Rapidly progressive cognitive impairment with neuropsychiatric symptoms as the initial manifestation of status epilepticus

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Abstract

The purpose of this article is to describe the clinical and electroencephalographic features of patients diagnosed with non-convulsive status epilepticus (NCSE) with uncommon cognitive and behavioral involvement. We present two cases with sub-acute cognitive impairment and neuropsychiatric disorders (including anxiety and transient behavioral changes) as their first manifestation of NCSE. A neuropsychological profile demonstrated executive dysfunction. In addition, the neurological examination revealed automatisms and 24-hour video EEG showed epileptiform activity. Although neuroimaging studies showed frontotemporal abnormalities, both neurophysiological and cognitive improvement after specific antiseizure drug treatment confirmed the diagnosis of non-convulsive status. Theoretical considerations between mental status changes and focal epilepsy will be reviewed. Our cases raise awareness of the importance of considering NCSE, a treatable condition, in the differential diagnosis of rapidly-progressive cognitive impairment with neuropsychiatric symptoms.

1. Introduction

Status Epilepticus (SE) is a medical emergency with significant morbidity and mortality, affecting mainly people with epilepsy on low-dose antiseizure drugs [1]. According to the ILAE, SE is defined either as a continuous seizure lasting 5 min or more, or two or more sequential seizures without full recovery of consciousness between them [2]. The prevalence of SE in epilepsy patients ranges from 1 to 16%. In the United States, its incidence is 6.2–18.3 per 100,000 [3].

Cognitive and emotional disorders in epilepsy patients are common and have an impact on quality of life and adaptive social behaviors. Chronic epilepsy, including an accumulation of single attacks, may lead to neurophysiological consequences, as well as mental decline [4, 5]. It is well known that cognitive dysfunction can be associated with drug-resistant epilepsy. Additionally, several studies indicate that SE may generate cognitive impairment through selective neuronal loss in vulnerable brain regions [6].

An increased prevalence of psychiatric disorders in epilepsy patients has been reported in epidemiologic studies, compared to the general population [7]. It is likely that focal areas involved in generating seizures interfere with brain structures which control emotional behavior. For instance, memory and anxiety disorders have been related to dysfunction of the hippocampus and amygdala in temporal lobe epilepsy, while executive and dyscontrol/impulsivity problems have been related to frontal lobe epilepsy [8]. The bidirectional relationship between behavioral disorders and epilepsy is probably a combined consequence of emotional side effects from antiseizure drugs, psychosocial factors, and a common neurobiological mechanism. Affective disturbances associated with non-convulsive status epilepticus (NCSE) have previously been reported by Geier and Profitlich [9,10]. Emotional symptoms in these patients includes dysphoria, irritation, and anger, as well as agitation, increasing anxiety and panic attacks. Depression and suicidal ideation have been apparent as well.

Whereas convulsive SE is a medical emergency, NCSE can be insidious, and remain undiagnosed for prolonged periods of time. Taking into account the infrequent primary presenting symptoms and the challenges associated with the diagnosis, there are few clinical reports which provide a sufficient description regarding cognitive and psychiatric manifestations as the initial manifestations of NCSE. The mental status changes may mislead the clinician to alternative diagnoses in the absence of physical signs suggesting seizures. We present two cases in which cognitive and behavioral involvement, as well as uncommon neuropsychological findings, were the first clinical manifestation of NCSE. Specific neuropsychological and mental tests were applied prior to, and following treatment, and suggest a causative role for sustained seizure activity.

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2. Case 1

2.1. Medical history and clinical features

A fifty-two year old male was admitted to the emergency department (ED) and was assessed by our neurology service (Hospital Mayor Mederi - Bogotá, Colombia) for a first episode of guttural sounds, eyeballs rolling back, hypersalivation, and generalized rigidity. The patient also had loss of consciousness during the attack with full spontaneous recovery, having over 5 min of amnesia following the event. The patient had a history of anxiety disorder four months prior, and obstructive sleep apnea (OSA) two months ago. A family member also reported jerking movements while asleep. These had worsened in the last week, and they persisted somewhat during wakefulness. His previous studies included normal brain CT and MRI scans, normal EEG and a polysomnogram study showing OSA (apnea-hypopnea index (AHI) 27.3; average desaturation 85%). He was on a SSRI antidepressant medication (Sertraline), 50 mg per day.

On neurological examination he was alert and oriented, having disorganized and incoherent thought content, hyporexia with defective fixation attention on a stimulus and bradydalia. His physical exam showed no cranial nerve abnormalities, no sensor or motor deficits, and no meningeal irritation signs. Initial neuropsychological assessments (Table 1) before antiseizure drugs (ASDs) showed low performance in both episodic declarative memory and verbal semantic fluency, according to the RAVLT and Isaac tests respectively. A dysexecutive syndrome was suggested by low performance in procedural and working memory, according to the WAIS III test.

