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RESEARCH ARTICLE

Gender, Psychiatric and Cognitive Status Related to Experiential Auras in Patients with Temporal Lobe Epilepsy

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ABSTRACT

Objective: To determine whether the experiential auras in patients with temporal lobe epilepsy (TLE) are related to gender, psychiatric comorbidity, material-specific memory impairment, lateralization by video-EEG and structural neuroimaging abnormalities.

Material and methods: Retrospective review (1998-2015) of clinical charts and video-EEG of patients with TLE and experiential auras followed at the JM Ramos Mejía and El Cruce Hospitals

Results: We included 35 patients, 51.4% were male, mean age 35 years, mean epilepsy duration 20.3 years. Laterality of the epileptogenic zone was right (57.1%) and left (37.1%) temporal. An epileptogenic lesion was detected in most of cases and hippocampal sclerosis was the most common finding. Seventy-four percent of patients underwent epilepsy surgery (Engel I-II: 65.4%).

The most frequent neuropsychological finding was visual memory deficit, and most patients had executive dysfunction. Almost half patients had a psychiatric comorbidity.

Déjà vu was the most frequent experiential aura (60%), followed by *jamais vu* (20%), strangeness (20%), depersonalization (14.3%), dreaminess (11.4%), autobiographical memory recall (8.6%) and time perception alteration (5.7%).

Most patients (62.9%) had a single experiential aura (*déjà vu* 54.5%, *jamais vu* 18.2%, strangeness 13.6%, depersonalization 9.1%, prescience 4.5%) associated with non-experiential auras in the majority of cases (81%).

Conclusion: Most of patients presented a single experiential aura, most frequently *déjà vu*, associated with non-experiential auras, mainly fear. A right temporal lobe seizure focus was the most frequent, including for patients with *déjà vu*. In relation to gender, *déjà vu* was more common in male patients. A high prevalence of psychiatric comorbidity was observed and despite of the reduced number of cases, the 3 patients with psychosis presented *déjà vu*. Most of patients presented visual memory deficit associated with executive dysfunction.

Introduction

Ictal symptomatology provides important lateralizing and localizing information in the presurgical assessment, mainly in patients with Temporal Lobe Epilepsy (TLE) [1]. Among the different auras of patients with TLE [2,3] experiential auras are the most intriguing and complex psychic phenomena reported as similar to a real-life experience with a combination of perceptual, mnemonic and affective elements [4,5]. Both temporal neocortical and limbic structures have been considered the substrates related with these experiential auras [4-7].

Different hypothesis have been proposed to explain the experiential auras, including the effect of the epileptic discharges with secondary release of inhibition of neocortical structures, or the activation of physiological mechanisms represented in temporal cortex, and synchronization and functional activation of widespread cortical networks [4,5,8-10].

Phylogenetic and ontogenetic backgrounds may play a role in the type and characteristics of the phenomena experienced by patients during seizures [11]. The same Epileptogenic Zone (EZ) may generate different cognitive and affective manifestations between patients and even in the same patient.

We investigated if gender, status of material-specific memory and psychiatric comorbidities affect the type and characteristics of the experiential auras in patients with TLE. Additionally, we analyzed the relationship between the characteristics of auras and laterality of EZ and neuroimaging findings in order to improve the understanding of the experiential auras.

Materials and Methods

We performed a retrospective review from 1998 to 2015 of the clinical charts and video-EEG studies of patients with diagnosis of TLE who referred experiential auras during the admission interview, which is based on a standardized questionnaire. All patients were assisted by the same team at the Epilepsy Units of two referral centers (JM Ramos Mejía and El Cruce Hospitals). The EZ was clearly localized and most of them lateralized, defined on the basis of ictal video-EEG recordings, brain MRI and neuropsychological testing.

Inclusion criteria were as follows: patients with 17 years of age or older with diagnosis of TLE who presented routinely experiential auras as part of their seizure semiology. All patients must have video-EEG monitoring, brain MRI with epilepsy protocol and neuropsychological and psychiatric evaluations. Patients with a diagnosis of Psychogenic Non-Epileptic Seizures (PNES) or those who did not accept to participate in this study were excluded. All patients signed a written informed consent to participate.

