el estado cognitivo y funcional a largo plazo de pacientes con encefalitis autoinmune anti-LGI1.

Para ello se realizó una entrevista telefónica a 37 pacientes con una mediana de seguimiento de 87 meses desde el inicio de la enfermedad, y 23 controles sanos emparejados por edad y sexo. El estado cognitivo se evaluó con el MMSE telefónico y 3 pruebas específicas que exploraron la memoria verbal, la fluidez y la función ejecutiva. El estado funcional se evaluó con el FAQ y la mRS. En todos los pacientes se evaluó la reserva cognitiva mediante un cuestionario estructurado.

Como resumen, este trabajo demuestra que la telemedicina es una herramienta factible para evaluar el estado cognitivo y funcional en pacientes con encefalitis autoinmune anti-LGI1. Se detectó un deterioro cognitivo en 27 pacientes (75%), 17 de ellos con deterioro cognitivo leve y 10 con demencia. Sin embargo, mediante la escala mRS, 26 pacientes (72%) eran funcionalmente independientes. La reserva cognitiva premórbida, y la presencia de hiperintensidad hipocampal bilateral en el momento del debut fueron predictores del deterioro cognitivo a largo plazo.

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Abstract

Objective

To assess the feasibility of a structured telephone interview examining the long-term cognitive and functional status in anti–leucine-rich, glioma-inactivated 1 (LGI1) encephalitis.

Methods

Telephone interviews were conducted with 37 patients after a median follow-up of 87 months from disease onset and 23 healthy controls matched for age and sex. Cognitive status was assessed with the telephone Mini-Mental State Examination (t-MMSE) and 3 tests exploring verbal memory, fluency, and executive function. Functional status was evaluated with the Functional Activities Questionnaire and the modified Rankin Scale (mRS). Patients were classified as normal, with mild cognitive impairment (MCI), or with dementia based on cognitive and functional status. Assessment of the cognitive reserve was performed with a structured questionnaire. Logistic regression analysis was applied to identify predictors of cognitive impairment.

Results

Telephone interviews were successful in 36/37 (97%) patients. Cognitive impairment was detected in 27 (75%) including 17 with MCI and 10 with dementia. Eight (29%) patients would have been misclassified using only the t-MMSE. Twenty-six (72%) patients were functionally independent according to the mRS, but only 9 (35%) were cognitively normal. Independent predictors for long-term cognitive impairment were a low cognitive reserve (OR = 1.36, 95% CI: 1.05–1.76; $p = 0.02$) and bilateral hippocampal hyperintensity at initial MRI (OR = 27.03, 95% CI: 1.87–390; $p = 0.02$).

Conclusions

Telemedicine is a feasible tool to assess the cognitive and functional outcome in patients with anti-LGI1 encephalitis. Cognitive impairment is often missed if only functional scales are used. Premorbid cognitive reserve and MRI with bilateral hippocampal hyperintensity were predictors for long-term cognitive impairment.

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Glossary

AUC = area under the curve; **FAQ** = Functional Activities Questionnaire; **LGI1** = leucine-rich, glioma-inactivated 1.

Anti–leucine-rich, glioma-inactivated 1 (LGI1) encephalitis is the second most frequent autoimmune encephalitis with an estimated annual incidence of 0.83 cases per million.[1] Patients with LGI1 antibodies develop subacute onset of memory impairment, behavioral changes, and hyponatremia. The encephalitic phase is frequently preceded by a variable period where patients have isolated seizures including, among others, faciobrachial dystonic seizures.[1,2] Symptoms usually respond to corticosteroids, and nearly 70% of patients have good functional recovery. However, only a third of patients return to their baseline premorbid status.[1,3]

Clinical assessment using only functional scales, such as the modified Rankin Scale (mRS) score, may overlook cognitive deficits that limit the return to previous activities and affect quality of life. However, studies that evaluate cognitive outcome in anti-LGI1 encephalitis are scarce and do not go beyond 2 years of follow-up. Previous research suggested that patients showed a marked impairment on memory, executive function, and processing speed at presentation, whereas some patients remained with residual deficits mainly observed on verbal memory.[1,4–7] In addition, the role of premorbid cognitive reserve that probably is relevant in the recovery of elderly patients after acute neurologic events has not been previously explored in cases of anti-LGI1 encephalitis.[8]

Telemedicine is a novel discipline that offers high-quality patient care through numerous applications and services that facilitate a direct, cost-effective exchange of information between patients and physicians.[9] In the case of rare diseases or patients' with restricted access to subspecialty care, such as autoimmune encephalitis, the use of telemedicine may be useful to assess cognitive performance in more detail over time.[10]

In this study, we assessed the feasibility of using a structured telephone interview to examine long-term cognitive performance and functional status of patients with anti-LGI1 encephalitis.

Methods

Patients

We reviewed all Spanish patients with anti-LGI1 encephalitis diagnosed at the Neuroimmunology laboratory of the Institut d'Investigació Biomèdica August Pi i Sunyer (IDIBAPS), Hospital Clinic (Barcelona, Spain), between September 1998 and June 2014. Patients were included if they fulfilled the following criteria: (1) age ≥18 years; (2) evidence of cognitive deterioration at diagnosis demonstrated by direct patient examination by one of the authors or provided by the referring physicians through a structured written questionnaire; and (3) minimum clinical follow-up of 4 years. We initially identified 49 patients, and 37 were finally included in the study. Reasons for exclusion were death (7 patients, 2 of them with dementia), severe dementia that precluded the telephone interview (3), and lost to follow-up (2). All 37 patients were invited by their referring physicians to participate in the study. After the patient's agreement to participate, one of the authors contacted the patient directly to explain the goals of the study and obtain informed verbal consent, witnessed by a relative. Appointments for the structured telephone interview were scheduled according to dates and times that were convenient for patients and relatives. Information on symptom onset and main syndromes, ancillary studies, treatment response to immunotherapy, and functional outcome at 24 months was previously reported.[3]

