Epilepsy & Behavior 138 (2023) 108993

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Association of depression and epilepsy in Rwanda: A prospective longitudinal study

Fidele Sebera [a,b,c,1], Peter Dedeken [c,d,e,1], Ieme Garrez [c,d], Josiane Umwiringirwa [a], Tim Leers [g,h], Jean-Pierre Ndacyayisenga [a], Sylvestre Mutungirehe [a], Arlene Ndayisenga [a,f], Odette Niyonzima [a,g], Georgette Umuhoza [a], Dirk E. Teuwen [c,d,*], Paul A.M.J. Boon [c,d]

[a] Neurology Department, CARAES Neuropsychiatric Hospital, Kigali, Rwanda
[b] Neurology Department, Centre Hospitalier Universitaire – Kigali (CHU-K), Kigali, Rwanda
[c] Department of Neurology, University Hospital, Ghent University, Ghent, Belgium
[d] 4Brain, Ghent University, Ghent, Belgium
[e] Department of Neurology, Heilig Hart Ziekenhuis, Lier, Belgium
[f] Neurology Department, King Faisal Hospital, Kigali, Rwanda
[g] WIWO Hospital, Nyarugenge District, Kigali, Rwanda
[h] Dataroots, Leuven, Belgium

ARTICLE INFO

Article history:
Received 7 July 2022
Revised 26 October 2022
Accepted 4 November 2022

Keywords:
Incidence
Prevalence
Depression
Epilepsy
Rwanda

ABSTRACT

Introduction: Depression is the most common psychiatric comorbidity for persons living with epilepsy. In Rwanda, the prevalence of epilepsy and depression are high, with 4,9% and 13.0% respectively. This prospective interventional study aimed to determine the prevalence and incidence of depression and the outcome of persons living with epilepsy (PwE) with depression attending the outpatient neurology department of a tertiary center.

Methods: Persons living with epilepsy enrolled between February and June 2018 in a screening cohort with a 12-month follow-up. At every 3-month study visit, PwE were screened for depression using the Patient Health Questionnaire (PHQ-9) questionnaire. Any positively screened subject was administered the Hamilton Depression Rating Scale (HDRS) to confirm the diagnosis and severity of depression. Subjects with moderate to severe depression (MSD), were started on treatment and were followed for another year. We describe the prevalence and incidence of depression, baseline characteristics, epilepsy and depression outcomes, and changes in PGI-C.

Results: Of 572 PwE enrolled, 46 were diagnosed with MSD in a twelve-month period, resulting in an incidence of MSD of 32.7/1000 patient-years. The prevalence of any depression and MSD was 14.2% and 4.7%, respectively. Longer epilepsy duration and seizure status at baseline were associated with MSD. Significant improvements in PGI-C and seizure frequency were observed after treatment optimization.

Conclusion: The use of PHQ-9 and HDRS proved successful in identifying depression in PwE. Combined treatment of epilepsy and depression resulted in improved outcomes, warranting the implementation of depression screening every six months in daily neurology practice.

1. Introduction

Worldwide, depressive disorders and anxiety have been identified as serious co-morbidities in persons living with epilepsy (PwE) [1,2]. The prevalence of depression varies between 17% and 49% [3–5]. The signs and symptoms of depression include changes in appetite, altered sleep habits, increased or decreased level of activity, diminished focus, and concentration, and dramatically reduced feelings of self-worth and extreme types, death desire or suicidal attempts [6,7].

Abbreviations: AD, Anti-Depressant; ASM, Anti-Seizure Medication; CBT, Cognitive Behavioral Therapy; CI, Confidence Interval; CS, Completer Set; HDRS, Hamilton Depression Rating Scale; MSD, Moderate to Severe Depression; MSD-CS, Moderate to Severe Depression-Completer Set; MSD-PPS, Moderate to Severe Depression-Per Protocol Set; n, number; PGI-C, Patient Global Impression of Change; PHQ-9, Patient Health Questionnaire-9; PPS, Per Protocol Set; PwE, Person living with epilepsy; PWED, Person living with epilepsy and depression; QOLIE, Quality-Of-Life-In-Epilepsy; scr-CS, screening-Completer Set; scr-PPS, screening-Per Protocol Set; SD, Standard Deviation; SSRI, Selective Serotonin Receptor Inhibitor; TCA, Tricyclic antidepressant; TSP, Total Study Population; y, year.

* Corresponding author at: Ghent University Hospital, Department of Neurology, Corneel Heymansstraat 10, B-9000 Ghent, Belgium.
E-mail address: dirk.teuwen@uzgent.be (D.E. Teuwen).

[1] Equal contribution.

https://doi.org/10.1016/j.yebeh.2022.108993
1525-5050/

The presence of depressive disorders in PwE is associated with poorer QoL and increased healthcare utilization, and may affect worse medical outcomes, *e.g.*, poorer seizure control and increased side effects associated with antiseizure medication (ASM) [2,8,9,10]. Furthermore, depression may exacerbate adverse events associated with ASM, *e.g.*, suicidal ideation, and may add to the perceived and felt stigma in PwE [2,11,12,13,14,15]. Screening for depression in PwE has therefore been recommended in clinical practice [16].

In Africa, the impact of perceived and felt the stigma of both medical conditions on the life of PwE and their families and treatment choices are vast. Religious and socio-cultural beliefs influence the choices of care and treatment and may result in important negative social, economic, and psychological consequences. As in other African communities, attitudes and beliefs regarding epilepsy contribute to the extensive epilepsy treatment gap, which includes patients without diagnosis and treatment [12].

Depression is associated with different endogenous, such as cognitive impairments, family history of mental illness, low educational status, and low monthly income. Exogenous factors associated with depression are a low level of awareness of depression, the unfavorable attitude of family or communities, and stigma, which further exacerbate the treatment gap [12,17,18].

In Rwanda, a low-income landlocked country in Eastern Africa, epilepsy and depression are both common medical conditions, with prevalence estimated at 4.9% and 13.0%, respectively [12,19,20]. Access to health centers is well organized, nonetheless, the epilepsy treatment gap in Rwanda is estimated between 68 and 91.5% [12]. Persons living with epilepsy receive a clinical follow-up and ASM during monthly follow-up visits at either primary, secondary, or tertiary centers. At primary health centers, phenobarbital (tablets and IV solution) is available as first-line ASM and amitriptyline as an anti-depressant (AD). Counseling is provided by mental health nurses. Only at secondary or tertiary centers, second-line ASM, ADs, and cognitive behavioral therapy (CBT) provided by psychologists, are available.

Screening for depression is not routinely applied, provided the constraints of a resource-limited environment. Incomplete screening and atypical symptomatology or clinical presentation of depression may lead to underdiagnosis and an unknown treatment gap for depression [21]. In 2013, a study in the Northern Province of Rwanda identified 105 PwE eligible for the evaluation of depression by the HDRS questionnaire. Almost half (48.6%) of the PwE presented depression, 51% severe, 29.4% moderate, and 19.6% mild depression [22].

In a resource-limited environment, the use of screening tools has proven useful to decrease the diagnosis gap [23]. In Rwanda, Kinyarwanda versions of the Patient Health Questionnaire-9 (PHQ-9) and Hamilton Depression Rating Scale (HDRS) have been validated with cut-off values for screening, diagnosis, and monitoring of depression [24,25].

The present study aimed to determine the prevalence and incidence of all and moderate-to-severe depression (MSD) in PwE in Rwanda by administering the PHQ-9 and HDRS questionnaires, explore a possible relationship to socio-demographic and clinical factors and evaluate treatment outcomes of PwE with MSD.

2. Methodology

2.1. Screening and diagnosis tools

Screening for depression was performed using the Kinyarwanda version of the PHQ-9, with validated cut-offs for screening for any and severe depression [24]. The PHQ-9 cut-off in this study for any depression was a total score > 5 [24]. The PHQ-9 is the nine-item depression screening tool for major depressive disorder, each scored between zero to three [26].

Diagnosis of depression was performed using the Kinyarwanda version of the HDRS, which has been validated against the gold standard of a standardized interview, resulting in a cut-off of > 17 for a definite diagnosis of MSD [25]. The HDRS is composed of 17 diagnostic questions, of which eight are scored on a 5-point scale, ranging from 0-4 and nine are scored from 0-2. Questions 18–21 further qualify the depression [27].

The aim of this study was to select PwE with MSD only, as these were deemed at the highest need for immediate therapeutic intervention. As the Rwandan PHQ-9 cut-off did not allow a categorical analysis of the severity of depression, we adopted HDRS categories for the absence of a depression (HDRS 0–7), or presence of mild (HDRS 8–16) moderate (HDRS 17–23), or severe depression (HDRS $\geq$ 24), as proposed by Zimmerman *et al.* [28].

In addition, each investigator provided his/her assessment of the presence and severity of depression, using a 4-category scale, *i.e.*, none, mild, moderate, and severe depression.

2.2. Study design and analysis sets

2.2.1. Study design

This prospective longitudinal interventional study was conducted at the tertiary CARAES neuropsychiatric hospital, at Ndera (Kigali, Rwanda). Patients aged $\geq$ 15 years and having signed an informed consent or assent form, and able to respond to the interviewer were enrolled. The diagnosis of epilepsy was defined as two unprovoked seizures occurring at least 24 hours apart, as recommended by the Operational Classification of the ILAE [29]. The study was approved by the Rwandan Ministry of Health and the Institutional Review Board (Approval N^{0}461/CMHS-IRB/2016).