Semiological and electrophysiological ictal changes allowed us to localize and lateralize the seizure origin. Long-term scalp EEG recordings (5 days on average) were obtained from all patients during inpatient video-EEG monitoring using digital equipment (*Cervello* and *Stellate Harmonie* systems) at a 200-Hz sample rate, using 20 or 32 electrodes according to the 10-20 International System. In some patients, additional temporal electrodes of the 10-10 system were used.

We reviewed the ictal clinical semiology from the videos of the seizures registered during the monitoring. For the purpose of this study, two qualified readers trained and experienced in video-EEG interpretation reviewed all video-EEG recordings. Each seizure was reviewed 3 to 4 times to identify every symptom. Seizure onset was defined as the first electrographic change in the background or any clinical sign indicating seizure onset, or when the patient indicated either verbally or gesturally that he or she was experiencing an aura. Seizure offset was identified when rhythmic activity finished, EEG showed a diffuse attenuation or slowing, or when more than 90% of the EEG channels were slow and the patient's stereotyped behavior ended, replaced epileptiform activity, and/or they began to interact with his or her surroundings differently than during the seizure.

We applied a systematic patient assessment during the ictal and postictal period performed by a qualified staff member (i.e., technician, nurse, or physician). During the ictal and postictal period, the patients were evaluated with a standardized questionnaire and an evaluation protocol that incorporates patients' subjective experiences before and after they watch a video-EEG

of their own seizure [12]. Patients were instructed to promptly advise the staff whenever they experienced an aura. Postictally, after patients had regained consciousness and were able to follow commands, they were again interviewed to see if they recalled having an aura prior to the seizure and could describe it in detail, the subjective sensation or feeling, and if they had any memory of what had occurred during the seizure.

For the analysis, we included the aura spontaneously reported by patients during video-EEG recordings, the data collected with the postictal guided questionnaire, and the aura referred by the patients during the admission interview.

Post-seizure language deficit was determined by asking the patient to name different objects.

The neuropsychological protocol used in this study was the same that was previously published by our group [13,14].

Handedness: Edinburgh Questionnaire (EHQ).

Intelligence quotient (IQ).

Attention: Forward and Backward Digit Span, WAIS, and Trail Making Test part A.

Verbal memory: Rey Auditory Verbal Learning Test (RAVLT) and List Learning Test.

Visual memory: Rey-Osterrieth Complex Figure Test (RCFT).

Language: Boston Naming Test (BNT), Token Test (TT).

Executive function: Wisconsin Card Sorting Test (WCST), Trail Making Test Part B. Verbal Fluency (FAS).

The results of the neuropsychological evaluation were compared with our control population according to age, sex, and formal education. For each patient the raw values of each data of the cognitive tests were normalized to a Z score. Patients were classified as "normal" when all the tests presented values superior to a Z score −2 (two standard deviation below normal values), or "abnormal" (deficit) when some of the results were inferior to a Z score −2.

Patients included in this study were assigned to standardized psychiatric interviews. Extensive historical and psychiatric data, together with information about social background, were obtained from each patient, supplemented by information from family or friends and medical records. The psychiatric assessment was performed by the same specialist trained in psychiatry using DSM IV instruments: SCID I Spanish Clinical Version for Axis I for psychiatric disorders, and SCID II to determine the presence of personality disorders [15,16].

High-resolution brain MRI on 1.5 or 3.0 Tesla equipment was performed using optimized imaging of the hippocampus and temporal lobe structures: sagittal T1-weighted, inversion-recovery (IR), fluid attenuated inversion-recovery (FLAIR) and volumetric acquisition, fast field echo 3D, perpendicular to the long axis of the hippocampus; and T2-weighted axial, parallel to the long axis of the hippocampus.

Of a total of 816 patients, 55% (449 patients) had a diagnosis of temporal lobe epilepsy. Of those patients, 35 patients (7.8%) met the inclusion criteria. The analyzed variables included: type of experiential and non-experiential auras, demographic characteristics (age, gender, handedness, educational level), past medical history, family history of epilepsy, psychiatric comorbidities, epilepsy duration, lateralization of EZ, material-specific memory deficits (verbal and/or visual), brain MRI results, treatment and postsurgical outcome was taken into account for those patients who underwent surgery.