Telephone intervention characteristics

Each telephone interview was performed by the same neurologist (N.S.) and lasted approximately 60 minutes. This included a structured interview with the patient about current clinical status, presence of comorbidities,[11] the cognitive reserve questionnaire, and the Functional Activities Questionnaire (FAQ). Patients answered all the questions, and the answers were corroborated by a family member. The cognitive reserve questionnaire measured 8 different aspects of the premorbid intellectual activity (educational level and training courses, educational level of parents, work occupation performed throughout life, musical education, and ability to speak several languages) and cognitive-stimulating activities such as reading and practicing intellectual games (table 1). The final score was the sum of the scores for each item (maximum 25 points, best cognitive reserve).[12] The FAQ is a standardized assessment of instrumental activities of daily living (11 items). Functional dependence is considered with scores ≥6 points.[13,14] Based on the aforementioned data, the mRS score was obtained, as this is the most widely used clinical outcome for measuring the degree of disability or dependence of patients with neurologic disability. The mRS is an ordered scale coded from 0 (no symptoms) through 5 (severe disability) and 6 (death). This scale has been shown to be reliable when obtained by telephone, and the Spanish version has been previously validated. Bad functional outcome was defined when the mRS score was ≥3.[15,16]

Before starting the brief cognitive battery, the family member was asked to leave the room and remove any calendars, clocks, or devices that could interfere with the cognitive evaluation. The brief cognitive battery comprised the Spanish telephone version of the Mini-Mental State Examination (t-MMSE) and evaluation of 3 specific cognitive domains: verbal memory, executive function, and language. The Spanish version of the t-MMSE score ranges from 0 to 26, and cognitive impairment

Table 1 Cognitive reserve questionnaire[12]

Item	Points
Educational level	
No formal schooling	0
Self-taught to read/write	1
Basic (<6 years)	2
Primary (>6 years)	3
Secondary (>9 years)	4
Higher (e.g., college and university)	5
Educational level of parents (best educational level)	
No formal schooling	0
Basic or primary	1
Secondary or higher	2
Training courses	
None	0
1 or 2	1
Between 2 and 5	2
More than 5	3
Work occupation outside the home	
None	0
Manual labor	1
Nonmanual labor (secretarial and technical)	2
Professional (requiring graduate or superior school)	3
Director/executive manager	4
Musical formation education	
No musical skills (does not play an instrument or listen to music frequently)	0
Plays an instrument (amateur) or listen to music frequently	1
Received musical training	2
Ability to speak different languages	
Only maternal language[a]	0
2 languages[a]	1
1 or 2 languages[a] + 1 foreign	2
1 or more languages[a] + more than 1 foreign	3
Reading skills	
Illiterate	0
Occasional (include newspapers/1 book per year)	1
Between 2 and 5 books per year	2
Between 5 and 10 books per year	3
More than 10 books per year	4
Practice of intellectual games (chess, puzzles, and crosswords)	
Never or sometimes	0
Occasional (between 1 and 5 per month)	1
Frequently (more than 5 per month)	2

[a] An officially recognized language in Spain (e.g., Spanish, Catalan, Gallego, or Euskera).

is defined when the score is ≤21 points.[17,18] Verbal memory was evaluated using the Free and Cued Selective Reminding Test modified from Buschke.[19] Briefly, this test consists of one immediate recall task in which participants have to recall as many as 16 words (first free and then using a semantic clue) and a delayed recall task after 30 minutes. Only the delayed recall score (the sum of free and facilitated) was used for the memory index, as this score was highly correlated with the immediate recall score in our study population (list recall: rho = 0.84, $p < 0.001$). Executive function was assessed using the oral Trial Making Test A and B.[20,21] In this test, participants are asked to count from 1 to 25 as quickly as possible (part A) and count again, but switching between numbers and alphabet letters until 13 (part B). The final score is the time in seconds needed to complete task B. Language was explored evaluating the verbal fluency asking the participants to say as many words as possible in 1 minute from a semantic category (e.g., fruits and vegetables), and the final score was the total number of words provided.

The brief cognitive battery was initially tested in a group of 23 healthy controls to ensure the feasibility to perform it by telephone and to obtain reference values for the cognitive tests. Controls had a median age of 74 years (interquartile range [IQR], 64–80) and 9 (39%) were male. No significant difference was observed in demographic variables or educational level between patients and healthy controls. To compare the cognitive performance across patients, raw scores from individual tests were converted to z-scores. Mild cognitive impairment (MCI) was considered when one or more cognitive domains showed a z-score below −1.5 SD of the healthy controls' distribution without interference in the activities of daily living.[22] Dementia was considered when these cognitive changes had a negative impact on the activities of daily living.

At the end of the telephone interview, all participants were assessed by the Hospital Anxiety and Depression Scale (score ≥11 points identified patients with mood disturbances) and the Pittsburgh Sleep Quality Index questionnaire (a score ≥6 points was indicative of poor quality of sleep).[23,24] Participants were also verbally assessed with the five-level version of the EuroQoL-5 dimensions instrument, which measures

health-related quality of life. This instrument comprises the European quality (EQ) index value divided into 5 dimensions (mobility, self-care, usual activities, pain/complaints, and anxiety/depression) and the visual analog score (EQ-VAS).[25]

Standard protocol approvals, registrations, and patient consents

The ethics committees of the Hospital Clinic approved the study. All patients or proxies gave written informed consent for the storage and use of serum, CSF, and clinical information for research purposes. All patients and healthy controls gave consent to participate in the telephone interview.

