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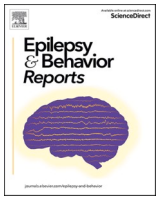

Opercular myoclonic-anarthric status (OMASE) secondary to anti-Hu paraneoplastic neurological syndrome

César Romero *, Alonso Quijada, Gabriel Abudinén, Catherine Céspedes, Ledda Aguilera

Neurology and Neurosurgery Department, Hospital Clínico de la Universidad de Chile, Santiago, Chile

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ABSTRACT

Focal Opercular Myoclonic – Anarthric Status Epilepticus (OMASE) is a rare form of focal motor status epilepticus caused by several etiologies. It is characterized by fluctuating dysarthria and epileptic myoclonus involving the bilateral glossopharyngeal musculature. We present the case of a 52-year-old woman who experienced gradual and progressive paralysis and myoclonus of facial and bulbar muscles; additional tests revealed the presence of right breast ductal adenocarcinoma and positive serum anti-Hu and anti-GAD65 antibodies. High doses of steroid pulses, anti-seizure therapy, and rituximab partially controlled myoclonus; the tumor resection improved dysphagia and dysarthria.

1. Introduction

Focal Opercular Myoclonic—Anarthric Status Epilepticus (OMASE) is an uncommon focal motor status epilepticus presentation. It is characterized by fluctuating cortical dysarthria without aphasia and epileptic myoclonus involving the bilateral glossopharyngeal musculature [1]. Few OMASE reports describe various etiologies, including cerebrovascular disease, tumors, infections, and immune-mediated encephalitis [1–4]. Here, we describe the presentation of OMASE as a paraneoplastic neurological syndrome (PNS) associated with anti-Hu antibodies and breast ductal cancer.

2. Case report

A 52-year-old woman without significant medical history presented with four months of fluctuating facial myoclonus, anarthria, and dysphagia. She was fully conscious and able to breathe normally. During the neurological examination, she had frequent hemifacial myoclonus, especially around the mouth, which was more noticeable when she was awake than when she was drowsy (See Video 1). Additionally, she had a mild right hemifacial weakness, with dissociation between automatic (smile) and voluntary movements. The patient was only able to produce unintelligible sounds and had moderate buccal-lingual apraxia without aphasia. Her soft palate had occasional myoclonus and reduced gag reflex. The motor examination was normal, and generalized hyperreflexia with unsteady gait was noted.

A video electroencephalogram (video-EEG) showed abundant generalized epileptiform activity (prevalence of 50 %) with a predominance in the right centro-parietal region and facial myoclonus as the clinical correlation (See Fig. 1). Electromyography, nerve conduction velocity, repetitive stimulation test, and single fiber EMG yielded normal results. Upon admission, there were no increased inflammatory parameters; VDRL and HIV were non-reactive; celiac disease serology and rheumatology panel were negative, but positive antinuclear antibodies (ANA) were present in a homogeneous and fine granular pattern (1/160 dilution) and in a centromere pattern (1/80 dilution). Unbalanced metabolic causes were ruled out.

The results of the brain MRI with contrast and perfusion protocol (1.5 T) indicated slightly reduced blood flow in the left fronto-insular region. Still, this was considered normal based on the perfusion study (Fig. 2). A videofluoroscopy revealed pharyngo-nasal reflux and laryngeal-tracheal aspiration. At the same time, a nasopharyngoscopy indicated velopharyngeal incompetence and reduced vocal cord mobility. The cerebrospinal fluid (CSF) appeared transparent, with a glucose level of 48 mg/dL and proteins of 13 mg/dL. No cells were present, but CSF tested positive for type 3 oligoclonal bands. Additionally, an autoimmune encephalitis panel (blood and CSF) was performed, which showed strong positivity for anti-Hu IgG (ANNA-1) and weak positivity for anti-GAD65 IgG –both in serum–. Concurrently, a locally invasive ductal breast adenocarcinoma was diagnosed.

Abbreviations: OMASE, Focal Opercular Myoclonic, Anarthric Status Epilepticus; PNS, paraneoplastic neurological syndrome; EEG, Electroencephalogram.