Statistical Analysis

The qualitative variables were analyzed based on the distribution of frequencies and percentages. For quantitative variables, average, standard deviation, median, minimum and maximum were calculated. To compare the relationship between qualitative variables, *Chi square* independence test was applied. For comparisons of dichotomous variables (tables of 2 x 2) and in case of finding frequencies less than 5, *Fisher's Exact Test* was used. *Bonferroni* correction was used to compare proportions between groups, and the 95% Confidence Intervals were calculated for the difference of proportions. In all cases the applied statistical tests are for independent samples. A significance level of less

Table 1: Aura features according to gender, presence of psychiatric comorbidities, status of material-specific memory and MRI findings (N=35).

Type of experiential aura n patients (%)	Gender	TLE lateralization	Neuropsychological evaluation: memory deficits	Psychiatric comorbidities (4 patients with ≥ 2 comorbidities)	MRI findings	
Déjà vu 21 (60%)	F 7 (33.3%) M 14 (66.6%)	12 R (57%) 8 L (38%) 1 NLT (5%)	15 (71.4%) -6 verbal, 7 visual, 2 both-	9 (42.8%) - 7 depression, 3 psychosis, 1 anxiety, 1 substance abuse-	18 abnormal (85.7%) 3 normal (14.3%)	15 underwent surgery - 8 Engel I-II* - 7 Engel III-IV
Déjà vu **(as the only type of aura)** 4 (11.4%)	M 4 (100%)	3 R (75%) 1 L (25%)	2 (50%) - 1 visual, 1 verbal -	1 (25%) - 1 depression and substance abuse	3 abnormal (75%), 1 normal (25%)	-1 Engel I* -2 Engel III -1 no surgery,
Jamais vu 7 (20%)	F 5 (71.4%) M 2 (29.6%)	3 R (42.8%), 4 L (57.2%)	6 (85.7%) -3 verbal, 2 visual, 1 both-	4 (57.1%) - 3 depression, 2 anxiety-	7 abnormal (100%)	7 underwent surgery -Engel I-II*
Strangeness 7 (20%)	F 4 (57.2%) M 3 (42.8%)	4 R (57.2%) 3 L (42.8%)	5 (71.4%) -2 verbal, 2 visual, 1 both-	3 (42.9%) - 3 anxiety, 1 depression-	6 abnormal (85.7%), 1 normal (14.3%)	5 underwent surgery -Engel I-II*
Depersonalization 5 (14,3%)	F 4 (80%) M 1 (20%)	3 R (60%) 1 L (20%) 1 NLT (20%)	2 (40%) -2 visual-	2 (40%) - 2 depression-	3 abnormal (60%), 2 normal (40%)	3 underwent surgery -1 Engel I* -2 Engel III-IV
Dreaminess 4 (11,4%)	F 3 (75%) M 1 (25%)	1 R (25%) 3 L (75%)	2 (50%) -1 visual, 1 both-	2 (50%) - 2 depression-	3 abnormal (75%), 1 normal (25%)	2 underwent surgery -Engel I*
Autobiographical memory recall 3 (8,6%)	M 3 (100%)	2 R (66.6%) 1 L (33.3%)	2 (66.6%) -1 visual, 1 both-	1 (33.3%) - 1 depression-	2 abnormal (66.6%), 1 normal (33.4%)	1 underwent surgery -Engel I*
Altered time perception 2 (5,7%)	F 1 (50%) M 1 (50%)	1 R (50%) 1 L (50%)	2 (100%) -2 visual-	None	1 abnormal (50%), 1 normal (50%)	No one underwent surgery
Associated non-experiential auras 28 (81%)						

R: right L: left NLT: non-lateralized F: female patients M: male patients
*The aura disappeared in all patients with Engel I ($p<0.001$)
Note: it is not necessary to use colors for this table.

than 5% was used to reject the null hypothesis. *SPSS 25.0* for Windows was used for statistical analysis.

Results

1. Patient data

We included 35 patients, 51.4% were male with a mean age of 35 years (17-69), with primary (12 p, 34.2%) and secondary (10 p, 37.1%) educational level in most of cases. The past medical history was remarkable for febrile seizures (5 p, 14.2%), neuroinfection (4 p, 11.4%), traumatic brain injury (4 p, 11.4%), neonatal hypoxia (3 p, 8.5%) and developmental delay (3 p, 8.5%). A family history of epilepsy was found in 9 p (25.7%). The mean age of epilepsy onset was 11.5 years (0-27 years) and the mean epilepsy duration was 20.3 years (3-50 years).