Upon enrolment, patients entered a one-year follow-up period. During these 12 months, PwE were screened for depression using the PHQ-9 questionnaire, at baseline, 3 months, 6 months, 9 months, and 12 months. In between those study-specific visits, PwE returned for their monthly routine consultation.

If at any study visit, the total PHQ-9 score was > 5, the patient was subsequently administered the HDRS to confirm the diagnosis of depression. If the HDRS total score indicated only mild depression, the patient continued in the PwE group without depression, considering no therapeutic intervention for depression was considered.

If the HDRS total score > 17 confirmed the MSD diagnosis, the PwE moved to the other study arm PwE with depression (PwED). In this PwED group, patients would be followed-up for one year for depression, with four study visits scheduled every three months for a follow-up assessment.

Epilepsy management and choice of ASM were left at the discretion of the treating physician during each outpatient and study visit. As per protocol, treatment for depression (Selective Serotonin Receptor Inhibitors (SSRI), Tricyclic Anti-depressant (TCA), CBT, or any combination) was started for all PwE with MSD. PwE with mild depression received no treatment [30]. At each visit, PwE with mild depression or MSD received psychological counseling upon recommendation by the treating physician. CBT was provided by trained psychologists at the tertiary center.

If a patient missed a study visit, a reminder phone call was made, and the study visit was rescheduled. If the subject missed the study end visit, home visits were organized for the administration of PHQ9 or HDRS for PwE with and without depression respectively.

As our study may have resulted in an outcome bias due to its interventional nature and not reflecting clinical practice, we also evaluated the outcome of PwED one year after the study ended, at which time they had returned to routine clinical care. We col-

lected data on ASM and depression treatment and administered HDRS and a single forward-translated Kinyarwanda version of the Quality-of-Life-In-Epilepsy 10 (QOLIE-10) questionnaire for epilepsy-related quality of life [31,32].

2.2.2. Analysis sets

The total study population (TSP) consisted of all enrolled subjects and is divided into cohorts with or without MSD.

As patients missed study visits, we defined a Completer Set (CS) and Per Protocol Set (PPS), by the status of the presence of MSD. The CS includes all subjects having a baseline and study end visit, which occurred at least 10.5 months after baseline, resulting in a CS for PwE without MSD in the screening group (scr-CS) and PwE with MSD (MSD-CS) (Fig. 1). Similarly, we defined the PPS for the respective groups as scr-PPS and MSD-PPS for PwE having attended all planned study visits.

2.3. Study variables

2.3.1. Demographic variables and epilepsy characteristics

Demographic variables and epilepsy characteristics were collected at baseline.

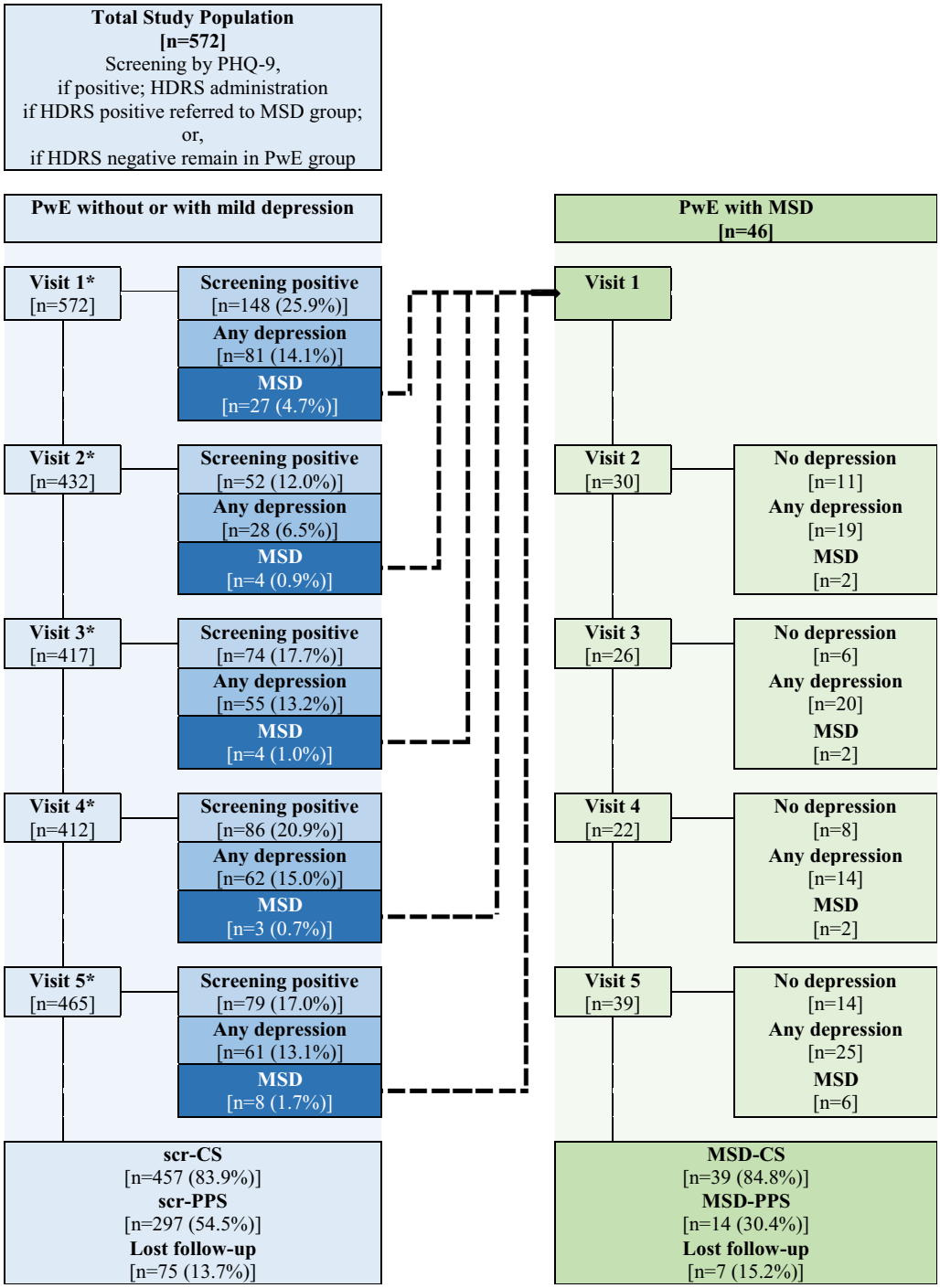

Fig. 1. Study flow diagram with number of subjects at each study visit (abbreviations: %: percentage; MSD: moderate to severe depression; MSD-CS: MSD-Completer Set; MSD-PPS: MSD-Per Protocol Set; n: number; scr-CS: screening-Completer Set; scr-PPS: screening-Per Protocol Set; *missing observations at visit 2, 3, 4 and 5 amounted to 140, 155, 160 and 107 PwE, respectively, and included missed study visits, death cases and lost to follow-up.

The etiology of epilepsy was determined based on the medical history (patient and/or family member), clinical examination, and lab and imaging results, if available. Using the ILAE 2017 guidelines, epilepsy onset and etiology were classified by consensus of three investigators following a review of the medical records, clinical seizure description, and technical investigations, if available [29,33].

2.3.2. Epilepsy treatment and outcomes

Data on previous and ongoing ASM were collected at each study visit and coded using WHODrug [34].

28-day seizure frequency was calculated based on the number of seizures reported by PwE between study visits. Mean baseline seizure frequency was calculated on the number of seizures since the last outpatient visit.

2.3.3. Depression prevalence at baseline, incidence at each visit, treatment, and evolution

At each visit, the presence of any depression in PwE was evaluated and categorized by mild depression or MSD.

Depression treatment at each visit was recorded as the active use of anti-depressant drugs (AD) and/or CBT and coded using the WHO Drug. Treatment outcome was measured using the HDRS score, and investigator assessment of depression severity.

2.3.4. Patient-reported outcomes

At each visit, all subjects assessed their overall improvement compared to the start of treatment using the Patient Global Impression of Change (PGI-C), a 7-point scale, ranging from 'no change (or condition got worse) to a 'great deal better, a considerable improvement that has made all the difference' [35,36].

The QOLIE-10 questionnaire consisting of 10 questions addressing epilepsy effects, mental health, and role functioning was administered to subjects diagnosed with MSD, one year after the study ended [31,32]. The relative scores range between 1.00 and 5.11.

Depression outcomes were described in the MSD-CS.

2.3.5. Statistical analysis

Data were analyzed using the statistical R package [37].

All analyses were descriptive. Comparison between subpopulations (male/female, PwE with and without MSD) was performed using either Pearson Chi^2 for all nominal or ordinal variables, and with ANOVA for all continuous variables where the normality assumption was met. Bonferroni adjustments were applied for all tests. Significance levels were determined at $p < 0.05$.

Demographics were described by the total population, and by the presence of MSD. Additional analysis by gender in each population was also performed.

In case of missing data, no imputations were used. As this study was intended as a real-life study, protocol deviations were included in the data analysis.

Despite efforts to ensure compliance with the study protocol, a high number of missed study visits was observed. A timeframe analysis to calculate the study duration of each study visit relative to baseline was used.