* Corresponding author.
E-mail address: cesarromero@ug.uchile.cl (C. Romero).

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The OMASE diagnosis was proposed and confirmed by a benzodiazepine test with video-electroencephalographic monitoring. The EEG tracing showed a nearly complete reduction of epileptiform activity and a 10 % decrease in myoclonic activity, which reappeared later. Valproic acid 1500 mg daily and methylprednisolone boluses for five days were started, followed by two initial doses of rituximab (1000 mg) and then one dose every six months, resulting in partial improvement of myoclonus. Surgical resection of the tumor led to improvement in dysphagia (and gastrostomy was removed) and had a slight effect in anarthria one year later. While there was a significant decrease in myoclonus, it did not completely disappear, and valproic acid treatment had to be maintained. As of now, there is no evidence of tumor recurrence.

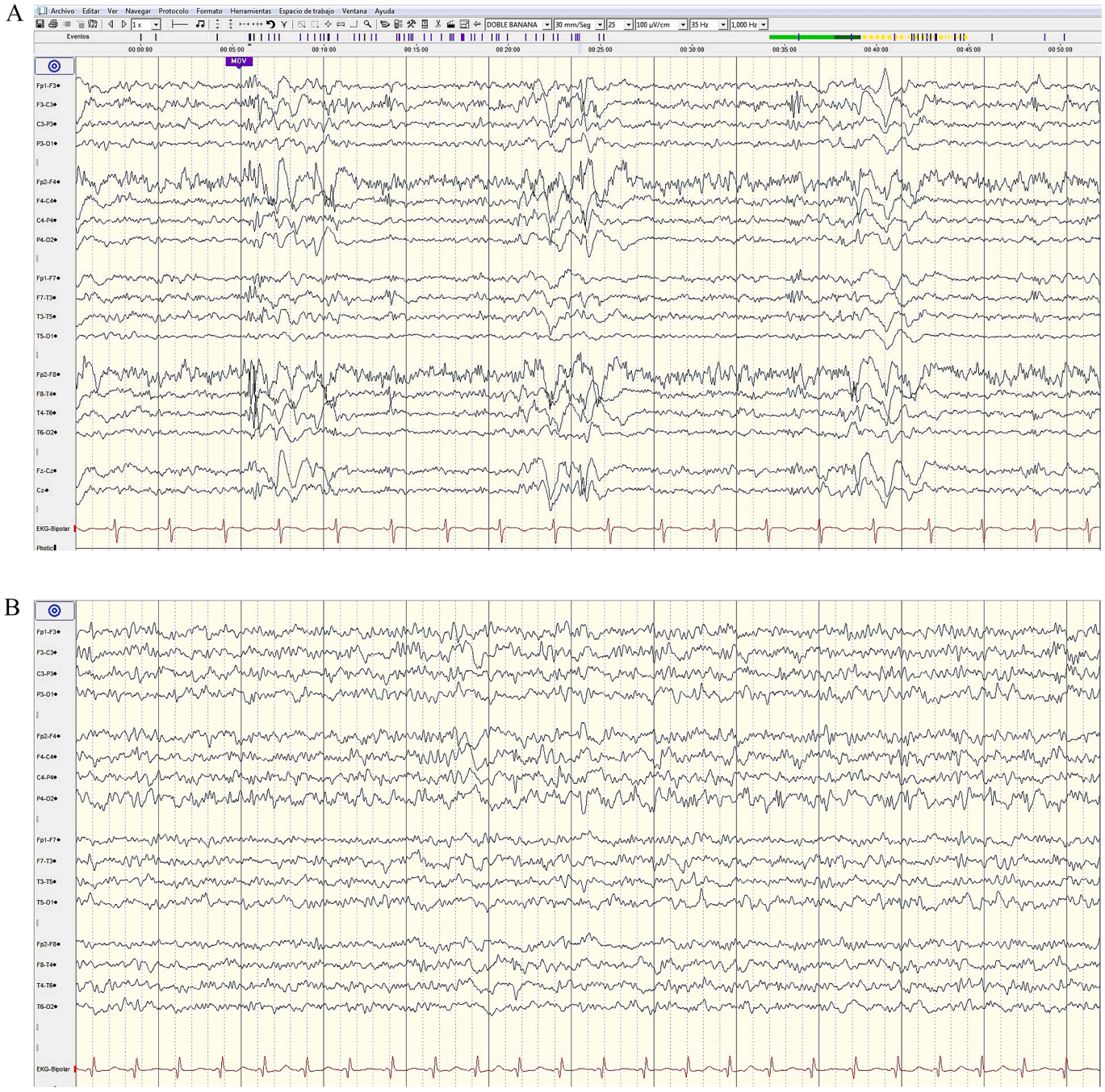

Fig. 1. A. Video electroencephalogram. Bipolar mounting. Sensitivity 7 uV; High-frequency cutoff 75 Hz; Low-frequency cutoff 1 Hz; speed 30 mm/sec. On a discreetly slow theta basis, frequent paroxysms of theta/delta waves are observed, interpolated by bilateral fronto-central focal epileptiform activity consisting of biphasic spikes, spike slow-wave complexes, and poly-spikes, with greater electronegativity on the right fronto-central region (C4/F4) with diffusion to the adjacent temporal region. This activity showed a prevalence of around 50 % of the total recording time (TTR). The video showed abundant bilateral and independent hemifacial myoclonus associated with myogenic artifacts. **B. Management with benzodiazepines. Post-benzodiazepine record. Bipolar montage. Sensitivity 7 uV; High frequency cutoff 75 Hz; Low frequency cutoff 1 Hz; speed 30 mm/sec.** Post midazolam 10 mg/IM (0.2 mg/kg), background slowing is diminished with diffuse beta rhythms (pharmacological) and alpha rhythm, with a significant decrease in epileptiform activity (around 10–20 % of the total recording time). Clinically, the patient was evaluated serially at 30 min, 60 min, and 180 min from administering Midazolam, showing a significant decrease in facial myoclonus. However, negative bulbar symptoms (anarthria, aphagia) persisted.