Statistics

Descriptive statistics were computed as median (IQR) unless otherwise noted. Differences among groups based on cognitive performance were studied using the χ^2 test and Mann-Whitney *U* test as convenient, with a significance level set to $p < 0.05$). Binary logistic regression was performed to identify predictors of cognitive impairment (MCI and dementia). Accuracy of the potential predictive value of clinical variables to detect patients with cognitive impairment was analyzed by the area under the curve (AUC). Statistical analyses were performed using SPSS version 25.0 (SPSS Inc, Chicago, IL) software.

Data availability

Data from the patients reported within the article are available and will be shared anonymously by request from any qualified investigator.

Results

Feasibility of telephone intervention and demographic characteristics

The telephone interview was successful in 36/37 (97%) patients. Only one patient complained about the length of the interview before starting the brief telephone cognitive battery and did not agree to continue. Clinical and demographic features of the 36 patients are summarized in table 2. The median age at diagnosis was 65 years (IQR: 56–74 years), and 23 (64%) were male. At the time of diagnosis of anti-LGI1 encephalitis, patients had a median mRS score of 4 (IQR: 3–4). All patients were treated with first-line immunotherapy (steroids ± IV immunoglobulin), and 18 (50%) also received second-line (11) or chronic (7) immunotherapy. At 2 years, 28 (78%) were functionally independent (mRS score <3). At the last visit, 12 (33%) patients were still on antiepileptic drugs, but only 3 patients (8%) had experienced seizures during the preceding year.

Long-term cognitive and functional status

Long-term evaluation of patients was analyzed after a median follow-up of 87 months (IQR: 63–136 months). Patients performed significantly worse in all cognitive tests compared with healthy controls (table 3), and 27/36 (75%) were considered to have cognitive impairment that was classified as MCI in 17 (63%) and dementia in 10 (37%). The t-MMSE and the assessment of specific cognitive domains showed moderate agreement in the detection of cognitive impairment (kappa coefficient = 0.54; 95% CI: 0.30–0.78; $p < 0.001$). Nineteen of the 36 (53%) patients were considered cognitive impaired using t-MMSE and the assessment of specific cognitive domains, and 8 (29%) of 27 patients were classified as MCI by the brief cognitive battery despite performing well on the t-MMSE. In contrast, none of the patients who performed well in the cognitive evaluation had a low score in the t-MMSE. Patients with dementia showed worse results in executive functioning and verbal fluency compared with patients with MCI ($p < 0.001$ in both domains) (figure). Overall, the most frequently affected cognitive domain was verbal fluency (N = 19, 53%), followed by verbal memory (N = 18, 50%) and executive functioning (N = 11, 31%).

Patients showed higher degrees of anxiety and/or depression and worse sleep quality than healthy controls (table 2). Six (17%) patients had symptoms of emotional distress, and 14 (39%) referred to poor quality of sleep. Quality of life perceived by the patients was not different from that of controls with the exception of the 10 patients with dementia (median EQ-VAS score: 69% vs 80% of controls; $p = 0.03$).

Twenty-six of the 36 patients (72%) were considered functionally independent (FAQ < 6 points). Eleven of them (42.3%) were functionally normal (mRS score = 0), 4 (15.4%) had symptoms without significant disability (mRS score = 1), and 11 (42.3%) were independent but unable to perform premorbid activities (mRS score = 2). Despite the good functional status, 17/26 (65%) patients had evidence of MCI. The remaining 10 (28%) patients were functionally dependent (FAQ ≥ 6) with an mRS score ≥3, and all had dementia.

Predictors of long-term cognitive outcome

Compared with cognitively normal patients, the estimated premorbid cognitive reserve of the 27 patients with cognitive impairment was lower (median [IQR]: 9 [7–13] vs 16 [9–17] points; $p = 0.02$), more frequent bilateral hippocampal hyperintensity on initial MRI (67% vs 11%; $p = 0.009$), poor response to first-line treatment (52% vs 11%; $p = 0.03$), required second-line treatment (41% vs 0%; $p = 0.02$), and had worse an mRS score at 2 years (mRS score ≥3 = 70% vs 33%; $p = 0.049$). No differences were observed regarding age at diagnosis, the presence of distinct clinical or paraclinical features, the delay to first-line treatment, the occurrence of relapses, or the time of follow-up. In the logistic regression analysis, including age, time of follow-up, and the existence of comorbidities as covariates, the estimated premorbid cognitive reserve (OR = 1.36, 95% CI: 1.05–1.76, $p = 0.02$) and the presence of bilateral hippocampal hyperintensity at the initial MRI (OR = 27.03, 95% CI: 1.87–390, $p = 0.02$) were independent predictors for long-term cognitive impairment. In fact, an estimated premorbid cognitive reserve cutoff point of 14.5 points was able to discriminate patients who developed cognitive

Table 2 Demographic and clinical description of 36 patients with anti-LGI1 encephalitis who completed the telephone interview