1.1. Electrophysiological data: A right TLE EZ lateralization was slightly more frequent (20 p, 57.1%; CI95%: 40.7-72.4); compared to 13 p (37.1% CI95%: 22.7-53.7) with left TLE. In 2 p (5.7%) the lateralization was undetermined (Table 1).

Twenty-two patients (62.9%) referred an aura during the video-EEG, and seven of them (31.8%) reported the experiential aura. In 22 patients (62.9%) the antiepileptic drugs (AEDs) were reduced during the video-EEG.

1.2. Neuropsychological evaluation: *Handedness:* 34 patients (97.1%) were right-handed.

Intelligence Quotient (IQ). The average of the total IQ score was 82 (range >69- 105) and mean verbal and non-verbal IQ were 82 and 83, respectively. Six patients presented an IQ≤70 (range 54-70).

Memory: Within memory evaluation, we observed visual recall deficits in 11 p (31.4%), verbal recall deficits in 8 p (22.9%), both types of memory impairment in six patients (17.1%) and normal performance in ten cases (28.6%). The recognition task showed frequent deficits in both memory types (45% and 31.4% of cases with deficient performance in visual and verbal recognition tasks respectively).

Executive function: 22 p (62.8%) had executive dysfunction.

No significant differences were found between subtypes of experiential auras.

1.3. Psychiatric evaluation: Psychiatric comorbidity was present in 16 patients (45.7%, mean 2 comorbidities/patient) being depression the most common (11 p, 68.8%) followed by anxiety (4 p, 25%) and psychosis (3 p, 18.8%). A personality disorder was present in one patient (2.9%), and 11 patients (31.4%) presented a personality trait. Seven patients (43.8%) were currently medicated with psychotropic drugs.

1.4. Neuroimaging data: Brain MRI was abnormal in 30 patients (85.7%) including: hippocampalsclerosis (19 p, 63.3%), tumor (4 p, 13.3%, low grade tumors -100%-), cavernoma (2 p, 6.7%) and other lesions (5 p, 16.7%). All the lesions were located in the temporal lobe, mainly affecting the mesial temporal structures. The lesion was unilateral in 28 p (93.3%) (right 60%, left 33.3%) and bilateral in 2 p (6.6%).

Except for patients with hippocampal sclerosis, the number of patients with other lesions was too small, thus preventing further analysis based on the type of lesion. In the subgroup of patients with hippocampal sclerosis, we did not find any difference in terms of neuropsychological performance based on the location of the lesion or if there was compromise of the temporal pole.

1.5. Classification and characterization of auras: Four patients (11.4%) referred only one type of aura -*déjà vu*-: 3 p right TLE and 1 p left TLE.

Thirty-one patients (88.6%) presented multiple auras: 28 patients presented non-experiential auras and at least one experiential, and 3 patients more than 1 experiential aura. The laterality of the EZ was: 17 p right (54.8%), 12 p left (38.7%) TLE, and 2 p (6.5%) undetermined.

Most patients (22 p, 62.9%, 10 female and 12 male) had a single experiential aura (*déjà vu* 12 p-54.5%, *jamais vu* 4 p-18.2%, strangeness 3 p-13.6%, depersonalization 2 p-9.1%, prescience 1 p-4.5%), associated with non-experiential auras in the majority of cases (18 p, 81.8%). Almost all male patients with a

single experiential aura referred *déjà vu* (10 p, 83%, p=0.05).

On the other hand, three experiential auras were always associated with other experiential auras: dreaminess, autobiographical memory recall and altered time perception (p=0.05).

No differences were found in terms of frequency of presentation when an aura was referred as a single experiential aura or associated with other experiential auras.

Déjà vu was present in 21 p (60%): as the only type of aura in 4 p (19%); associated with other experiential auras in 9 p (42%), mainly strangeness; and with non-experiential auras in 8 p (38%), mainly epigastric sensation, fear and unexplainable sensation.

In relation to gender, *déjà* vu was more common in male patients (14 p, 77.8%, p=0.06), and even in 4 of them was present as the only type of aura. In female patients, *déjà vu* was also the most frequent experiential aura, and its presence was significantly associated with other experiential auras (71.4%, p=0.05) compared to male patients.

