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Vagus nerve stimulation and psychosis. A single case report

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The appearance of behavioral disorders in the context of a decrease in the number of seizures in epileptic patients is a fact that was already described in Landolt's theory of forced normalization in the middle of the XX century. Through this clinical case, we propose several mechanisms that aim to give a general explanation to the physiopathology of this condition. Among them, the theory which suggests increased alertness as a result of inhibitory mechanisms secondary to a long lasting epileptic condition stands out. In addition, we consider the possibility that left vagus nerve stimulation (VNS), a procedure used as a second line treatment in epileptic patients refractary to multiple drug therapy, may cause an inhibitory reaction of similar characteristics as the previously described, and could therefore lead to different psychiatric disorders. Lastly, we bring up several alternatives that will try to throw some light on the physiopathological condition that leads to the chronification of this disease, the theory regarding a cognitive deterioration associated to the appearance of negative symptoms in patients with temporal lobe epilepsy standing out.

Key words:
Epilepsy. Psychosis. Left vagus nerve stimulation.

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Estimulación del nervio vago y psicosis. A propósito de un caso

La aparición de alteraciones del comportamiento en el contexto de una disminución en el número de crisis en pacientes epilépticos es un hecho que ya fue descrito por Landolt a mediados del siglo XX en su teoría de la normalización forzada. Aquí proponemos, a través de un caso clínico, una serie de mecanismos que pretenden explicar a grandes rasgos la fisiopatología de este fenómeno. Entre ellos destaca la teoría del aumento en el estado de alerta provocado por los mecanismos inhibitorios secundarios a una epilepsia de varios años de evolución. Por otra parte, se plantea la posibilidad de que la estimulación intermitente del nervio vago izquierdo (ENV), procedimiento empleado como terapia coadyuvante en el manejo de pacientes epilépticos refractarios a politerapia farmacológica, pueda provocar una respuesta inhibitoria de características similares, que pudiese por sí misma originar una serie de cuadros psiquiátricos. Finalmente se barajan diversas alternativas en relación con el proceso fisiopatológico que conlleva la cronificación de dicha patología, entre las cuales destaca un deterioro cognitivo asociado al desarrollo de síntomas negativos en pacientes con epilepsia del lóbulo temporal.

Palabras clave:
Epilepsia. Psicosis. Estimulación intermitente del nervio vago izquierdo.

INTRODUCTION

During the last decades, the relationship between behavior disorders associated to anti-seizure therapy has become clear. With the appearance of new anti-epileptic therapies, interest has reappeared for the fact that Landolt already described in the middle of the XX century, characterized by the increase in the incidence of psychiatric disease secondary to the decrease in the number of seizures in chronic epilepsy patients. As an example of these new therapies, intermittent stimulation of the left vagus nerve (LVN) stimulation stands out. In addition to having shown its efficacy in this area, it has shown a potential antidepressive effect[1] as well as an effect on memory potentiation[2].

We present the clinical case of a patient who was seen in our hospital's psychiatry unit. His evolutive picture manifests the relationship existing between epilepsy and psychiatry disease.

CLINICAL CASE

V. M. J., 29 year old male, single, without children, who lives with his parents. Up to a few months ago, he had worked

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with his mother in a children's dining room. He came to the Emergency Service due to behavior disorders (he went out into the street nude after a discussion with his father).

He was diagnosed of epilepsy at five years of age. He has had several types of seizures over time, going from simple partial ones, more frequent in childhood, to the generalized ones, which occur for the first time at about 25 years of age. He has been under multiple drug anti-epileptic treatment since he was 13 years old. At sixteen 16 years of age, he was asymptomatic from the point of view of his epilepsy, the seizures reappearing 2 years later in a probable relationship with increase in alcohol consumption. During that period, the patient had up to forty seizures per day. In 1993, at 19 years of age, the Wechsler Adult Intelligence Scale (WAIS) was applied. He obtained the result of a 98 intellectual quotient (IQ), without differences between the verbal/manipulative area and without significant neuropsychological disorders. In other tests, a visuospatial apraxia and Rorschach test with a series of responses (among which some related with aliens) that were interpreted at that time as a possible psychotic predisposition stand out. In June 1994, due to the failure of polytherapy to control the seizures, a resection was performed in the left supplementary motor area. After the surgery, the seizures persisted, although in a lower number. In January 2001, a VNS was implanted, which led to a considerable decrease in the number of seizures. After a few weeks, obsessive type ideas, related with the number 33, as well as influence ideas that the patient related with the stimulator, appeared. The patient reported having felt very nervous and aggressive as the discharge intensity increased, a situation that finally generated a great emotional impact. Thus, he came to the Neurosurgery out-patient clinic, requesting the withdrawal of the stimulator, a fact that took place in July 2001. Since then, his family has reported that he neglects his physical aspect, has lost most of his friends and is more isolated, occasionally spending the entire day without leaving his room. His sleep-wakefulness rhythm has been reversed. Speech has become monotonous, dysprosodic, with low volume. Frequent unmotivated laughter and rare behaviors. The responses are tangential and sometimes incoherent.