Characteristics	Anti-LGI1 encephalitis (N = 36)
Male, n (%)	23 (64)
Actual age, in years, median (IQR)	74 (63–81)
Age at onset, in years, median (IQR)	65 (56–74)
Cognitive reserve score, median (IQR)	11 (8–14.8)
Symptoms at diagnosis, n (%)	
Memory deficit	36 (100)
Seizures	27 (75)
Faciobrachial dystonic seizures	9 (25)
Mood/behavior	28 (77.8)
Sleep disorders	13 (36.1)
Other[a]	5 (13.9)
Hyponatremia, n (%)	14/31 (38.9)
MRI at disease onset, n (%)	
Unilateral hippocampal hyperintensity	10 (28)
Bilateral hippocampal hyperintensity	19 (53)
Normal	7 (19)
CSF pleocytosis, n (%)	5 (13.9)
Treatment delay, in days, median (IQR)	125 (45–188)
First-line immunotherapy (steroids ± IVIG)	36 (100)
Second-line immunotherapy	11 (30.6)
Chronic immunotherapy	7 (19.4)
Relapses, n (%)	12 (33.3)
mRS score at 24 months, median (IQR)	2 (0–2)
Comorbidities[b]	26 (72)

Abbreviations: IQR = interquartile range; IVIG = IV immunoglobulin; LGI1 = leucine-rich, glioma-inactivated 1; mRS = modified Rankin Scale.
[a] Other: daily headache (N = 1), anorexia (N = 1), hyperphagia (N = 2), weight loss (N = 1), dysautonomia (N = 2), and cramps in lower limbs (N = 1).
[b] Comorbidities that may have a functional impact in daily living: cardiovascular disease (N = 19), pulmonary disease (N = 2), endocrine disorder (N = 3), eye disorder (N = 2), and rheumatologic disease (N = 1).

Table 3 Results of the brief cognitive battery and related assessments obtained by telephone interview

Test (data expressed in median [IQR])	Patients (N = 36)	Healthy controls (N = 23)	*p* Value
Telephone MMSE score	21 (15–22)	23 (22–24)	0.02
Verbal memory			
FCSRT free delayed recall	2.5 (0–6)	7 (4–9)	0.001
FCSRT total delayed recall	7 (5–11)	11 (8–13)	0.02
Executive function			
Oral TMT-A	8.2 (7.6–10.1)	7.3 (6.3–8.4)	0.005
Oral TMT-B	60.2 (41.2–180)	46.6 (33.8–55.4)	0.01
Verbal fluency	14 (10.5–16)	19 (17–22)	<0.001
HADS score	5.5 (3–9)	2 (0–5)	0.01
PSQI score	4 (3–6.5)	2 (2–4)	0.001
EQ-5D-5L score			
Index value score	0.9 (0.7–1)	0.9 (0.8–0.9)	0.05
Quality of life, %	80 (60–90)	74 (60–100)	0.61

Abbreviations: EQ-5D-5L = five-level EuroQoL 5D dimensions; FCSRT = free and cued selective reminding test; HADS = Hospital Anxiety and Depression Scale; IQR = interquartile range; MMSE = Mini-Mental State Examination; PSQI = Pittsburgh Sleep Quality Index; TMT = Trial Making Test.
The Mann-Whitney *U* test was used for statistical analysis.

impairment from those who did not (sensitivity 0.67, specificity 0.89, and accuracy AUC = 0.75, 95% CI = 0.53–0.98, $p = 0.03$).

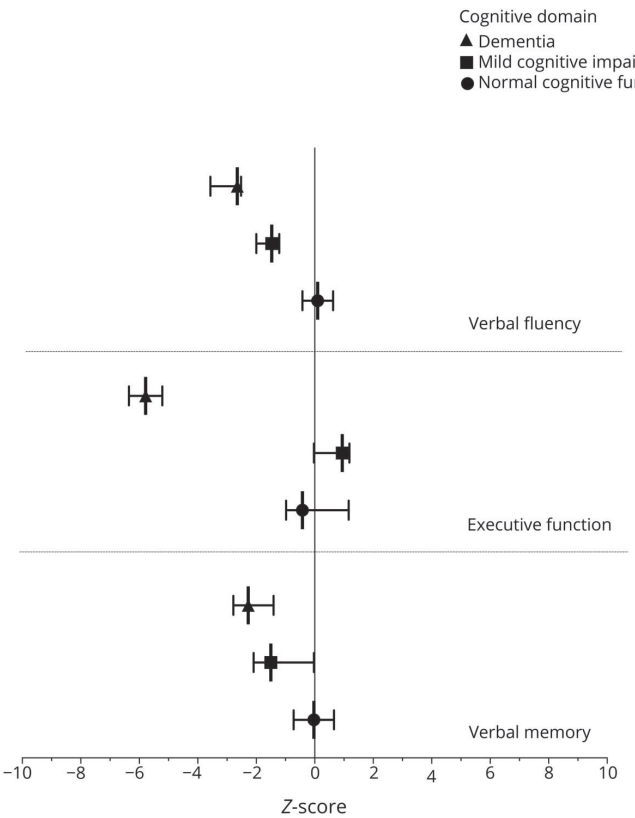
Discussion

This study shows the advantages and feasibility of using a structured telephone interview to assess the cognitive and functional status of patients who had anti-LGI1 encephalitis. Our findings show that the outcome evaluation of autoimmune encephalitis only based on the mRS score is not optimal and often misses the detection of cognitive deficits. Concerning the long-term outcome of patients with anti-LGI encephalitis, we found that 75% had cognitive deficits, ranging from MCI to dementia, and that the estimated premorbid cognitive reserve and presence of bilateral MRI hippocampal hyperintensity at disease onset are independent predictors for long-term cognitive impairment.