Prevalence of MSD and any depression was calculated at baseline and included subjects who screened positive on PHQ9 and with HDRS total scores ≥ 6 and ≥ 18, respectively.

The incidence of MSD and any depression during the one-year follow-up was calculated on the number of PwE with a positive HDRS score at any follow-up visit. Prevalence and incidence of depression after one year werer analyzed using the TSP.

A sensitivity analysis was conducted using censoring for study drop-outs and using only PPS.

3. Results

3.1. Study disposition

The TSP consisted of 572 PwE with 58.6% males enrolled between 21st February 2018 and 7th June 2018.

As 27 cases of MSD were confirmed at baseline first visit, the screening cohort continuing to visit 2 consisted of 545 subjects. As MSD incident cases occurred during the one-year follow-up, they progressively decreased to 526 PwE at the study closure. The MSD group increased from 27 to 46 subjects after one year (see Fig. 1). In total, 82 subjects were lost to follow-up, seven of which were in the MSD cohort.

The scr-CS consisted of 457 PwE and the scr-PPS consisted of 297 PwE. The MSD-CS and MSD-PPS consisted of 39 and 14 PwE, respectively.

3.2. Demographic variables

Baseline demographics by TSP and by the status of MSD are described in Table 1.

Geographically, most patients (57%) originated from the city of Kigali, where the CARAES neuropsychiatric hospital is located. No geographical differences were observed between study subpopulations.

Of note, more than 7 out of 10 PwE, remained single, both male and female.

An analysis by gender (male/female) did not reveal any significant differences. A comparison of male/female subjects by status of MSD did not reach significance for any of the variables.

The presence of comorbidities, such as HIV or diabetes, was not associated with depression, considering the low reported rate of comorbidities.

3.3. Epilepsy characteristics

Characteristics of epilepsy categorized by the presence of MSD are described in Table 2 and Table 3.

Of all seizure types, tonic-clonic seizures were most prevalent in 319 (55.8%) of patients, and 230 (40.2%) were classified as focal-onset, similar in PwE with or without MSD.

Nearly all patients (97.4%) had an electroencephalogram (EEG) performed at any stage prior to study inclusion. Computed tomography (CT) was performed in 112 (19.6%) persons and magnetic resonance imaging (MRI) in 25 (4.4%).

Epilepsy etiology and seizure onset were unknown in 425 (74.5%) and 211 (36.9%) PwE, respectively. The etiology is most often described as an underlying structural lesion, noted in 115 (20.1%) persons. Traumatic head injuries and hypoxic-ischemic origin, including perinatal asphyxia, were reported in 64 (11.2%) and 35 (6.1%), respectively. Infectious etiology was noted in 29 (5.1%) PwE, including bacterial meningitis (n = 10 (1.7%)), malaria (n = 4 (0.7%)), and neurocysticercosis (n = 3 (0.5%)).

No, statistical differences in seizure types and epilepsy etiology were found when categorized by MSD status.

A longer mean duration of epilepsy was significantly associated with the occurrence of MSD. Seizure frequency, analyzed by intervals, was also significantly different between subjects with and without MSD, with fewer patients with MSD being seizure-free.

3.4. Incidence of MSD or any depression

Nineteen new cases of MSD were identified at visit 2 (n = 4), visit 3 (n = 4), visit 4 (n = 3), and visit 5 (n = 8), respectively. This resulted in an incidence of MSD of 32.7/1,000 patient-years (CI

Table 1
Demographics at baseline by TSP, and by status of MSD.

Overview of demographics, stratified by population and sub-populations Variable	TSP	No MSD	MSD	p-value
Number	572	526	46	
Gender [n (%)]				p = 0.184
Female	237 (41.4)	214 (40.7)	23 (50.0)	
Male	335 (58.6)	312 (59.3)	23 (50.0)	
Age group (y) [n (%)]				p = 0.432
15 ≤ 19	99 (17.3)	84 (17.9)	5 (10.9)	
20–29	230 (40.3)	208 (39.8)	22 (47.8)	
30–39	133 (23.3)	124 (23.6)	9 (19.6)	
≥40	109 (19.1)	99 (18.9)	10 (21.7)	
Age (y) [mean (SD)]	30.6 (12.1)	30.5 (12.2)	31.4 (10.7)	p = 0.695
Insurance category [n (%)]				p = 0.136
No insurance	12 (2.1)	10 (1.9)	2 (4.3)	
Private/MMI	11 (1.9)	11 (2.1)	0 (0.0)	
RSSB (formerly RAMA)	47 (8.2)	47 (8.9)	0 (0.0)	
Social Security	502 (87.8)	458 (87.1)	44 (95.7)	
Education [n (%)]				p = 0.966
Primary	217 (37.9)	198 (37.6)	19 (41.3)	
Secondary	223 (39.0)	206 (39.2)	17 (37.0)	
Tertiary	65 (11.4)	60 (11.4)	5 (10.9)	
Without schooling	67 (11.7)	62 (11.8)	5 (10.9)	
Occupation [n (%)]				p = 0.758
Employed	162 (28.3)	150 (28.5)	12 (26.1)	
Self-employed, farmer	179 (31.3)	161 (30.6)	18 (39.1)	
Student	146 (25.5)	137 (26.0)	9 (19.6)	
Unemployed	85 (14.9)	78 (14.8)	7 (15.2)	
Marital status [n (%)]				p = 0.628
Married	151 (26.4)	136 (25.9)	15 (32.6)	
Single	416 (72.7)	385 (73.2)	31 (67.4)	
Widowed	5 (0.9)	5 (1.0)	0 (0.0)	
Comorbidities at baseline [n (%)]				
Diabetes	5 (0.9)	5 (1.0)	0 (0.0)	
Cardiovascular conditions	18 (3.1)	17 (3.2)	1 (2.2)	
HIV	16 (2.8)	15 (2.9)	1 (2.2)	
Province home address [n (%)]				p = 0.793
North	28 (4.9)	25 (4.8)	3 (6.5)	
East	140 (24.5)	127 (24.1)	13 (28.3)	
South	61 (10.7)	58 (11.0)	3 (6.5)	
West	20 (3.5)	18 (3.4)	2 (4.3)	
Kigali	323 (56.5)	298 (56.7)	25 (54.3)	

19.7 – 59.1). The mean time to MSD diagnosis was 10.6 ± 6. 0 months.

Based on Rwandan cut-offs, we observed 108 PwE with mild depression or MSD after the one-year follow-up, resulting in an incidence of any depression of 225.5/1,000-years (CI 185.0 – 27/2.2).

3.5. Prevalence of MSD or any depression

Of 572 patients, 148 (25.9%) had a positive PHQ-9 at baseline (Fig. 1). Of those patients, 81 had any depression using the HDRS score, resulting in a prevalence of 14.2% (CI 11.41 – 17.29) and 27 were diagnosed with MSD, resulting in a prevalence of 4.7% (CI 3.13 – 6.79). Of the 27 patients diagnosed at baseline with active MSD, only two reported a history of depression.

In those who were not having any signs or symptoms of active depression at baseline, we identified 21 subjects with a history of previous depression, based on medical records. Thus, a total of 102 PwE had a history of or had been diagnosed with any depression, yielding a 17.8% lifetime prevalence of any depression at baseline.

3.6. MSD treatment and outcomes

The evolution of HDRS scores over time for subjects with MSD is shown in Fig. 2a. We observed a decrease in the HDRS score from visit 1 to visit 2, with mean HDRS scores remaining stable until the study ended. Improvements in depression severity are provided in Fig. 2b. Of the 46 PwED seven were lost to follow-up (dashed lines), 20.5% still had MSD after 12 months and 35.9% presented no depression.

The mean HDRS scores for patients having > 10 months duration of any depression treatment, from 22.04 (SD 3.669) at visit 1 to 12.75 (SD 8.644) at visit 5, reflecting a clinically significant decrease of nearly 10 points ($p < 0.001$) (see Fig. 2c).

A decrease in HDRS scores is higher for PwED with CBT, AD treatment, or combination for ≥ 10 months when compared to shorter duration or no treatment (see Fig. 2d). The types of AD treatment were 52.7% SSRIs and 47.4% TCA.

We performed a follow-up one year after the study ended in subjects with MSD. Forty-two PwED could be contacted. Three were not able to participate (coma, inability to speak). The HDRS and QOLIE-10 were completed by 39 PwED. The results are summarized in Table 4.

One year after the study ended, the proportion of subjects with MSD remained unchanged compared to the study ending at 20%. One-way variance analysis (ANOVA) was significant between the three groups relative to treatment. The mean QOLIE-10 score of 2.78 ± 0.68 and the mean HDRS score was 6.

A total of five subjects with MSD at the study end had withdrawn their ASM and AD treatment.

3.7. Epilepsy treatment and outcome

At the study onset, 298 patients (52.2%) of the TSP reported no seizures since the last outpatient visit. The 28-day baseline seizure

Table 2
Epilepsy onset, time to diagnosis, and seizure frequency.