3. Discussion

We report an OMASE caused by a paraneoplastic neurological syndrome (PNS) associated with anti-Hu antibodies and breast ductal cancer. The patient showed a partial response to immunosuppressive and anti-seizure therapy. However, improvement in bulbar symptoms was obtained after breast tumor resection [2,4].

The clinical presentation was characterized by an increasing rate of facial myoclonus, dysphagia, and anarthria in a previously healthy middle-aged woman. An abnormal EEG revealed diffuse theta slow waves, intermittent bursts of sharp and slow waves over right centro-frontal regions, and occasionally generalized epileptiform discharges (50 % of prevalence) [2,4,5]. The epileptic discharges preceded myoclonic jerks; however, occasional waves of similar morphology occurred randomly without subsequent muscular contraction.

The few OMASE reports in the literature describe various etiologies, including stroke [1], tumors [1], drugs (specifically oxycodone) [2], herpes simplex virus infection [3], and anti-GAD65-associated encephalitis [4]. OMASE usually shows a good response to anticonvulsant therapy [6]; nevertheless, clinical symptoms and EEG were refractory in our patient, probably due to the paraneoplastic-specific presentation nature of this disease.

Paraneoplastic neurological syndromes (PNSs) are immune-mediated manifestations of a distant cancer [7]. The diagnosis criteria were revised by an expert panel in 2021 [7]. Based on this, our patient meets the criteria for probable paraneoplastic neurological syndrome due to (1) an intermediate-risk clinical phenotype (rapidly progressive onset of seizures), (2) a high-risk antibody (anti-Hu), and (3) although ductal breast cancer is an unusual type of cancer associated with the found antibody [7], there have been reports of associations between this neoplasm and anti-Hu antibody in patients with paraneoplastic neurological syndromes [8–10]. In 1999, Shavit described the association between anti-Hu and epilepsia partialis continua (EPC) [11], and subsequent reports confirmed this association [12–14].