The use of our structured telephone intervention provides more reliable information than that obtained only assessing the functional status according to the impression of patients' physicians or relatives, and it is particularly useful for patients with rare diseases who often come from distant geographical locations or patients whose clinical status limits follow-up visits.[9] The observed moderate agreement between the t-MMSE and the cognitive battery of tests suggests that it is worth including the t-MMSE in the routine outcome assessment of autoimmune encephalitis, although it does not capture all cases with MCI (29% missed in this study). Adding the indicated cognitive battery of tests increases the length of the interview but provides relevant information on distinct cognitive functions, which may potentially be affected differently depending on the type of autoimmune encephalitis.[26]

As far as the evaluation of the functional status is concerned, the inclusion of the FAQ helps to confirm the mRS score. The

Figure Comparison among the z-scores of patients with anti–leucine-rich, glioma-inactivated 1 encephalitis with normal cognitive function, mild cognitive impairment, and dementia



The graph represents the median and interquartile range of the z-score in each cognitive domain for patients with normal cognitive function (closed circle), mild cognitive impairment (closed square), and dementia (closed triangle).

FAQ is focused on the ability to perform the activities of daily living (e.g., preparing meals or managing personal finances) that are affected at early stages of dementia development, probably before the mRS score is affected.[27] Other comorbidities could affect the mRS score but not specific items of FAQ. In our study, 72% of patients had a good functional status (mRS score <3) after a median follow-up of 7 years. This figure would decrease to 67% if we include the 3 patients with severe dementia that could not carry out the interview. In any case, the frequency is similar to that reported in a Dutch series (67%)[1] and our own series (71%)[3] in which the follow-up was 2 years.

Among the 26 patients who were functionally independent, only 9 (35%) had normal cognitive function emphasizing the need to include a formal cognitive evaluation to assess the full effect of anti-LGI1 encephalitis in patients' outcome. We detected lower scores in cognitive domains beyond memory deficits.[5] A similar result, including visuospatial memory deficits, was identified in a series of 30 patients examined a median of 2 years after onset of anti-LGI1 encephalitis.[4] Another series consisting of 11 patients with a good mRS score (0–2) who had neuropsychological assessment after a median of 44 months from disease onset showed that visuospatial recognition memory was the main residual deficit.[1] This cognitive domain could not be assessed in our telephone interview, suggesting that the frequency of cognitive impairment could be even higher than that reported here.

Our study shows that a lower estimated premorbid cognitive reserve and the presence of bilateral MRI hippocampal hyperintensity at disease onset are 2 independent predictors of long-lasting cognitive impairment. Cognitive reserve is defined as the adaptability of cognitive processes to brain aging, pathology, or insult. It is influenced by innate individual differences and the exposure to different socio-occupational factors such as early life education, profession, leisure activities, and/or social engagement.[28,29] Among several different approaches to assess cognitive reserve, we used a questionnaire that assesses a limited number of intellectual activities to ease the telephone interview, but the activities selected are among the most important.[12] High cognitive reserve has been found associated with a reduced rate of cognitive decline and dementia.[30] Prospective longitudinal studies of patients who developed mild cognitive impairment or Alzheimer showed that a higher

premorbid cognitive reserve delayed the onset of cognitive decline, although this decline accelerated as soon as the symptoms of dementia started.[31] A high educational level, the most commonly assessed cognitive reserve indicator, has been associated with a reduced risk of postoperative cognitive dysfunction or better cognitive outcome after traumatic brain injury.[32,33] Therefore, it is likely that a high cognitive reserve also influences the outcome in patients with anti-LGI1 encephalitis.

The cognitive deficits of patients with anti-LGI1 encephalitis have been found associated with the presence of residual structural damage to the hippocampus as evaluated by MRI.[4] We postulate that patients with bilateral hippocampal MRI abnormalities at disease onset probably have more brain inflammation than those with unilateral lesions or normal MRI and are at risk to eventually develop more severe hippocampal atrophy explaining the association we found with poor cognitive outcome.

Our study has several limitations. First, we used a transversal design that prevents ascertaining if the long-term cognitive changes result from the acute stage of the encephalitis or from a prolonged, albeit mild, inflammatory activity that contributes to irreversible deficits. Moreover, considering the median age of patients with anti-LGI1 encephalitis, the worsening cognitive status over time of some patients could potentially have been influenced by unrelated comorbidities (e.g., neurodegenerative processes) that were unmasked or aggravated by the autoimmune inflammatory changes. Telephone assessment could only be performed to patients with good familiar support and accessible by phone, which may limit the assessment of institutionalized patients or with advanced dementia downplaying the real impact of anti-LGI1 encephalitis in the cognitive status. Last, we could only explore the cognitive reserve by partially assessing various aspects of life experience but the concept of reserve also accounts for individual differences in susceptibility to age-related brain changes that could not be assessed in this study.[28]

A comprehensive evaluation of the long-term outcome of patients with anti-LGI1 encephalitis is essential for a better knowledge of the cognitive domains predominantly affected by the disease and optimal assessment of the efficacy of immunotherapies. We have demonstrated that telemedicine through a structured telephone interview is feasible and provides a good instrument to address these issues. Future studies are encouraged to confirm these results and to validate the brief cognitive battery for its standard use in the evaluation of anti-LGI1 and other autoimmune encephalitis, and it should be considered, along with the mRS, for the long-term assessment of autoimmune encephalitides.

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9. DISCUSIÓN

9. Discusión

El conjunto de los trabajos que conforman esta tesis doctoral aporta una serie de conocimientos que pueden ser útiles a la hora de adoptar la telemedicina como una herramienta adicional en la monitorización clínica de pacientes con enfermedades autoinmunes del SNC.

La creciente demanda de una atención sanitaria especializada junto con el envejecimiento de la población, y la restricción de movilidad de los ciudadanos, son algunos de los factores que promueven el uso de las TIC en un entorno sanitario con limitaciones presupuestarias y contención del gasto (129). Los trabajos de esta tesis han demostrado que la telemedicina es una herramienta viable en pacientes de nuestro entorno con enfermedades autoinmunes del SNC. La participación en los estudios fue alta (89%) e independiente de la edad, la modalidad, o método de telemedicina utilizado.