At the time of admission, 3 years after the implantation of the VNS, he was still receiving treatment with topiramate 200 mg/day, carbamazepine 1,200 mg/day (levels of 7.46 µg/ml) and valproic acid 2,000 mg/day (levels of 31.17 µg/ml). In this content, he has passed several months without suffering seizures.

In the Emergency Service, the patient was conscious and oriented in person and space. Disoriented in time. He did not know facts such as the war in Iraq or the name of the president of the government. Vague, limited, faltering and inexact language, focused on the idea of looking for work. Confused attitude. Limited spontaneity. Tendency to isolation. Unmotivated smiles. Difficulty to describe his mental state. Disorganized behaviors.

In the EEG, an area of irritative-lesional character in left hemisphere, with frontal-rolandic-temporal focalization, potentially epileptogenic (without significant differences in regards to the former). A new WAIS was performed, with an IQ of 89, without differences between verbal/manipulative and a 23 % deterioration index.

During his admission, the Valproic Acid dose was increased to 3,000 mg/day to obtain levels of 61.73 µg/ml and a regime of risperidone 9 mg/day was initiated. After a few days, the patient's attitude had improved mildly, and he was slightly more sociable and communicative. On discharge, he was diagnosed of organic psychosis.

POTENTIALLY INVOLVED PATHOGENIC MECHANISMS

Forced normalization

In 1953, Landolt coined the concept of forced normalization to describe a phenomenon characterized by the appearance of psychotic episodes associated to total or partial normalization of the previously pathological electroencephalographic registries in patients diagnosed of epilepsy[3]. Krishnamoorthy et al. propose the following diagnostic criteria[4]:

Major criteria

1. Diagnosis of epilepsy based on the clinical history, electroencephalogram (EEG) and neuroimaging.
2. The presence of acute/subacute appearing behavior disorders characterized by one or more of the following:
   - *a)* Psychotic picture with thought, delusional, hallucinatory, etc., disorders.
   - *b)* Mania/hypomania type mood state disorders or depression.
   - *c)* Anxiety pictures with depersonalization, derealization, etc.
   - *d)* Motor or sensory hysteria, astasia-abasia, etc.
3. The presence of one of the following changes in relationship with the epilepsy:
   - *a)* A reduction in the total number of peaks in the EEG greater than or equal to 50 % in comparison with another one performed previously in the basal state, without behavior disorders, awake, during a one hour period.
   - *b)* A report made by a relative or any caretaker claiming complete disappearance of the seizures.

Minor criteria

A. A recent change (in the last 30 days) in the drug regime.

B. A report that mentions similar pictures of behavioral disorders associated to a decrease in the seizure number, provided by a close relative, caretaker, primary health care physician or by hospital reports with or without electroencephalographic registries.

To be able to make the forced normalization diagnosis, major criteria 1, 2 and 3a or major criteria 1, 2 and 3b and one minor criteria must occur.

ALTERNATIVE PSYCHOSIS

The alternative psychosis, concept introduced by Tellenbach in 1965[5], refers to the phenomenon characterized by the appearance of behavior disorders (not exclusively psychotic) in epileptic patients when the seizure frequency decreases. On the contrary to forced normalization, this concept does not consider electroencephalographic criteria but rather exclusively clinical ones.