2.2. Paraclinical tests

A brain MRI showed bilateral mild atrophy of the temporal lobes (Supplementary Fig. 1A). He had a non-reactive VDRL, and normal vitamin B12 levels. Twelve seizures were recorded during the 24-h video-EEG monitoring. Electrographic seizures were manifest as rhythmic delta and theta rhythmic frequencies with amplitudes of 30-to 60-μV activity arising from rhythmic activity of 30–60 μV increased in frequency and amplitude arising from the right fronto-central region subsequently involving a bihemispheric field. This activity was correlated with hand automatisms of 20 to 40 s in duration (Fig. 1B). The paroxysmal events were followed by left gaze deviation. Background suppression of the EEG activity with a symmetric posterior dominant rhythm of 9 Hz was observed during the postictal state.

2.3. Treatment

Given the evidence of seizure activity, a phenytoin loading dose of 1200 mg was given intravenously (IV) and followed by 300 mg Oral Administration (P.O.) daily; 2000 mg of IV valproic acid was added and followed by 500 mg P.O. every 12 h.

2.4. Outcome and follow-up

Given the adequate clinical response, the antiepileptic medication was switched from the IV to oral route, and sertraline was discontinued. The patient showed significant clinical improvement with coherent thought content and euprosexia, and full resolution of both seizure activity and anxiety. Compared with the initial neuropsychological profile, there was improvement in procedural (below the 90th percentile), working memory and episodic declarative memory.

On the other hand, impairment in verbal semantic fluency remained Table 1 after ASDs. Follow up examination two months later revealed that the patient was seizure-free, and return to his baseline work activity. A second video EEG showed no seizures, but right fronto-central cortical dysfunction and rhythm. slow theta activity at 6 Hz was found (Fig. 1C).

3. Case 2

3.1. Medical history and clinical features

A sixty-two year old female was admitted to the ED with a 10-day history of aggressive behavior, working memory impairment and transient dyscognitive episodes. Over the last week she had complained of moderately-strong tension-type headaches.

She had a history two years prior to admission, of a right middle cerebral artery aneurysm clipping complicated by a right temporal arteriovenous malformation.

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<table>
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<tr>
<th>Table 1</th>
<th>Neuropsychological (NP) findings before and after ASDs in patients with focal NCSE.</th>
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<td>Pre ASD</td>
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<td>WAIS III Digit Span</td>
<td>Digits forward: 4</td>
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<tr>
<td>Digit backwards: 2</td>
<td>Raw score: 4</td>
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<td>Isaac test</td>
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<td>TMT</td>
<td>Nt</td>
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Abbreviations: expected score (Es); Not Tested by fluctuating clinical condition of the patient (Nt); Non Convulsive Status Epilepticus (NCSE); Rey Osterrieth Complex Figure (ROCF); Rey Auditory Verbal Learning Test (RAVLT); Trail Making Test (TMT); Antiseizure Drug (ASD).

a Early NP test after ASD treatment (early post ASD).

b Late NP test after hospital discharge with oral ASD treatment (late post ASD).
were reduced, but still higher than expected (Table 1) in the late ASD period. The TMT test scores (Table 1) in the early ASD treatment period.

There was only mild recovery in working memory and inhibitory control, as documented by repeat neuropsychological testing. There was full resolution of her anxiety disorder, after which sertraline was discontinued and she was discharged from the hospital. There was no evidence of NCSE.

These results, together with the previous neuropsychological assessment, yielded a working diagnosis of dysexecutive disorder with associated amnesia and impaired inhibitory control.

3.2. Paraclinical tests

A brain MRI showed a right temporal encephalomalacia and bilateral atrophy, predominantly frontal and temporal (Fig. 2A). She had a nonreactive VDRL, as well as normal vitamin B12 and folate acid levels. An initial EEG showed slowing in the right temporal region, without evidence of epileptiform activity, and there were no major findings in her CSF study.

During her clinical admission she experienced recurrent focal seizures with impairment of consciousness; head turned to the left and tonic posture of the left arm, with evolving to a bilateral convulsion lasting 2 min. A 24-h video-EEG showed focal SE with multiple seizure episodes (around 18). The patient had diaphoretic episodes and head deviation to the left lasting 2 min, followed by bilateral symmetric tonic posture. The seizures correlated with 80–120 μV sharply contoured activity arising from right temporal–parietal region, with rhythmic delta activity of 1.5 to 2 Hz spreading contralaterally lasting 150–300-s. Frequent spike-and-slow waves were present spikes-slow waves in the right posterior-temporal region, were recorded (Fig. 2B).

3.3. Treatment

Therapy was started with levetiracetam 500 mg IV every 12 h. During her admission, she manifested delusional beliefs, depression and worsening of the anxiety. This was thought to be a medication side effect, and levetiracetam was switched to clonazepam 10 mg every 12 h and lacosamide 100 mg every 12 hours. Neither delirium nor psychiatric symptoms were reported after the medication change.