La existencia de una barrera física en la intervención remota, puede condicionar o limitar aspectos tanto de la anamnesis como de la exploración médica. La clave del éxito de toda intervención telemática se basa en la creación de un vínculo entre los interlocutores para contrarrestar la barrea física, y mantener la adherencia al programa. La utilización de escalas clínicas con características psicométricas apropiadas al objetivo de la intervención, y validadas para su uso remoto es otro aspecto fundamental para obtener información apta y veraz. En la actualidad existen pocos estudios que hayan validado las escalas más utilizadas en la práctica asistencial para su uso remoto en pacientes con enfermedades autoinmunes del SNC, y la mayoría se han realizado en lengua inglesa. En pacientes con EM, la escala EDSS telefónica se validó en 2003 en lengua inglesa como una alternativa útil a la EDSS convencional para estudios clínicos con períodos de seguimiento extensos, o en circunstancias en las que el desplazamiento de los pacientes estuviese limitado (34). La escala PDDS en inglés ha sido ampliamente utilizada en uno de los registros más grandes de Estados Unidos, donde es el mismo paciente quien introduce los datos epidemiológicos y clínicos (46). En nuestro estudio la validación de ambas escalas al castellano mostró propiedades psicométricas similares a sus homólogas inglesas. El análisis de la concordancia entre la EDSS convencional y telefónica fue similar al observado en otros estudios de evaluación remota (31-39), y al obtenido entre dos evaluadores presenciales (40-42). De igual forma, la concordancia entre la PDDS convencional y telefónica fue similar a la versión inglesa (47). En ambas escalas, dicha concordancia fue superior en los pacientes más discapacitados (EDSS >4.0), lo que enfatiza el potencial beneficio de la evaluación remota en los pacientes con discapacidad grave y relacionada con la marcha, quienes por sus limitaciones pueden requerir con mayor frecuencia este tipo de intervenciones. La concordancia fue mayor en los SF piramidal, y menor para el mental, reforzando

un aspecto conocido deficitario de la escala, y la contribución del sistema motor en la puntuación de la EDSS telefónica.

El porcentaje de pacientes con un resultado idéntico en el test-retest fue más alto en la PDDS (81%) que en la EDSS (48%). Este hallazgo puede deberse a que la EDSS convencional y telefónica son dos escalas distintas, una basada en la exploración neurológica objetiva, y la otra es un cuestionario auto administrado por el paciente. Además, el cuestionario presenta una serie de limitaciones como la falta de preguntas detalladas sobre los SF, y la imposibilidad de puntuar los SF con un cero. La existencia de factores externos como fluctuaciones, síntomas asociados y barreras físicas no controlables en el ámbito hospitalario puede también influir en la percepción del paciente sobre su grado de discapacidad.

A pesar de la existencia de una buena correlación entre la PDDS y la EDSS, no se debería de recomendar su uso de forma indistinta, pues no valoran exactamente lo mismo. Por ende, no existe un buen patrón de conversión entre ambas escalas telefónicas, siendo mayor la variabilidad en los pacientes con una discapacidad moderada (PDDS 3-4; EDSS 2.5-6.0). Si se pretende comparar ambas escalas, es más fiable establecer un punto de corte que permite caracterizar mejor a los pacientes según estado neurológico con una mayor sensibilidad y especificidad (una PDDS mayor o igual a 3 engloba a los pacientes con EDSS $\geq$ 4.5). Como limitación, el trabajo 1 fue un estudio unicéntrico, y no se evaluaron a pacientes en los grados extremos de la escala. Sin embargo, estaban representados los pacientes dentro del rango habitual de discapacidad observado en la práctica clínica.

La utilización de herramientas multimedia como el video, permite recuperar la objetividad de la escala EDSS remota para la puntuación de ciertos SF (especialmente los que pueden visualizarse por video como el piramidal, cerebelo y tronco del encéfalo y parcialmente el sensitivo). La modalidad asíncrona del video aporta flexibilidad al usuario, pero requiere una formación previa específica para adecuar el contenido del video a los requerimientos establecidos. Casi la mitad de los pacientes tuvieron algún problema menor en el envío del video, o la realización de los cuestionarios; sin embargo, el 85% de los pacientes estuvieron satisfechos con la intervención, y un 35% la consideraron útil. De forma similar a la EDSS telefónica, la concordancia global fue moderada y buena en los pacientes con alteración de la marcha (EDSS >4.0). Cuando se asumió que cierto grado de variabilidad no era clínicamente significativa, la concordancia global mejoró hasta ser excelente (>81%), y esta mejora fue independiente del grado de discapacidad. Los SF que fueron evaluados mediante la EDSS multimedia obtuvieron una concordancia superior a los SF obtenidos mediante

teléfono, especialmente aquellos SF evaluados por video como el piramidal, el cerebelo y el tronco del encéfalo independientemente del grado de discapacidad. La mejoría en la concordancia de los SF es importante porque a su vez influye en la puntuación final de la EDSS. Si realizamos una comparación entre los resultados del trabajo 1 y 2, la concordancia observada fue similar en ambas cohortes de pacientes utilizando el teléfono o herramientas multimedia. Las diferencias pudieron deberse al tamaño de la muestra y a las características clínicas de los pacientes, pues en el trabajo 2 hubo un mayor porcentaje de pacientes con formas progresivas y mayor discapacidad. En cualquier caso, la utilización indistinta de una modalidad u otra permite obtener una información válida sobre el estado clínico de los pacientes, si bien el uso del video mejora la obtención de una información veraz y detallada de la exploración neurológica.