A case of OMASE associated with high titers of anti-GAD65 serum antibodies has been reported [4]. In our patient, we also detected this antibody in the serum but at low levels. Although a low serum level of anti-GAD65 may be related to a heterogeneous and less specific symptom spectrum [15], assigning a pathological role to this finding is challenging. Serum antibodies against intracellular GAD can occur at low titers in 1 % of healthy people [16]. Moreover, it seems that only high titers of GAD antibodies are strongly associated with autoimmune neurological disorders (>2000 IU/mL with radioimmunoassay) or if there is an intrathecal synthesis of them, as opposed to patients without neurological manifestations [17]. These levels are 100–1.000 times higher than those seen in people with diabetes [18]. Other antibodies with a more defined pathogenic role, such as anti-g-aminobutyric acid (GABA) B receptor, can be associated with anti-GAD65 antibodies in patients with autoimmune encephalitis [19]. We also note its concurrent appearance with high levels of anti-Hu antibodies in our patient. Additionally, anti-GAD65 is not usually associated with neoplasia and is not considered a typical paraneoplastic antibody [20].

The patient received high doses of steroids and rituximab, with partial clinical and electrical responses. Early identification of breast cancer allowed for a successful curative surgery, and one year later, there was no evidence of tumor recurrence. The median survival of anti-Hu paraneoplastic neurological syndrome is 11.8 months, with a 3-year actuarial survival of 20 % based on a report of 200 cases [8]. The early diagnosis of cancer and prompt management were crucial in the clinical improvement and survival of our patient.

4. Conclusions

OMASE is a rare form of focal motor status epilepticus, and its association with anti-Hu antibodies and ductal breast cancer is also rare. In this case, the patient did not fully respond to immunosuppressive and anti-seizure therapy. As in other paraneoplastic neurological syndromes, the mainstay of treatment was cancer management.

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CRediT authorship contribution statement

César Romero: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Alonso Quijada:** Writing – original draft, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Gabriel Abudinén:** Project administration, Methodology, Investigation, Formal analysis, Data curation. **Catherine Céspedes:** Methodology, Investigation, Formal analysis, Data curation. **Ledda Aguilera:** Visualization, Validation, Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.

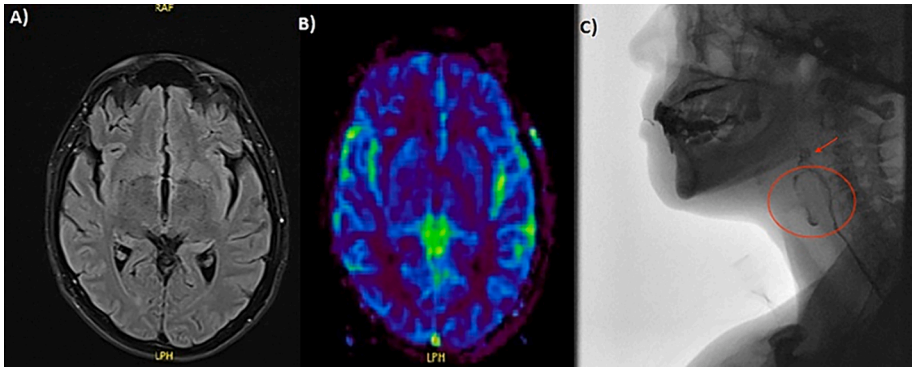

Fig. 2. A and B. Brain MRI with gadolinium and perfusion MRI. The T2 FLAIR sequence only highlights minimal puncta-form foci of bilateral frontal and parietal cortical-subcortical signal increase in the left semioval center through the subcortical white matter, with a nonspecific gliotal appearance. **C. Video-fluoroscopy.** Little contraction of the nasal and oropharynx, with incomplete posterior displacement of the base of the tongue; abundant retention in valleculae and pear-shaped sinuses (arrow), associated with pharyngo-nasal reflux and laryngeal-tracheal aspiration (red circle), without cough. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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