Overview of epilepsy characteristics **Study population**	**TSP**	**no MSD**	**MSD**	
Number	572	526	46	
Age at first seizure (y) [n (%)]				p = 0.9
≤ 5	43 (7.5)	39 (7.4)	4 (8.7)	
06 – 10	43 (7.5)	39 (7.4)	4 (8.7)	
11 – 15	130 (22.7)	119 (22.6)	11 (23.9)	
16 – 20	124 (21.7)	113 (21.5)	11 (23.9)	
21 – 25	85 (14.9)	81 (15.4)	4 (8.7)	
≥ 26	147 (25.7)	135 (25.7)	12 (26.1)	
Mean age first seizure (y) [mean ± SD]	20.8 ± 12.4	20.9 ± 12.5	19.4 ± 10.9	p = 0.451
Age epilepsy diagnosis (y) [n (%)]				p = 0.871
≤ 5	17 (3.0)	16 (3.0)	1 (2.2)	
06 – 10	35 (6.1)	34 (6.5)	1 (2.2)	
11 – 15	95 (16.6)	87 (16.5)	8 (17.4)	
16 – 20	143 (25.0)	130 (24.7)	13 (28.3)	
21 – 29	144 (25.2)	134 (25.5)	10 (21.7)	
30 – 39	86 (15.0)	78 (14.8)	8 (17.4)	
≥ 40	52 (9.1)	47 (8.9)	5 (10.9)	
Mean age epilepsy diagnosis (y) [mean ± SD]	23.2 ± 12.4	23.2 ± 12.5	23.7 ± 11.1	p = 0.793
Interval first seizure to diagnosis (y) [n (%)]				p = 0.1
0 – < 1	286 (50.0)	268 (51.0)	18 (39.1)	
≥ 1 – ≤ 4	177 (30.9)	163 (31.0)	14 (30.4)	
≥ 5 – ≤ 10	52 (9.1)	47 (8.9)	5 (10.9)	
≥ 11 – ≤ 15	23 (4.0)	19 (3.6)	4 (8.7)	
≥ 16	34 (5.9)	29 (5.5)	5 (10.9)	
Mean interval first seizure to diagnosis (y) [mean ± SD]	2.5 ± 7.0	2.3 ± 6.8	4.3 ± 8.7	p = 0.063
Interval first seizure to baseline visit (y) [n (%)]				p = 0.061
Missing observations	7 (1.2)	7 (1.3)	0 (0.0)	
≤ 5	190 (33.6)	181 (34.9)	9 (19.0)	
≥ 6 – ≤ 10	150 (26.5)	138 (26.6)	12 (26.1)	
≥ 11	225 (39.8)	200 (38.5)	25 (54.3)	
Mean interval first seizure to baseline visit (y) [mean ± SD]	9.8 ± 8.8	9.6 ± 8.8	12.0 ± 9.1	p = < 0.0001
28-day baseline seizure frequency [n (%)]				p = 0.009
Missing observations	1 (0.2)	0 (0.0)	1 (2.2)	
0	298 (52.2)	286 (54.4)	12 (26.7)	
1–2	209 (36.6)	185 (35.2)	24 (53.3)	
3–5	46 (8.1)	40 (7.6)	6 (13.3)	
6–29	17 (3.0)	14 (2.7)	3 (6.7)	
≥ 30	1 (0.2)	1 (0.2)	0 (0.0)	
Mean baseline 28-day seizure frequency [n (%)]	1.0 (3.1)	1.0 (3.1)	1.7 (3.3)	p = 0.1446

frequency ranged from 0 to 27.6 and decreased to 0 to 11.9 seizures at the study end ($p < 0.001$). The seizure frequency per month decreased significantly in both subpopulations with 53.7% and 30.8% seizure freedom in scr-PPS and MSD-PPS, respectively.

In the scr-CS at baseline, 49.5% of PwE were on monotherapy, 32.0% on dual ASM therapy, and 16.5% on 3 or 4 different ASM (with 1.0% without ASM). Whereas there was no change in the mean number of ASM, the mean 28-day seizure frequency decreased from 0.879 ± 2.631 towards 0.209 ± 0.836 after twelve months. A similar decrease was observed in the scr-PPS from 0.8 37 ± 2.897 to 0.201 ± 0.871. Up to 38.6% of subjects in scr-CS reported a seizure frequency decrease and 7% reported an increase at the study end.

In the MSD-CS and MSD-PPS at baseline, 26.1% of PwE were on monotherapy, 50.0% on dual therapy, 19.6% on three ASM, and 4.3% on four ASM. In MSD-CS and MSD-PPS, the mean 28-day seizure frequency decreased from 1.071 ± 2.139 to 0.377 ± 0.787 and 1.3 46 ± 2.366 to 0.405 ± 0.670, respectively. In patients with MSD, a decrease was noted in 43.6%, and 25.7% reported an increase at the study end. Seizure frequency at baseline ranged from 0 to 9.2 seizures and decreased to 0 to 4.0 seizures at the study end ($p < 0.027$).

The mean number of concomitant ASM did not change in the scr-CS whereas it increased from three to four ASM in the MSD-CS.

3.8. Patient Global Impression of Change

The evolution of PGI-C is summarized in Table 5.

The mean score at study enrolment in the two subpopulations is similar. The individual-level meaningful change improvement between the study enrolment (or first visit) and the fifth visit is highly significant in the PwE group and significant in the PwED group, although the lower end of the range improved in the latter group.

3.9. Adverse events

Only 14 subjects reported adverse events during the study period, six women and eight men. Twelve PwE and two PwED reported a total of 30 signs and symptoms (see Table 6). Eight events were considered drug-related, with one to monotherapy and two to combination therapy. ASM treatment was changed in three PwE due to adverse events. Six deaths were reported during the study, none in the MSD group. Home visits were organized to interview relatives to determine the cause of death using the WHO Verbal Autopsy questionnaire [38,39]. Based on the 581.46 study observation years a mortality rate of 10.3/1,000 year could be calculated.

Table 3
Epilepsy onset, etiology classification, and technical investigations.

Overview of epilepsy, according to the 2017 ILAE classification				
Study population	**TSP**	**no MSD**	**MSD**	
Number	572	526	46	
Epilepsy onset classification [n (%)]				p = 0.63
Focal	248 (43.4)	225 (42.5)	23 (50.0)	
Generalized	100 (17.5)	90 (17.1)	10 (21.7)	
Unknown	211 (36.9)	198 (37.6)	13 (28.3)	
Unclassified	13 (2.3)	13 (2.5)	0 (0.0)	
Etiology classification (ILAE levels) [n (%)]				p = 0.72
Genetic etiology	3 (0.5)	3 (0.6)	0 (0.0)	
Infectious etiology	29 (5.1)	28 (5.3)	1 (2.2)	
– *Bacterial meningitis*	*10 (34.5)*	*10 (35.7)*	*0 (0.0)*	
– *Cerebral malaria*	*4 (13.8)*	*4 (14.3)*	*0 (0.0)*	
– *HIV*	*2 (6.9)*	*1 (3.6)*	*1 (3.6)*	
– *Neurocysticercosis*	*3 (10.3)*	*3 (10.7)*	*0 (0.0)*	
– *Other infections*	*6 (27.6)*	*8 (28.6)*	*0 (0.0)*	
– *Viral encephalitis*	*2 (6.9)*	*2 (7.1))*	*0 (0.0)*	
Structural etiology	115 (20.1)	108 (20.5)	7 (15.2)	
– *Hippocampal sclerosis*	*1 (1.0)*	*1 (1.0)*	*0 (0.0)*	
– *Hypoxic-ischemic*	*35 (33.3)*	*33 (33.3)*	*2 (33.3)*	
– *Hypoxic-ischemic brain injury*	*31 (88.6)*	*29 (87.9)*	*2 (100)*	
– *Stroke*	*4 (11.4)*	*4 (12.1)*	*0 (0.0)*	
– *Traumatic brain injury*	*64 (61.0)*	*61 (61.6)*	*3 (50.0)*	
– *Tumors*	*5 (4.8)*	*4 (4.0)*	*1 (16.7)*	
Undetermined etiology	425 (74.3)	387 (73.6)	38 (82.6)	
Technical investigations				
MRI				
Performed	25 (4.4)	23 (4.4)	2 (4.3)	p = 0.67
– *Abnormal*	*11 (44.0)*	*11 (47.8)*	*0 (0.0)*	
– *Normal*	*5 (20.0)*	*4 (17.4)*	*1 (50.0)*	
– *Result unavailable*	*9 (36.0)*	*8 (34.8)*	*1 (50.0)*	
Not performed	547 (95.6)	503 (95.6)	44 (95.7)	
CT				
Performed	112 (19.6)	105 (20.0)	7 (15.2)	p = 0.75
– *Abnormal*	*29 (25.7)*	*27 (25.5)*	*2 (28.6)*	
– *Normal*	*41 (36.3)*	*40 (37.7)*	*1 (14.3)*	
– *Result unavailable*	*43 (38.1*	*39 (36.8)*	*4 (57.1)*	
Not performed	460 (80.4)	421 (80.0)	39 (84.8)	
EEG				
Performed	556 (97.2)	511 (97.1)	45 (97.8)	p = 0.17
– *Abnormal*	*223 (40.1)*	*197 (38.6)*	*26 (57.8)*	
– *Abnormal, result unavailable*	*90 (16.2)*	*86 (16.8)*	*4 (8.9)*	
– *Normal*	*195 (35.1)*	*183 (35.8)*	*12 (26.7)*	
– *Result unavailable*	*48 (8.6)*	*45 (8.8)*	*3 (6.7)*	
Not performed	16 (2.8)	15 (2.9)	1 (2.2)	