Otro aspecto importante en la evaluación clínica de los pacientes con EM es la monitorización de la marcha porque es un síntoma guía de progresión de la discapacidad, y un factor clave para puntuar la escala EDSS. Los trabajos 1 y 2 pusieron de manifiesto las discrepancias que existe entre la percepción del paciente sobre su capacidad para caminar, y el que se obtiene de forma objetiva evaluando la marcha mediante tests específicos (índice de kappa= 0,52-0,87). Un 30% de los pacientes con EDSS $\leq$ 4.0 en el trabajo 2 infraestimó la distancia que podían caminar, y el porcentaje era más variable en pacientes que presentaban una mayor discapacidad (EDSS >4.0: 12% la infraestimó y un 25% la sobreestimó). Estos resultados refuerzan la necesidad de utilizar tests objetivos para la monitorización de la marcha, aún a sabiendas de que no han demostrado ser muy sensibles para detectar la progresión de la discapacidad. Además, los tests tienden a sobrevalorar el estado clínico dado que se realizan en un ambiente controlado, con una duración determinada, y bajo la atenta mirada del/a profesional sanitario (130). La preferencia del uso de tests considerados largos como el 6MWT permite disminuir el efecto techo observado en el T25FW en los pacientes menos discapacitados, y detectar cambios en el patrón de la marcha asociados a factores como fatiga o espasticidad (57, 62). En el trabajo 2 se confirmó que la evaluación del 6MWT se puede realizar de forma remota mediante el uso de un acelerómetro, y el estudio demostró una buena correlación entre el número de pasos totales durante 6 minutos y los metros realizados en el 6MWT presencial (r = 0.76). Además, puso de manifiesto que el acelerómetro podía detectar cambios longitudinales en la actividad diaria anticipándose a la progresión de la EDSS, un aspecto que hasta ahora no se había podido demostrar utilizando otros tests convencionales. Así, el acelerómetro detectó a lo largo de 2 años una reducción de la actividad diaria en el grupo de pacientes con alteración de la marcha sin que ello se asociara a un empeoramiento en la EDSS o tests de la marcha convencionales. Además,

la actividad diaria medida por el acelerómetro se correlacionó de manera fuerte con la EDSS (r =-0.86), y su monitorización permitió diferenciar con una elevada sensibilidad y especificidad a los pacientes con un trastorno de la marcha que a su vez tenían una peor CdV. Estos resultados del trabajo 2 deberán ser confirmados con estudios prospectivos que incluyan a un mayor número de pacientes, y con ello se podrá validar la actividad diaria como herramienta y marcador de progresión de discapacidad en la EM. Así, si se confirman los resultados aquí mencionados, se podría posicionar el acelerómetro como una herramienta telemática altamente sensible, y útil, para el seguimiento clínico de los pacientes con EM (131).

Otro aspecto a destacar, es que la telemedicina puede contribuir en el manejo clínico de los pacientes, y en la toma de decisiones terapéuticas. La administración de fampridina-LP está condicionada a la evaluación de la marcha mediante tests validados y debe objetivarse una mejoría, que no se define de forma específica en ficha técnica. Por ello, y antes que se definieran unos criterios consensuados a nivel autonómico, en el trabajo 3 se determinó la respuesta a fampridina-LP mediante el uso de varios tests de la marcha convencionales y medidas funcionales, entre las que se incluyó la evaluación de la actividad diaria mediante un acelerómetro. Dado que se trataba de un estudio observacional, y no se pretendía alterar la práctica clínica habitual, se definió como respuesta clínicamente significativa la mejoría de un 20% o superior en el test T25FW, por ser el criterio más ampliamente aceptado y asociarse con cambios en actividades cotidianas. Utilizando este criterio, se observó un porcentaje elevado de pacientes con respuesta beneficiosa (78%) a fampridina-LP que se mantuvo durante un año. La tasa de respondedores fue similar a la observada en otros estudios de práctica clínica real con diferentes criterios de respuesta, y superior a la observada en los ensayos clínicos pivotales (63-70). Además, se observó que la respuesta óptima en dos tests de forma persistente (T25FW y MSWS-12 con ≥ 6 puntos) se asociaba a una mejoría significativa en parámetros funcionales como la actividad diaria medida por el acelerómetro, y la CdV medida por la EuroQoL-5D. De hecho, los pacientes con respuesta combinada obtuvieron incrementos de actividad diaria de 12,5-27,6% en comparación con los que respondieron sólo a T25FW que mostraron un descenso en la actividad diaria (-1,3 -14,2%). Además, la buena asociación entre la actividad diaria y la escala MSWS-12 pon de manifiesto que la percepción de mejoría probablemente está asociada a cambios beneficiosos en la vida real. Por ello su uso en la monitorización clínica es altamente recomendable, especialmente en aquellos casos en los que la respuesta de fampridina-LP a los tests convencionales se encuentre en el límite para ser considerada como efectiva. Otro aspecto importante a considerar en estos pacientes es la necesidad de re-evaluación periódica, ya que existe

un porcentaje de pacientes en los cuales se pierde la efectividad del tratamiento, y en algunos se debe a la propia progresión de su discapacidad. Los resultados del trabajo 3 proporcionan información práctica sobre el uso combinado de dos tests de rápida cumplimentación como herramientas útiles en la toma de decisiones sobre el efecto de fampridina-LP y contribuye a la experiencia real con este fármaco.