ACTION MECHANISM

To explain these phenomena, the mechanism proposed by Wolf especially stands out. It is based on the disappearance of the abnormal electrical activity on the cortical level secondary to antiepileptic treatment, associated to the persistence of subcortical epileptic activity, which, by itself, could explain the behavior disorders. This phenomenon lacks validity when explaining the alternative psychosis theory, since it does not take the electroencephalographic registry into account.

On the other hand, the inhibitory mechanisms secondary to a several year long epilepsy, that could be responsible for an insomnia condition, hypervigilance and dysphoria, would remain active[6,7]. This situation would act as a precipitating factor for the development of psychotic pictures in persons with a previous predisposition. Among these inhibitory mechanisms, those related with gabaergic neurotransmission stand out. In fact, the antiepileptic drugs that increase GABA levels are associated with psychopathological phenomena in up to 10 % of the cases, the mood state disorders, agitation and even paranoid type psychotic symptoms standing out[4].

Blumer et al. suggest that interictal psychotic and dysphoric pictures, which he related with forced normalization and alternative psychosis, develop progressively as the epileptic condition worsens. These symptoms become clearer during the pre- and postictal periods, due to the potentiation of the inhibitory mechanisms after an excess of excitatory activity. They also describe how these symptoms disappear in a 6 to 18 month period after the surgical excision of the epileptogenic focus, as a consequence of the slow disappearance of this inhibitory activity[8]. The doubt remains on whether the eradication of the episode is a sufficient condition to generate the disappearance of this inhibitory activity or if, on the contrary, it is necessary to excise the epileptogenic focus, whose abnormal functioning in spite of not causing new episodes, could maintain the excess of this activity that is responsible for the behavior disorders. In principle, we could argue that the disappearance of the episodes would be a sufficient condition to soften and even eliminate the inhibitory activity. This is justified by the fact that the pictures precipitated due to the improvement in the epilepsy in the patient series described by Krishnamoorthy and De Herdt abated after the administrationof neuroleptics, without presenting relapses when this treatment was suspended in spite of maintaining the absen-ce of episodes with anti-seizure therapy, independently of whether drug treatment[4] or VNS[1] were used.

On the other hand, Blumer et al. suggest the use of low antidepressive drug doses, sometimes associated to the use of atypical antipsychotics, to control the symptoms derived from alternative psychosis and forced normalization[8].

In a minority of cases with mild ictal pictures that generate a scarce impact on the patient's life, decrease of the antiseizure therapy[8] and even its total suppression[9] has been suggested, risking the reappearance of the episodes, to avoid the psychiatric symptoms in the case that these generate greater limitations than the epilepsy itself in its basal functioning.

VAGUS NERVE STIMULATION AND PSYCHOSIS

The VNS is performed in a standard way, implanting a neurostimulator (fig. 1). It was approved by the Food and Drug Administration (FDA) in 1997 as an additional treatment to decrease the partial epileptic seizures refractory to antiepileptic medication in adults and adolescents. The neurostimulator is made up of two parts: a bipolar current generator, similar to the pacemakers, with a mean life between 5-10 years depending on the stimulation parameters chosen and two helicoidal electrodes that are placed in the left vagus nerve on the cervical level and are connected to the generator. The seizure appearance frequency decreases by 27.9 %[10].

De Herdt et al. describe a group of four patients with refractory epilepsy who developed psychotic episodes while they received treatment with VNS. This technique has been shown to increase alertness and reduce sedation[1], possibly by a system analogue to that of the previously mentioned inhibitory mechanisms. In fact, Ben-Menachem et al.[12] describe an increase in the inhibitor neurotransmitter concentration and a decrease in that of the excitors in the cerebrospinal fluid of epileptic patients subjected to VNS therapy. On the other hand, Krahl et al.[13] as well as other authors[14], have recently demonstrated that type A and B myelinized fibers from the vagus nerve have a hyperpolari-