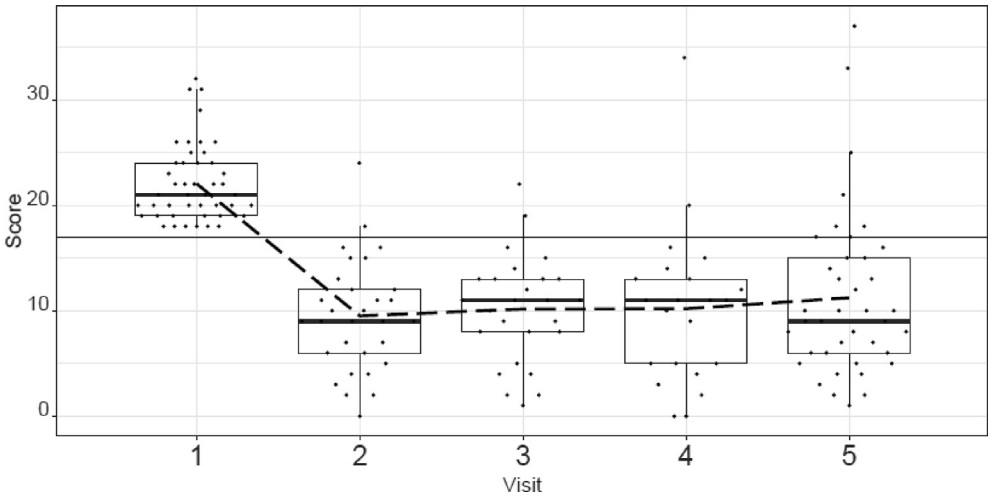

Fig. 2a. Boxplot of HDRS score for the PwED sub-population over the five visits (dots represent single subjects; horizontal line is mean value).

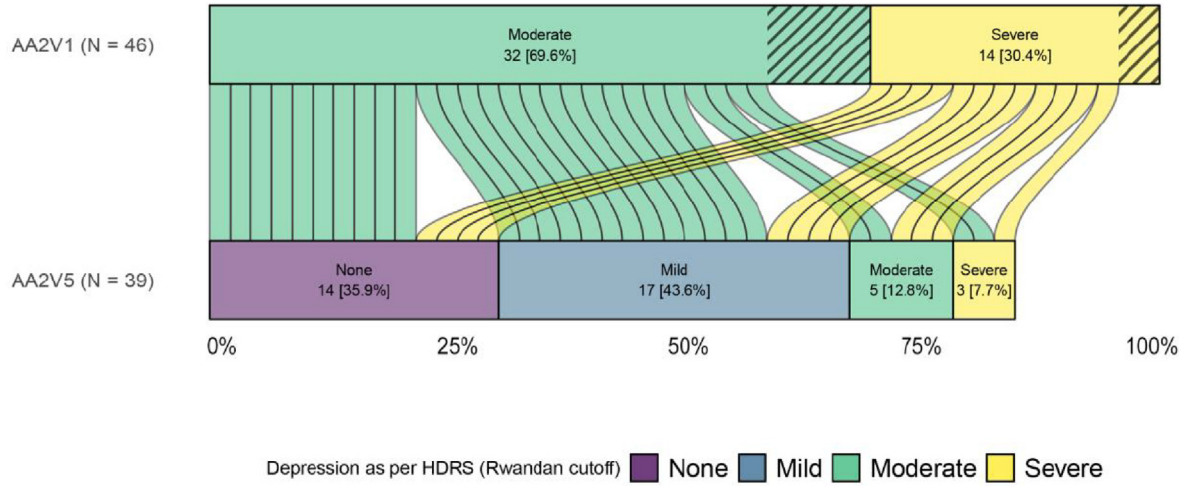

Fig. 2b. Shift table of 46 PwED with MSD at first visit and 39 PwED at fifth visit study end.

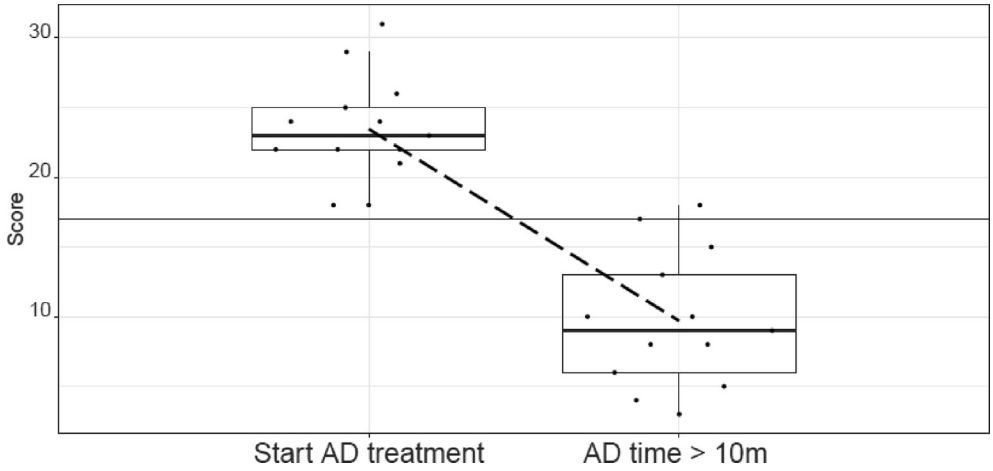

Fig. 2c. Boxplot figure of change of total HDRS score in function of antidepressant (AD) treatment with duration ≥ 10 months (dots represent single subjects; horizontal line is mean value).

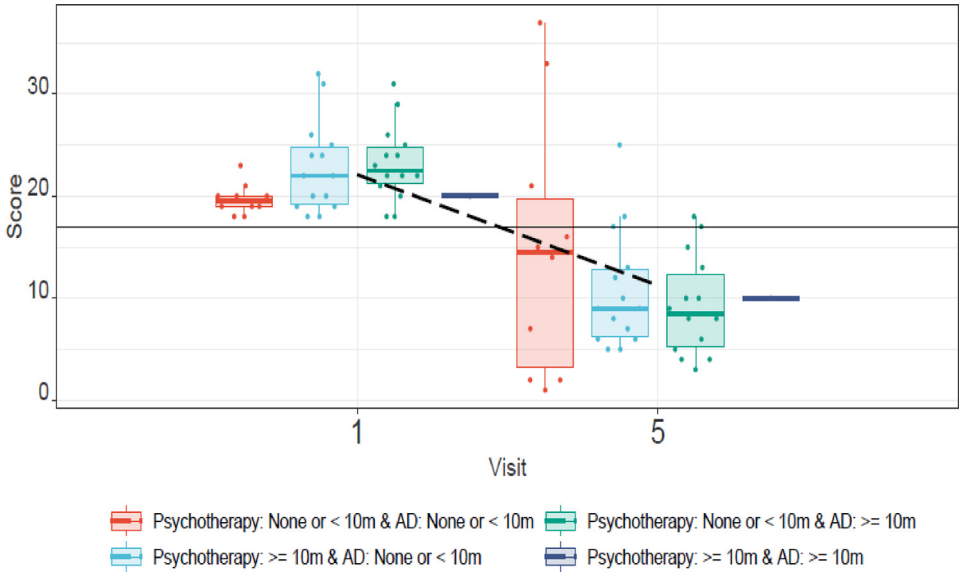

Fig. 2d. Boxplot of total HDRS score by type of depression treatment from treatment start to study end (dots represent single subjects; horizontal line is mean value).

Table 4
Results HDRS and QOLIE-10 scores and ongoing treatment by MSD, mild and no depression subgroups one year after study end.

	Depression		
	MSD	Mild	No depression
Number	8	16	15
Gender (male/female)	5/3	5/11	9/6
HDRS score			
– Mean score ± SD	23.9 ± 6.0	11.1 ± 3.2	3.9 ± 2.3
– Range	18 – 36	8 – 17	0 – 7
Relative QOLIE-10			
– Mean score ± SD	3.67 ± 0.43	3.30 ± 0.52	2.56 ± 0.50
– Range	3.00 – 4.22	2.44 – 4.11	1.78 – 3.33
Treatment			
– ASM + AD	0	4	5
– ASM alone	4	10	9
– AD alone	2	0	0
– No treatment	2	2	1
Employment (yes/no)	0/8	3/13	8/7

4. Discussion

4.1. Depression

4.1.1. Incidence of depression

During the one-year follow-up, 3.4% (19/545) PwE were newly diagnosed with MSD and one in five had any type of depression (19.8%, 108/545). To our knowledge, this is the first study to report the incidence of depression in sub-Saharan Africa in a prospective cohort of PwE.

The high number of PwE having any depression warrants regular follow-up.

Based on the eight new cases of MSD in the first six months and 11 new cases of MSD in the second six months, we recommend screening PwE for depression every six months by administering a PHQ-9 and confirming depression diagnosis with HDRS, as per protocol.

The cut-offs for screening with PHQ9 in more resource-limited settings may require adjustments given the high number of false positive screens to optimize the use of resources. Alternatively, it is also worthwhile to explore whether the clinical relevance of screening with PHQ-9 may be optimized and if additional research could address appropriate PHQ-9 scores allowing for a definite diagnosis of MSD, thereby reducing the need for a confirmatory HDRS administration and thus workload for healthcare professionals [24,25].