La telemedicina puede ser particularmente útil en el estudio de enfermedades con baja prevalencia como es el caso de la encefalitis anti-LGI1. Series pequeñas sugerían que los pacientes podían tener secuelas a nivel cognitivo tras la encefalitis sin que estas conllevaran un empeoramiento en su capacidad funcional (132). De ahí que en el trabajo 4 investigáramos la viabilidad de una evaluación remota cognitiva, y funcional, a largo plazo. El estudio confirmó que la administración de una batería cognitiva breve por teléfono era viable, y permitía obtener información sobre el estado cognitivo de estos pacientes. El uso de tests específicos dentro de la batería cognitiva breve, detectó un 29% más de pacientes con deterioro cognitivo respecto a la MMSE telefónica, y permitió caracterizar los dominios cognitivos afectados que pueden variar según el tipo de encefalitis. De forma global, el 75% de los pacientes tenían un deterioro cognitivo, la mayoría leve (63%), un dato que pone de manifiesto la importancia de incluir una evaluación cognitiva formal en la evaluación de estos pacientes. Como era de esperar el dominio más afectado fue la fluencia verbal (53%) seguido de la memoria verbal (50%) (86-89). Si bien, el pronóstico funcional de los pacientes a largo plazo fue bueno (67% con mRS<3 tras una mediana de 7 años). Un aspecto relevante del estudio fue la demostración de que una baja reserva cognitiva previa, junto con la presencia de daño estructural bilateral en el hipocampo en la fase aguda, son factores independientes de deterioro cognitivo a largo plazo. Un dato que va en la línea de estudios longitudinales en pacientes con deterioro cognitivo leve, que muestran que la reserva cognitiva premórbida retrasa la aparición de los síntomas de demencia a largo plazo (133, 134). En la fase aguda, el daño estructural del hipocampo bilateral probablemente está indicando una mayor inflamación, y este hecho puede favorecer el desarrollo de atrofia, y de ahí la asociación con deterioro cognitivo (92). El estudio al ser transversal no permite confirmar si el deterioro cognitivo se debe a cambios residuales del episodio de encefalitis o debido a un deterioro cognitivo progresivo posterior a la actividad inflamatoria. El hecho de que se ajustara por la presencia de algunas comorbilidades externas más prevalentes, y que se comparara con una muestra apareada de personas sanas, no permite descartar de forma completa que otros factores intrínsecos tal como cambios neurodegenerativos hayan influido en el resultado. La evaluación cognitiva remota, al igual que la presencial está limitada por el estado clínico de los

pacientes, infraestimando en todo caso aquellos pacientes más gravemente afectados que no pueden realizar la evaluación cognitiva. Además, la batería cognitiva breve incluyó solo un test por dominio cognitivo, para evitar la fatiga de los participantes, y existen ciertas funciones cognitivas como las funciones visuoperceptivas que no pueden evaluarse por teléfono. A pesar de ello, hubo una buena concordancia entre la escala MMSE telefónica y la batería cognitiva breve, por lo que la MMSE telefónica puede considerarse una buena escala cognitiva de cribaje.

En definitiva, un estudio que ha permitido mejorar el conocimiento sobre el estado cognitivo de los pacientes con encefalitis anti-LGI1 a largo plazo. Sería bueno que se validara la escala cognitiva breve para su uso estandarizado en este tipo de pacientes, y con su evolutivo determinar el estado clínico y la respuesta a terapias.

Para concluir y como reflexión personal, la incorporación de las TICs en el ámbito de la salud ha generado enormes expectativas, y a su vez se ha encontrado con dificultades en la aplicación de la metodología habitual de los estudios a la práctica clínica asistencial. El éxito de proyectos de telemedicina como el programa de tele-ictus es el resultado de la interacción de la tecnología y el entorno en que se aplica, y no sólo de los resultados obtenidos. La telemedicina no pretende ser un sustituto de la evaluación física, los estudios incluidos en esta tesis confirman la viabilidad de la implementación de herramientas telemáticas en la práctica asistencial, y respaldan su aplicación como una herramienta válida en diferentes aspectos de la evaluación médica y el seguimiento de forma periódica de pacientes con enfermedades autoinmunes del SNC.

10. CONCLUSIONES

10. Conclusiones

1. La evaluación física y cognitiva mediante herramientas telemáticas es factible en pacientes con enfermedades autoinmunes del SNC.

2. Los cuestionarios adaptados al español de las escalas telefónicas del EDSS y PDDS son herramientas útiles, y fiables para conocer el estado neurológico y la discapacidad de los pacientes con EM. Además, ambos cuestionarios proporcionan información complementaria.

3. Si bien la monitorización de las medidas estándar de discapacidad en los pacientes con EM mediante una plataforma multimedia es factible, la concordancia entre EDSS presencial y el evaluado de forma remota solo es buena para los pacientes más discapacitados. El incluir la filmación en video de la exploración neurológica, mejora la concordancia de los resultados en los sistemas funcionales que aportan mayor valor a la exploración neurológica.

4. La actividad diaria medida mediante un acelerómetro es una herramienta más sensible que la proporcionada por la escala del EDSS y los tests de la marcha para detectar cambios clínicos evolutivos en los pacientes con EM.

5. La monitorización de la actividad diaria mediante acelerómetro contribuye a detectar el efecto beneficioso de la fampridina-LP en la práctica clínica. La combinación de medidas objetivas (T25FW) y subjetivas (MSWS-12) identifica aquellos pacientes que presentarán una respuesta clínicamente significativa en su entorno habitual.

6. La mayoría de los pacientes con encefalitis autoinmune anti-LGI1 presentan signos de deterioro cognitivo, a pesar mantener un buen estado funcional a largo plazo. La presencia de hiperintensidad hipocampal bilateral al debut y una baja reserva cognitiva son factores predictores independientes de deterioro cognitivo a largo plazo.

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