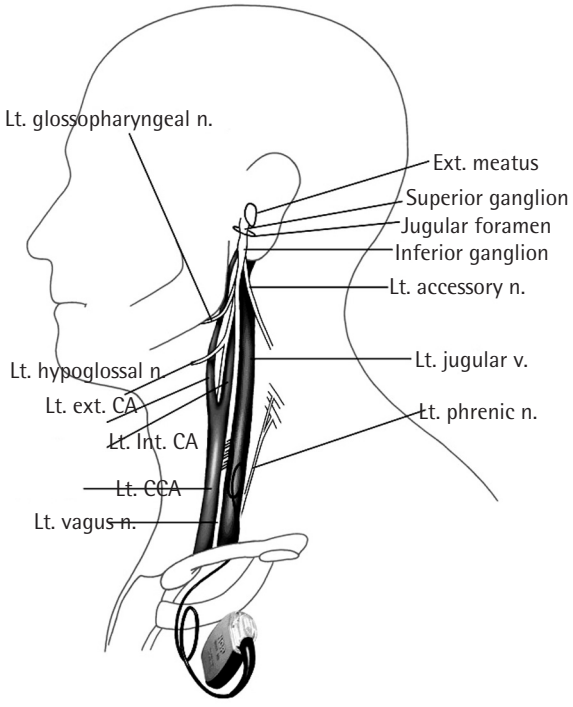

Figura 1 *Implanting a neurostimulator. Modified by Henry TR[11].*

zing effect on the cortical pyramidal cells, thus decreasing their excitability.

As predisposing factors, one of the patients of De Herdt had a background of psychotic episodes and depressive pictures. The other three had a background of mental retardation. In the period in which the psychotic disorders appeared, all the patients suffered frequent seizures, so that it was not possible to justify the appearance of these pictures with the forced normalization or alternative psychosis theories.

In a series of 81 epileptic patients treated with VNS described by Blumer et al.[8], seven developed psychiatric complications, including psychotic symptoms in five of them (two of which had a background of psychotic episodes). These pictures appeared after a reduction in the number of seizures of at least 75 %. Thus, he argues that these symptoms should not be considered as direct effects of VNS, but rather should be attributed to the forced normalization and alternative psychosis phenomena. In our opinion, there are no data that make it possible to deny a direct action of the VNS, so that we propose the possible existence of a mixed action mechanism, capable of generating psychiatric disease through the predominance of the inhibitory activity, once the number of seizures is reduced, associated to a potentiation of this activity by the VNS.

CONCLUSION

In the case of V. M. J., as predisposing factors, we stress the Rorschach test prior to the implantation of the VNS in which he offered a range of responses that were interpreted at that time as a possible psychotic predisposition, as well as a series of drawings in which visuo-spatial apraxia stood out, a phenomenon that is highly suspicious of organic disease. In spite of the reduction in the number of seizures, the electroencephalographic registries obtained before and after the VNS implantation do not show significant differences, so that we rule out the forced normalization phenomenon. The possibility of there being an alternative psychosis, on the contrary, still remains feasible.

The temporal relationship between the appearance of the first symptoms and the VNS implantation is manifest. Thus, in this case, we could opt for, as De Herdt et al. did in his time, the hypothesis that the increase in the alertness level in a patient with a psychotic predisposition may have precipitated the initial psychotic picture.

When bringing up the present condition of the patient, we cannot ignore the clinical picture that generated the psychiatric admission three years after the VNS implantation, characterized essentially by the residual: manifest apathy, abulia, difficulty to initiate tasks, lack of interest towards the setting, affective blunting, perplexity, difficulty to concentrate and unorganized behaviors, in absence of productive psychotic activity.

How can we explain the deterioration suffered due to the VNS implantation?

In the first place, we should establish the possibility of cognitive deterioration secondary to the epileptic condition itself. As Getz et al. report, patients with temporal lobe epilepsy have a greater tendency to develop negative symptoms than the non-epileptic ones (which is not true in regards to the positive symptoms). They also report greater cognitive deterioration than in those patients with temporal lobe epilepsy lacking negative symptoms, a fact that they relate with a greater degree of cortical atrophy[15].

Symonds relates temporal lobe epilepsy with psychotic pictures, specifically schizophrenia type, so that neuronal loss secondary to the former could generate the appearance of aberrant circuits in the temporal-limbic region[16]. These circuits, and not the neuronal loss in itself, would be responsible for the chronification of the picture in question.

It is not possible to rule out as another diagnostic possibility that the patient is under the influence of residual defect secondary to a possible schizophrenic episode suffered several years ago, that was never diagnosed as such, and that could have been precipitated by the stressing stimulus meant by the greater state of alertness caused by the VNS.

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