4.1.2. Prevalence of depression and risk factors

The prevalence of any newly diagnosed depression at baseline based on combined screening with PHQ-9 (score $\geq$ 6) and diagnosis confirmation with the HDRS tool (score $\geq$ 18), amounted to 14.2% (81/572) and 4.7% (27/572) for MSD. This is comparable to a previously documented prevalence of depressive episodes of 11.9% in a general health survey in Rwanda in 19,110 respondents [40]. The calculated lifetime prevalence of 17.8% may be a conservative estimate as mild depression may not have been detected or reported.

Our point prevalence is at the lower end of prevalence data reported in several studies, including a systematic review and a meta-analysis reporting 23.1% and 22.9%, respectively [41,42]. Individual prevalence studies in Africa report a wide range and often higher prevalence of depression in PwE. Prevalence data for southern and eastern Africa vary between 19% and 45% [3,4,6,43,44,45,46,47,48,49].

Variability of prevalence within a country or between regions can be explained by the assessment tools, different cut-off scores for diagnosis even for the same scale as well as demographic, sociocultural, and behavioral-related factors. Our conservative approach of combining a screening and diagnosis confirmation tool may be one of the reasons for lower prevalence, as other studies often used only a single screening or diagnostic method. Culturally, in Africa, depression is heavily associated with stigma. Subjects may have adjusted their responses to conceal the condition, yet this needs to be elaborated. Our study was conducted in a tertiary center, where resources for specific epilepsy awareness and education programs are available, having contributed to better coaching of PwE compared to other settings. Future studies in rural areas are needed to compare healthcare settings. Lastly, demographic differences in particular ages may have impacted our results. Depression in Rwanda and epilepsy in African, European, and South-East Asian countries have been found related to older age [40,50]. In our population, nearly 60% of subjects were below the age of 30y, perhaps contributing to a lower prevalence.

In other regions, risk factors associated with depression were female gender, older age, low education level, being unemployed, poor ASM adherence, stigma, and anxiety are considered significant factors associated with an increased risk of depression whereas marital status, age at seizure onset, economic level, and seizure control did not increase the risk of depression [50,51,52,53,54,55]. The 2018 Rwandan Mental Health survey showed significant differences towards higher prevalence in females, and low education level groups [40]. In our study, only longer epilepsy duration and a higher seizure frequency at baseline were associated with MSD, in line with a recent meta-analysis [50]. It is not unexpected that depression may be influenced by the clinical features of epilepsy, *e.g.*, seizure frequency and duration of illness. The combination of duration, intensity, and stress results in

Table 6
Reported signs and symptoms in the adverse event reports.

Sign/symptoms	number	Sign/symptoms	number
Anxiety	1	Loss of appetite	1
Asthenia	1	Memory problems	2
Behavior problems	1	Nausea	1
Constipation	1	Shaking upper extremities	1
Cutaneous rash	5	Somnolence	4
Fatigue	2	Vertigo	1
Gastric pain	2	Vomiting	1
Gingivitis	1	Weight loss/gain	2
Headache	3		

Table 5
Patient Global Impression of Change at the time of the enrolment in the study (visit 1) and at the study end visit (visit 5).

Group	$PGI\text{-}C_{study\ admission}$		$PGI\text{-}C_{fifth\ visit}$		p-value
	Number	mean score ± SD (range)	number	mean score ± SD (range)	
PwE	526	5.713 ± 1.274 *(1.000 – 7.000)*	457	6.653 ± 0.851 *(1.000 – 7.000)*	≤0.001
PwED	46	5.630 ± 1.339 *(2.000 – 7.000)*	39	6.179 ± 0.970 *(4.000 – 7.000)*	≤0.05

sleep deprivation, more pronounced anxiety severity, sadness, loneliness, and low self-esteem because of lack of control over, uncertainty, or unpredictability of the seizures; as well as lack of social coping or adaptation skills [52].

4.1.3. Depression treatment and outcomes

The combination of the CBT referral in 47.8% of PwED and of AD treatment in 56.5% of PwED resulted in a reduction of the HDRS scores at the subsequent visit. In our study, no difference was observed between different types of treatment for depression with a sustained effect after one year. Future studies are required to assess whether CBT and/or AD treatment are most effective in a Rwandan setting. Although AD treatment is still preferred for persons with MSD, a recent study suggests that CBT may be more effective and with a longer-lasting effect [56,57].

After the study ended, PwED returned to routine outpatient care, and no change in MSD rate compared to the one-year study follow-up was noted (20.5%). Of PwE with no or mild depression one year after the study ended, more than 90% were on ASM, compared to only 50% of PwE with MSD. This underlines the importance of ASM treatment as low ASM adherence may lead to poor quality of life [58].

4.2. Epilepsy

4.2.1. Seizure onset classification

In our study seizure onset was unknown in 418 (74.8%), focal-onset in 136 (23.8%), and generalized-onset in 8 (1.4%) PwE. Although all our patients had had an EEG investigation, its contribution to classifying the onset of seizures was limited. A limited number of PwE having had imaging also limited the classification of seizures by type of onset.

A comparison of the seizure classification reported in other studies in low- and middle-income countries is challenging. Our findings are different from a study in Nigeria in which generalized seizures were seen in 202 (79.2%) patients, followed by focal seizures and focal secondary generalized seizures in 50 (24.0%) [46]. Our study used the 2017 revised ILAE seizure-onset and seizure-type classification requiring differentiation between unknown-onset and generalized-onset seizures. When combining these two groups, results in both studies seem similar.

4.2.2. Etiology

In the screening population, no etiology could be confirmed in 392 (or 74.5%) PwE, and 39 (or 84.8%) in the MSD sub-population.

An underlying structural etiology could be confirmed in 104 (or 19.6%) PwE in the screening and in six (or 13.0%) of the MSD group. An infectious etiology was only reported in 29 patients (or 5.1%) of the TSP, with 28 patients (or 5.3%) in the screening sub-population and only one patient having an infectious etiology in the MSD subpopulation.

Comparison of etiologies described in other published studies in developing countries was challenging. In a recent study from India, a structural etiology was reported in 56 PwE, 33 (34.7%) in PwED, and 23 (41.8%) in PwE, whereas a genetic/unknown etiology was reported in 67 PwE, 44 (46.7%) in PwED and 23 (41.8%) in PwE, respectively [59].

4.2.3. Seizure onset and time to diagnosis

The mean age of seizure onset was 20.8 ± 12.4 years, and the mean age of epilepsy diagnosis was 23.2 ± 12.4 years. These are comparable to the mean age of seizure onset and epilepsy diagnosis reported in other studies in Africa and Europe [60,61].

The mean interval between the first seizure and diagnosis was 2.5 ± 7.0 years in the study population, with one out of two persons having more than one year delay between the first seizure and confirmed diagnosis. This interval is, however, lower than the one observed in another study in Rwanda which reported delays of 8.3 ± 11.3 years [20]. This may be a result of the provenance from Kigali of over 50% of PwE resulting in easier access to the primary health care center as well as to the tertiary referral center for diagnosis and initiation of ASM.

4.2.4. Epilepsy treatment and outcomes

Over 50% of PwE were seizure-free when enrolled in the study. Nonetheless, there was a difference in seizure freedom of 54.4% in the screening group compared to 26.7% in the MSD group. Seizure frequency between groups differed significantly and may be a risk factor for MSD in Rwanda, as observed in other individual studies [6,62]. However, these observations are not confirmed by a meta-analysis of 51 studies [50].

The results of our study showed that the seizure frequency decreased by less than 40% after the therapeutic intervention for epilepsy and/or depression. This is in line with the results of a Canadian population-based primary care cohort study where treated depression was found to be associated with worse epilepsy outcomes [63]. Further research is recommended to understand whether depression and epilepsy have a common pathogenesis. A recent review explored how early diagnosis and adequate treatment of depression in PwE contributed to better prognosis and improved quality of life [64]. In this study, AD treatment did not result in a clinically relevant seizure reduction but did increase the quality of life. In our study, we observed a significant change in PGI-C after one year in both screening and MSD subpopulations.

4.3. Study limitations

There are several limitations that should be considered when interpreting the findings of the present study.

First, the number of PwE lost to follow-up and PwE missing their scheduled visit was large, despite the concerted efforts of research assistants. The travel time to cover the distance to the tertiary referral center, the travel cost, and the time required to complete the questionnaires no doubt played a role. Nonetheless, the impact on results may have been limited as the number of positively screened subjects and those diagnosed with any depression or MSD remained stable during follow-up visits 3–5.

Second, the therapeutic management of depression may not reflect routine practice in Rwanda. Given the CARAES neuropsychiatric hospital offers CBT, which is not readily available in rural areas or primary health centers, additional research is conducted to investigate the therapeutic management of depression and its outcome in PwE in rural and primary centers.

Third, our number of subjects with MSD is lower compared to studies reported in meta-analyses [42,50]. This may have impacted our analysis of risk factors as also Bonferroni adjustments were made.

Fourth, our analysis of risk factors for depression may have been hampered by the lack of imaging, lack of seizure onset, and etiological diagnosis. On the other hand, we were able to analyze many known risk factors associated with the occurrence of depression in patients with epilepsy and only found a possible association between the duration of epilepsy and seizure-free status at baseline.

Notwithstanding these limitations, our results add to our in-depth knowledge of depression as a comorbidity in epilepsy in Rwanda.