3.4. Outcome and follow-up

The ASDs controlled the seizures and associated emotional symptoms, after which sertraline was discontinued and she was discharged from the hospital. There was full resolution of her anxiety disorder and moderate improvement in the executive dysfunction, declarative memory and inhibitory control, as documented by repeat neuropsychological testing. There was only mild recovery in working memory (Table 1) in the early ASD treatment period.

At two months follow up she remained seizure-free with mild improvement in working memory performance. The TMT test scores were reduced, but still higher than expected (Table 1) in the late ASD treatment period. No aggressiveness was reported. A second follow-up video-EEG did not show epileptiform discharges or seizures. However, the interictal EEG recorded an intermittent slowing in the right temporal region. Video-EEG demonstrated right mid-to posterior-temporal theta-delta slowing and right temporal sharp waves persisting (Fig. 2C).

4. Discussion

We present two clinical cases of NCSE with neuropsychological changes, automatisms and dyscognitive involvement on neurological examination. A 24-h video-EEG showed epileptiform activity consistent with focal SE epilepticus. Cognitive dysfunction may arise early during the course of patients with epilepsy and indicate a structural or functional brain abnormality. Our cases demonstrate that neuropsychiatric changes associated with NCSE can precede the diagnosis of epilepsy. In fact, previous reports indicate that psychiatric and behavioral disorders (i.e. depression and suicide attempt) may antedate the diagnosis of epilepsy [11,12]. However, the neurobiological mechanisms underlying this effect remain to be determined. Variable confusion and responsiveness, lateralizing signs and automatisms are usually present in dyscognitive focal SE. However, in our clinical cases, anxiety disorder, as well as changes in cognition and behavior preceded the onset of automatisms or any motor manifestation of seizure activity.

Abnormal neuroimaging findings in our patients suggest that some of the neuropsychological symptoms may be explained by previous brain damage. However, the neurophysiological features on the EEG, as well as the clinical improvement after ASDs indicated NCSE. Epileptiform activity of frontal and temporal origin may explain aggressiveness and memory impairment, respectively. NCSE is defined as a change in behavior and/or mental processes from baseline, associated with continuous epileptiform discharges in the EEG [13]. Additionally, it is may be characterized by confusion and impaired consciousness. Less common clinical signs include language and cognitive difficulties. Although uncommon psychic phenomena have also been reported [10,14,15], we found neuropsychiatric involvement in mood and affect, language and executive dysfunction, and, finally, both working and procedural memory impairment, as initial manifestations of SE, without apparent impairment of consciousness. This particular clinical feature was revealed only after extensive neurocognitive testing of both patients.

Taking into account the initial neurological symptoms and the improvement in neuropsychological tests following initiation of ASDs, NCSE should be considered in the differential diagnosis of the initial presentation of rapidly-progressive dementia (RPD) with psychiatric features. RPD constitutes a subtype onset problem with serious cognitive and functional deterioration over the course of less than two years. Moreover, rapidly progressive dementias (RPD) with neuropsychiatric symptoms that develop subacutely over weeks to months, or rarely, acutely over days, have been reported [16].

The relationship between the EEG features and both cognitive and neuropsychological changes is quite complex. In fact, the possibility of detecting transient cognitive impairment during a solitary epileptiform discharge is low [17]. Because cognitive and behavioral symptoms were described in the very early onset of the present clinical cases, a previously normal EEG supports the features of cognitive impairment and psychiatric disorders were secondary to episodes of subclinical electrographic seizures. “Transient cognitive impairment” has been proposed for episodes of interictal epileptiform discharges associated with selective cognitive deficits [17,18]. On the other hand, more global significant cognitive impairment has been related to short nonconvulsive epileptic seizures [19]. We found epileptiform discharges in frontal and temporal sources during video-EEG telemetry. As mentioned before, anxiety and loss of impulse control is related to medial temporal and frontal lobe dysfunction, respectively. Because seizures can be intermittent and subtle, prolonged EEG monitoring is necessary for a diagnosis of NCSE.

There is some degree of neurologic co-morbidity in patients with epilepsy, including migraine, stroke, traumatic brain lesions, and dementia. The choice of the type of ASDs to use for controlling seizures must
take into account these co-morbidities, and, likewise, the medications for controlling the co-morbidity should take into account their effect on the susceptibility to seizures [20]. Adequate seizure control is the key to reducing progressive cognitive impairment. However, synergistic effects between previous or acquired brain lesions and mental aging have to be considered. Approximately 50% of epilepsy cases have no known etiology which may delay diagnosis [1].

Cumulative evidence indicates that the imbalance between excitatory and inhibitory neurotransmitter systems will result in altered net-effects between previous or acquired brain lesions and mental aging. Rapid cognitive impairment with neuropsychiatric symptoms may be the initial clinical presentation of focal epilepsy and SE. This clinical manifestation should be considered within the differential diagnosis of acute cognitive impairment, rapidly-progressive dementias and psychiatric disorders. Because seizures can be intermittent, EEG monitoring may be necessary for a diagnosis of NCSE. Therefore, only a high index of clinical suspicion will lead to request prolonged neurophysiological assessment.

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Conflict of interest statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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