Concerning EZ lateralization, the presence of *déjà vu was* significantly associated with a right TLE (12 p, 57%, p=0.05) (Table 1).

On the other hand, most patients (25 p, 71.4%) presented memory deficit: visual 11p (45%), verbal 8p (32%), and both memories 6p (24%). Analyzing the neuropsychological findings, there was no association between memory impairment and type of experiential aura -including *déjà vu*- or presence of single and multiple experiential auras.

In relation to psychiatric comorbidities, 16 patients (45.7%) had at least one comorbidity. Considering the sample in each subgroup of patients with comorbidities, we could not perform a conclusive statistical analysis. In patients with psychosis, *déjà vu* was the only described aura. *Déjà vu* was also the predominated aura in patients with depression, compared to the feeling of strangeness, frequently observed in patients with anxiety (Table 1).

Twenty-eight patients presented concomitant non-experiential auras. The most frequent was fear (13 p, 46.4%), and in the majority of cases was associated to other non-experiential auras (61.5%). Other non-experiential auras were epigastric sensation (8 p, 28.6%), followed by palpitations (3 p, 10.7%) and thoracic sensation -heat/oppression- (3 p, 10.7%). Nine patients (31.1%) reported an unexplainable sensation. We analyzed the subgroup of patients who experienced fear, and no association was found with any type of experiential aura, gender or lateralization of the EZ.

1.6. Treatment: Twenty six patients underwent epilepsy surgery (74.2%). In patients with an Engel class I (follow up: 1-7 years), the aura disappeared in all the subjects (p<0.001) (Table 1).

Discussion

Experiential auras are probably one of the symptoms that most anguish provoked in patients and their relatives, by relating them to psychiatric illness. Even today, contribute to the stigma surrounding epilepsy, and they have been a source of diagnostic errors among health care professionals. These types of auras are an interesting aspect for research in cognitive and behavioral neurosciences. They have been described typically in patients with TLE and frequently reported as a similar to a real-life event in both vividness and complexity, combine with elements such as perception (mainly visual and auditory modalities), memory (recall of a past situation or the feeling of hyperfamiliarity or unfamiliarity) and affect (a full array of associated emotional states) representing an erroneous interpretation of the present experience in which the stream of consciousness is mislabeled and contaminated by remote memories and false emotions [4,5,9].

In our series, at least a third of patients did not report an aura during the video-EEG, and when they did, most of the time the experiential aura was not report. Possible hypothesis trying to explain the lack of report of the aura during video-EEG included higher intensity of the seizures and a quickly and widely spread of the epileptic discharges secondary to the reduction of the AEDs avoiding the clinical presentation of the aura [1].

Most of our patients presented a single type of experiential aura associated with non-experiential auras. The most frequent experiential aura was *déjà vu* and the most commonly associated non-experiential aura was fear, followed by epigastric and thoracic sensations and palpitations in accordance with previous reports of auras in patients with TLE [1,4,5,17-19]. In the case of patients with experiential auras, previous studies had found a frequent association with fear or anguish [4], in agreement with our findings. The main hypothesis to explain the association is that these symptoms are produced by a partially common network [4,18].

Our series showed that patients with *déjà vu* presented most frequently a right TLE. These findings are comparable with previous descriptions of a non-dominant hemisphere predominance for the sensation of *déjà vu* [4,5,7,20,21]. On the other hand, some authors suggested a dominant hemisphere predominance for the experiential phenomena (vivid memory-like hallucinations from the past) [22] or did not find a significant lateralization [4–6,22,23]. In patients who experienced fear (most frequent reported non-experiential aura) we did not observed a clear lateralization of the EZ.

A special mention deserves the presence of multiple auras during seizures [2,24,25] mainly because little is known about their clinical implications and pathogenesis [2,24]. It has been postulated that a possible mechanism may be a spreading but restricted seizure to the region of origin, activating sequential symptomatogenic zones, but without involvement of deeper or contralateral structures and without loss of awareness, and therefore enabling the recollection of auras [24]. In our study, most of patients presented multiple auras. Those patients presented a tendency for higher frequency of a right temporal lobe EZ. In accordance with our results, some authors suggested that most of the patients who report multiple aura types in the same seizure have a right/non-dominant seizure onset [24]. Other authors did not find an association with lateralization of the EZ and proposed that possibly the recollection of multiple auras is associated with a restricted ictal discharge to one temporal lobe, whether left or right [2].