5. Conclusion

Epilepsy is a common and widespread neurological condition in Rwanda, with a nationwide prevalence of 47/1,000 [12,20].

Depression in epilepsy is a debilitating psychiatric comorbidity with a significant socio-economic burden given its incidence of 32.7/1,000 patient-years of moderate to severe depression and 225.5/1,000-years (CI 185.0 – 27/2.2) for any type of depression. The 14,2% point prevalence was low and warrants further investigations.

In the resource-limited setting of Rwanda, the administration of the PHQ-9 and HDRS questionnaires, validated in the local Kinyarwanda language, by healthcare professionals may prove particularly useful in identifying PwE with MSD. Based on the data in our study, we recommend screening PwE every six months for the identification and follow-up of any depression in epilepsy.

The impact of the management of moderate to severe depression in PwE on depression outcomes, combined with improvements in epilepsy outcomes, is illustrated. The implementation of a standardized approach to routine screening and diagnosis for depression in PwE should be considered at primary, secondary as well as tertiary centers.

Ethics statement

The study protocol was reviewed by the Institutional Review Board of the University of Rwanda and the CARAES neuropsychiatric hospital (Approval N^{0}461/CMHS-IRB/2016). The participants provided their written informed consent to participate in this study.

We confirm we read the journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Data availability

All relevant data are within the manuscript.

CRediT authorship contribution statement

Fidele Sebera: Conceptualization, Data curation, Formal analysis, Data interpretation, Funding acquisition, Investigation, Methodology, Resources, Supervision, Validation, Writing – original draft, Writing – review & editing, Prepared manuscript. **Peter Dedeken:** Conceptualization, Data curation, Formal analysis, Data interpretation, Funding acquisition, Investigation, Methodology, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing, Prepared manuscript. **Ieme Garrez:** Formal analysis, Data interpretation, Writing – review & editing. **Josiane Umwiringirwa:** Data curation, Investigation, Project administration, Resources, Software, Writing – review & editing. **Tim Leers:** Formal analysis, Data interpretation, Validation, Visualization, Writing – review & editing. **Jean-Pierre Ndacyayisenga:** Data curation, Writing – review & editing. **Sylvestre Mutungirehe:** Data curation, Investigation, Writing – review & editing. **Arlene Ndayisenga:** Data curation, Investigation, Writing – review & editing. **Odette Niyonzima:** Data curation, Investigation, Writing – review & editing. **Georgette Umuhoza:** Data curation, Investigation, Writing – review & editing. **Dirk E. Teuwen:** Conceptualization, Data curation, Formal analysis, Data interpretation, Funding acquisition, Methodology, Project administration, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing, Prepared manuscript. **Paul A. M.J. Boon:** Conceptualization, Formal analysis, Data interpretation, Methodology, Project administration, Supervision, Writing – review & editing, Prepared manuscript. All authors reviewed and approved manuscript.

Data availability

All relevant data are within the manuscript.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: The authors declare that this study received funding from the UCB Societal Responsibility Fund. The funder was not involved in the study design, data collection, analysis, interpretation, the writing of the manuscript, or the decision to submit it for publication. The study was conducted by the principal investigator, FS, within the framework of his Ph.D. research at the Department of Neurology, Ghent University (Ghent, Belgium). DET was a UCB employee at the time of study conceptualization, conduct, data cleaning, and analysis and has now retired. PD received consultancy fees from UCB Pharma, Merck, and Novartis. PAMJB received speaker and consultancy fees from UCB Pharma, LivaNova, and Medtronic, and research grants from the same companies through his institution. Other authors have no competing interests.

Acknowledgements

The authors appreciate the funding from the UCB Societal Responsibility Fund. The authors also acknowledge and thank wholeheartedly the many study investigators and participants of this study. We truly appreciate the patience of study participants for their valuable information, cooperation, and participation and for their valuable time when completing the PHQ-9 and HDRS questionnaires. Without their generosity, this study would not have been feasible.

References

[1] Tellez-Zenteno JF, Patten SB, Jetté N, Williams J, Wiebe S. Psychiatric comorbidity in epilepsy: a population-based analysis. Epilepsia 2007;48(12):2336–44.
[2] Kanner AM, Schachter SC, Barry JJ, Hesdorffer DC, Mula M, Trimble M et al. Depression and epilepsy, pain and psychogenic non-epileptic seizures: clinical and therapeutic perspectives. Epilepsy Behav 2012;24(2):169–81. Erratum in: Epilepsy Behav 2014;32:171. LaFrance, W Curt Jr [added]; Hersdorffer, Dale C [corrected to Hesdorffer, Dale C].
[3] Bifftu BB, Dachew BA, Tiruneh BT, Birhan TN. Depression among people with epilepsy in Northwest Ethiopia: a cross-sectional institution-based study. BMC Res Notes 2015;8:585.
[4] Chaka A, Awoke T, Yohannis Z, Ayano G, Tareke M, Abate A, et al. Determinants of depression among people with epilepsy in Central Ethiopia. Ann Gen Psychiatry 2018;17:27.
[5] Sylla M, Vogel AC, Bah AK, Tassiou NR, Barry SD, Djibo BA, et al. Prevalence, severity, and associations of depression in people with epilepsy in Guinea: A single-center study. Epilepsy Behav 2020;113:107475.
[6] Addis B, Wolde M, Minyihun A, Aschalew AY. Prevalence of depression and associated factors among patients with epilepsy at the University of Gondar Comprehensive Specialized Hospital, Northwest Ethiopia, 2019. PLoS One 2021;16(10):e0257942.
[7] Gandy M, Sharpe L, Perry KN, Miller L, Thayer Z, Boserio J, et al. The psychosocial correlates of depressive disorders and suicide risk in people with epilepsy. J Psychosom Res 2013;74(3):227–32.
[8] Johnson EK, Jones JE, Seidenberg M, Hermann BP. The relative impact of anxiety, depression, and clinical seizure features on health-related quality of life in epilepsy. Epilepsia 2004;45(5):544–50.
[9] Petrovski S, Szoeke CE, Jones NC, Salzberg MR, Sheffield LJ, Huggins RM, et al. Neuropsychiatric symptomatology predicts seizure recurrence in newly treated patients. Neurology 2010;75(11):1015–21.

[10] Siarava E, Hyphantis T, Katsanos AH, Pelidou SH, Kyritsis AP, Markoula S. Depression and quality of life in patients with epilepsy in Northwest Greece. Seizure 2019;66:93–8.
[11] Leaffer EB, Hesdorffer DC, Begley C. Psychosocial and sociodemographic associates of felt stigma in epilepsy. Epilepsy Behav 2014;37(8):104–9.
[12] Sebera F, Munyandamutsa N, Teuwen DE, Ndiaye IP, Diop AG, Tofighy A, et al. Addressing the treatment gap and societal impact of epilepsy in Rwanda-Results of a survey conducted in 2005 and subsequent actions. Epilepsy Behav 2015;46:126–32.
[13] Mesafint G, Shumet S, Habtamu Y, Fanta T, Molla G. Quality of Life and Associated Factors Among Patients with Epilepsy Attending Outpatient Department of Saint Amanuel Mental Specialized Hospital, Addis Ababa, Ethiopia, 2019. J Multidiscip Healthc 2020;13:2021–30.
[14] Molla A, Mekuriaw B, Habtamu E, Mareg M. Knowledge and attitude towards epilepsy among rural residents in southern Ethiopia: a cross-sectional study. BMC Public Health 2021;21(1):420.
[15] Kaddumukasa M, Smith PJ, Kaddumukasa MN, Kajumba M, Almojuela A, Bobholz S, et al. Epilepsy beliefs and misconceptions among patient and community samples in Uganda. Epilepsy Behav 2021;114(Pt B):107300.
[16] Yue L, Yu PM, Zhao DH, Wu DY, Zhu GX, Wu XY, et al. Determinants of quality of life in people with epilepsy and their gender differences. Epilepsy Behav 2011;22(4):692–6.
[17] Anbesaw T, Fekadu B. Depression and associated factors among older adults in Bahir Dar city administration, Northwest Ethiopia, 2020: Cross-sectional study. PLoS One 2022;17(8):e0273345.
[18] Mlaki DA, Asmal L, Paddick SM, Gray WK, Dotchin C, Walker R. Prevalence and associated factors of depression among older adults in rural Tanzania. Int J Geriatr Psychiatry 2021;36(10):1559–66.
[19] Munyandamutsa N, Mahoro Nkubamugisha P, Gex-Fabry M, Eytan A. Mental and physical health in Rwanda 14 years after the genocide. Soc Psychiatry Psychiatr Epidemiol 2012;47(11):1753–61.
[20] Dedeken P, Sebera F, Mutungirehe S, Garrez I, Umwiringirwa J, Van Steenkiste F, et al. High prevalence of epilepsy in Northern Rwanda: Exploring gender differences. Brain Behav 2021;11(11):e2377.
[21] Kanner AM, Barry JJ. Is the Psychopathology of Epilepsy Different from That of Nonepileptic Patients? Epilepsy Behav 2001;2(3):170–86.
[22] Sizebera V, Nyirasafari D. Incidence of depression in epilepsy patients. Rwanda J, Series F 2013;1(1):67–77.
[23] Sebera F, Dedeken P, Kayirangwa J, Umwiringirwa J, Kajeneza D, Dos Reis NA, et al. Effectiveness of community health workers on identification and mobilization of persons living with epilepsy in rural Rwanda using a validated screening tool. Hum Resour Health 2022;20(1):10.
[24] Sebera F, Vissoci JRN, Umwiringirwa J, Teuwen DE, Boon PE, Dedeken P. Validity, reliability and cut-offs of the Patient Health Questionnaire-9 as a screening tool for depression among patients living with epilepsy in Rwanda. PLoS One 2020;15(6):e0234095.
[25] Dedeken P, Vissoci JRN, Sebera F, Boon PAJM, Rutembesa E, Teuwen DE. Validity, Reliability, and Diagnostic Cut-off of the Kinyarwandan Version of the Hamilton Depression Rating Scale in Rwanda. Front Psychol 2020;11:1343.
[26] Kroenke K, Spitzer RL, Williams JB, Löwe B. The Patient Health Questionnaire Somatic, Anxiety, and Depressive Symptom Scales: a systematic review. Gen Hosp Psychiatry 2010;32(4):345–59.
[27] Williams JB. Standardizing the Hamilton Depression Rating Scale: past, present, and future. Eur Arch Psychiatry Clin Neurosci 2001;251(Suppl 2):II6-12.
[28] Zimmerman M, Martinez JH, Friedman M, Boerescu DA, Attiullah N, Toba C. How can we use depression severity to guide treatment selection when measures of depression categorize patients differently? J Clin Psychiatry 2012;73(10):1287–91.
[29] Fisher RS, Cross JH, French JA, Higurashi N, Hirsch E, Jansen FE, et al. Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology. Epilepsia 2017;58(4):522–30.
[30] Elger CE, Johnston SA, Hoppe C. Diagnosing and treating depression in epilepsy. Seizure 2017;44:184–93.
[31] Cramer JA, Perrine K, Devinsky O, Meador K. A brief questionnaire to screen for quality of life in epilepsy: the QOLIE-10. Epilepsia 1996;37:577–82.
[32] QOLIE 10. https://www.epilepsy.com/sites/core/files/atoms/files/QOLIE-10-P.pdf [accessed January 24, 2021].
[33] Fisher RS, Cross JH, D'Souza C, French JA, Haut SR, Higurashi N, et al. Instruction manual for the ILAE 2017 operational classification of seizure types. Epilepsia 2017;58(4):531–42.
[34] World Health Organization. WHODrug Global. https://who-umc.org/whodrug [accessed January 24, 2021].
[35] Forkmann T, Scherer A, Boecker M, Pawelzik M, Jostes R, Gauggel S. The Clinical Global Impression Scale and the influence of patient or staff perspective on outcome. BMC Psychiatry 2011;11:83.
[36] Lepping P, Whittington R, Sambhi RS, Lane S, Poole R, Leucht S, et al. Clinical relevance of findings in trials of CBT for depression. Eur Psychiatry 2017;45(9):207–11.
[37] Rosseel Y. lavaan: An R package for structural equation modeling. J Statistical Software 2012:48(2):1–36. Retrieved from http://www.jstatsoft.org/v48/i02/.
[38] World Health Organization. The 2016 WHO Verbal Autopsy Instrument, http://www.who.int/healthinfo/statistics/verbalautopsystandards/en/ [accessed June 1, 2017].
[39] Sebera F, Uwacu BH, Nsanzabaganwa W, Umwiringirwa J, Dedeken P, Teuwen DE, et al. Mortality of all causes and Sudden Unexplained Death in Epilepsy (SUDEP) in a cohort of 235 persons living with epilepsy in Rwanda using WHO Verbal Autopsy Questionnaire. Epilepsy Behav Rep 2020;14:100383.
[40] Kayiteshonga Y, Sezibera V, Mugabo L, Iyamuremye JD. Prevalence of mental disorders, associated co-morbidities, health care knowledge and service utilization in Rwanda - towards a blueprint for promoting mental health care services in low- and middle-income countries? BMC Public Health 2022;22(1):1858.
[41] Fiest KM, Dykeman J, Patten SB, Wiebe S, Kaplan GG, Maxwell CJ, et al. Depression in epilepsy: a systematic review and meta-analysis. Neurology 2013;80:590–9.
[42] Scott AJ, Sharpe L, Hunt C, Gandy M. Anxiety and depressive disorders in people with epilepsy: A meta-analysis. Epilepsia 2017;58(6):973–82.
[43] Tunde-Ayinmode MF, Abiodun OA, Ajiboye PO, Buhari OI, Sanya EO. Prevalence and clinical implications of psychopathology in adults with epilepsy seen in an outpatient clinic in Nigeria. Gen Hosp Psychiatry 2014;36(6):703–8.
[44] Tegegne MT, Mossie TB, Awoke AA, Assaye AM, Gebrie BT, Eshetu DA. Depression and anxiety disorder among epileptic people at Amanuel Specialized Mental Hospital, Addis Ababa. Ethiopia BMC Psychiatry 2015;15:210.
[45] Fela-Thomas A, Akinhanmi A, Esan O. Prevalence and correlates of major depressive disorder (MDD) among adolescent patients with epilepsy attending a Nigerian neuropsychiatric hospital. Epilepsy Behav 2016;54:58–64.
[46] Owolabi SD, Owolabi LF, Udofia O, Sale S. Depression in patients with epilepsy in Northwestern Nigeria: Prevalence and clinical correlates. Ann Afr Med 2016;15(4):179–84.
[47] Dessie G, Mulugeta H, Leshargie CT, Wagnew F, Burrowes S. Depression among epileptic patients and its association with drug therapy in sub-Saharan Africa: A systematic review and meta-analysis. PLoS One 2019;14(3):e0202613.
[48] Nigussie K, Lemma A, Sertsu A, Asfaw H, Kerebih H, Abdeta T. Depression, anxiety and associated factors among people with epilepsy and attending outpatient treatment at primary public hospitals in northwest Ethiopia: A multicenter cross-sectional study. PLoS One 2021;16(8):e0256236.
[49] Tsigebrhan R, Fekadu A, Medhin G, Newton CR, Prince MJ, Hanlon C. Performance of primary health care workers in detection of mental disorders comorbid with epilepsy in rural Ethiopia. BMC Fam Pract 2021;22(1):204.
[50] Yang Y, Yang M, Shi Q, Wang T, Jiang M. Risk factors for depression in patients with epilepsy: A meta-analysis. Epilepsy Behav 2020;106:107030.
[51] Harden CL. The co-morbidity of depression and epilepsy: epidemiology, etiology, and treatment. Neurology 2002;59(6 Suppl 4):S48–55.
[52] Błaszczyk B, Czuczwar SJ. Epilepsy coexisting with depression. Pharmacol Rep 2016;68(5):1084–92.
[53] Keezer MR, Sisodiya SM, Sander JW. Comorbidities of epilepsy: current concepts and future perspectives. Lancet Neurol 2016 Jan;15(1):106–15. Erratum in: Lancet Neurol 2016;15(1):28.
[54] Thijs RD, Surges R, O'Brien TJ, Sander JW. Epilepsy in adults. Lancet 2019;393(10172):689–701.
[55] Alhashimi R, Thoota S, Ashok T, Palyam V, Azam AT, Odeyinka O, et al. Comorbidity of Epilepsy and Depression: Associated Pathophysiology and Management. Cureus 2022;14(1):e21527.
[56] Mula M, Kanner AM, Jetté N, Sander JW. Psychiatric Comorbidities in People With Epilepsy. Neurol Clin Pract 2021;11(2):e112–20.
[57] Hollon SD, DeRubeis RJ, Andrews PW, Thomson Jr JA. Cognitive therapy in the treatment and prevention of depression: a fifty-year retrospective with an evolutionary coda. Cogn Ther Res 2021;45:402–17.
[58] Minwuyelet F, Mulugeta H, Tsegaye D, Lake B, Getie A, Tsegaye B, et al. Quality of life and associated factors among patients with epilepsy at specialized hospitals, Northwest Ethiopia; 2019. PLoS One 2022;17(1):e0262814.
[59] Chandrasekharan SC, Menon V, Wadwekar V, Nair PP. High Frequency of Depressive Symptoms among Adults with Epilepsy: Results from a Hospital-based Study. J Neurosci Rural Pract 2017;8(Suppl 1):S13–S19.
[60] Wiglusz MS, Landowski J, Cubała WJ. Prevalence of anxiety disorders in epilepsy. Epilepsy Behav 2018;79(2):1–3.
[61] Yaria JO, Ogunniyi A. Calibration of the Epilepsy Questionnaire for Use in a Low-Resource Setting. J Environ Public Health 2020:5193189.
[62] Feldman L, Lapin B, Busch RM, Bautista JF. Evaluating subjective cognitive impairment in the adult epilepsy clinic: Effects of depression, number of antiepileptic medications, and seizure frequency. Epilepsy Behav 2018;81:18–24.
[63] Josephson CB, Lowerison M, Vallerand I, Sajobi TT, Patten S, Jetté N, et al. Association of depression and treated depression with epilepsy and seizure outcomes: a multicohort analysis. JAMA Neurol 2017;74(5):533–9.
[64] Borgmann M, Holtkamp M, Adli M, Behr J. Depression und Epilepsie: Zwei Krankheitsbilder mit gemeinsamen Ursachen? [Depression and epilepsy: Two clinical pictures with common causes?]. Nervenarzt 2016;87(7):724–30.