The presence of reliable auras is extremely valuable in order to identify the EZ. Our results showed a favorable seizure outcome (Engel class I-II) in 70% of patients with multiple auras. In the literature, there is some evidence that the presence of multiple auras in the same seizure [24] or during life [2] is not a negative prognostic indicator for epilepsy surgery probably related with the described hypothesis of a restricted activation without compromise of other structures or contralateral spreading, and thereby without loss of awareness and amnesia of auras [2,24,25].

The most common non-experiential aura was fear followed by epigastric sensation, symptoms typically described in patients with mesial temporal lobe involvement of the epileptogenic network [1,18,19,26]. In patients who reported fear, we did not find a significant gender difference compared to previous studies that reported a higher frequency in female patients [19,27]. Few studies had showed that there are clinical, electrical and neuroimaging, gender differences [19,27–29]. Our study showed that *déjà vu* was more common in male patients and in fact, four of them presented it as the only type of experiential aura without non-experiential auras. Additionally, in our female patients, *déjà vu* was more frequently associated with other experiential auras, compared to male patients in whom the presence of other experiential auras was less frequent. In contrast with our results, isolated auras had been more frequently reported in women hypothesizing a different or less widespread seizure propagation in them [29,30].

In terms of neuropsychological deficits, our findings showed that most of patients presented visual memory deficit associated with executive dysfunction. These findings could be partially explained by a predominant right EZ. *Déjà vu* was the most frequent experiential aura in both, patients with and without memory impairment. In accordance with our findings, some authors reported difficulties in short- and long-term memory for nonverbal material (but not verbal material), nonverbal perception, conceptualization, information integration, and impairment in learning and recall on a list learning tasking patients with *déjà vu*

[31–33]. *Martin et al*, described that patients with unilateral TLE and *déjà vu* displayed recognition impairments, and these impairments spared their ability to engage recollective processes so as to counteract familiarity. The selective deficits that they observed, contrasted with the broader pattern of recognition-memory impairments that was present in patients with unilateral TLE without *déjà vu*. MRI volumetry revealed that ipsilateral medial temporal structures were less broadly affected in TLE with *déjà vu*, with a trend for more focal volume reductions in the rhinal cortices [34]. Finally, *Moulin et al*, found *déjà vecu* to be associated with high levels of false-positive errors on a verbal and visual recognition task [35]. In our study we found frequent memory deficits with no performance differences in delayed recollection and familiarity recognition processes between experiential subtypes of auras. However, we have not compared memory abilities between patients with experiential and non-experiential auras in this study.

In terms of psychiatric comorbidities, we found a frequent association with depression followed by anxiety, in accordance with previous reports [36-40]. Additionally, three patients had a diagnosis of psychosis; all of them had *déjà vu* as experiential aura. Few data suggest a relationship between this type of ictal psychiatric manifestations and the development of interictal psychiatric symptoms including the study published by *Manchanda et al* who found a psychiatric comorbidity in more than a half of the patients with experiential auras, irrespective of seizure focus [23,33]. On the other hand, almost a third of patients presented a personality trait but only one patient was diagnosed with a personality disorder. Few data have been published trying to address the relationship between the type of personality and the presence of ictal psychic symptoms [23,33]. Some authors had suggested a role for the patient personality in the presentation of mental phenomena by arguing that both, form and content of the psychotic symptoms, are symbolically related to ongoing psychodynamic processes with significant elements of the patient´s past and current emotional life [10].

Conclusion

Most of patients with experiential auras presented a single experiential aura, most frequently *déjà vu*, associated with non-experiential auras, mainly fear. A right temporal lobe seizure focus was the most frequent, including for patients with *déjà vu*. In relation to gender, *déjà vu* was more common in male patients. A high prevalence of psychiatric comorbidity was observed and despite of the reduced number of cases, the 3 patients with psychosis presented *déjà vu*. Most of patients presented visual memory deficit associated with executive dysfunction.

Ethical Approval

The ethics committee of both hospitals approved the study. All patients signed a written informed consent to participate. The study was performed in accordance with the ethical standards of the Declaration of *Helsinski*.

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