CASE REPORT

Ammonia encephalopathy and awake craniotomy for brain language mapping: Cause of failed awake craniotomy

G. Villalba Martínez, J.L. Fernández-Candil, R.M. Vivanco-Hidalgo, S. Pacreu Terradas, A. León Jorba, R. Arroyo Pérez

*A Neurosurgery Department, Hospital del Mar, Barcelona, Spain
B Anesthesiology and Resuscitation Department, Hospital del Mar, Barcelona, Spain
C Neurology Department, Hospital del Mar, Barcelona, Spain
D Neurophysiology Department, Hospital del Mar, Barcelona, Spain

Received 19 February 2014; accepted 22 September 2014
Available online 1 December 2014

KEYWORDS
Awake craniotomy; Ammonia levels; Ammonia encephalopathy; Valproic acid; Insular glioma

Abstract We report the case of an aborted awake craniotomy for a left frontotemporalinsular glioma due to ammonia encephalopathy on a patient taking Levetiracetam, valproic acid and clobazam. This awake mapping surgery was scheduled as a second-stage procedure following partial resection eight days earlier under general anesthesia. We planned to perform the surgery with local anesthesia and sedation with remifentanil and propofol. After removal of the bone flap all sedation was stopped and we noticed slow mentation and excessive drowsiness prompting us to stop and control the airway and proceed with general anesthesia. There were no post-operative complications but the patient continued to exhibit bradyphacia and hand tremor. His ammonia level was found to be elevated and was treated with an infusion of l-carnitine after discontinuation of the valproic acid with vast improvement. Ammonia encephalopathy should be considered in patients treated with valproic acid and mental status changes who require an awake craniotomy with patient collaboration.

© 2014 Sociedad Española de Anestesiología, Reanimación y Terapéutica del Dolor. Published by Elsevier España, S.L.U. All rights reserved.

PALABRAS CLAVE
Craneotomía con el paciente despierto; Niveles de amonio;

Resumen Se presenta el caso de un paciente con un glioma insulofrontotemporal izquierdo, tratado con levetiracetam, valproato y clobazam. Se realizó una primera cirugía bajo anestesia...
Encephalopathy

por amonio;
Ácido valproico;
Glioma insular

Introduction

Awake craniotomy is performed in patients with a tumor located in close proximity to eloquent areas of the brain. This procedure needs the collaboration of the patient to successfully map cortical and subcortical structures. Therefore, sedation effects should be absent or negligible at this point.1

Different anesthetic strategies have been described to perform the awake craniotomy and language mapping with local anesthetic: IV sedation (IVS) and asleep–awake–asleep (AAA).2–4 AAA technique consists in general anesthesia induction with laryngeal mask (Mayfield head holder placement, scalp and dura mater incision) followed by total awakening for intraoperative cerebral mapping, and finally general anesthesia with laryngeal mask for the dura mater and scalp closure.

IVS is the usual technique used in our center. It consists of conscious sedation using low doses of an opioid analgesic such as remifentanil with or without propofol, and local anesthesia for the surgical wound and for the regional nerves using bupivacaine 0.25%. Invasive blood arterial pressure, heart rate, oxygen saturation (SpO2) and end-tidal CO2 (etCO2) were recorded at baseline and during all the procedures via nasal cannula.

During the Mayfield head holder placement, scalp and dura mater incision the remifentanil (with or without propofol) infusion is maintained. The surgeons then proceed to map and resect the tumor with an awake and cooperative patient. During closure the remifentanil is reestablished at the same rate or at a higher dose because patient cooperation is not required.

The success of awake surgery is dependent on an adequate selection of patients. Obstructive sleep apnea syndrome (OSAS), obesity, gastroesophageal reflux, chronic cough, dysphasia, impaired consciousness and language barrier have been reported as relative contraindications to awake surgery.9

The majority of patients with a low-grade glioma undergoing surgery receive antiepileptic treatment, as seizures occur frequently in these patients.

Ammonia encephalopathy is not a frequent complication derived from the treatment with valproic acid. Patients with normal levels of valproic acid may suffer hyperammonemia, while patients suffering hyperammonemia do not necessarily have to suffer encephalopathy.10 An association between a daily intake of valproic acid and the appearance and severity of ammonia encephalopathy has not been found. A relation between the duration of the treatment and the ammonia levels has not been found either. Valproic acid, can induce hyperammonemia by acting in the mitochondria of the hepatocyte, inhibiting the carbamoyl phosphate synthetase 1, and decreasing ammonia utilization.11 Valproic acid also increases renal excretion of carnitine, which reduces fatty acids available for B-oxidation, increasing protein metabolism. In addition, an altered B-oxidation can decrease the ammonia metabolism in the cycle of urea.11,13

Symptoms of ammonia encephalopathy can be: lethargy, bradypsychia, decreased level of consciousness, vomiting, focal neurological deficits and even death. A clear correlation between clinical severity and ammonia blood levels has not been obtained. Diagnosis is based on clinical picture, blood test and electroencephalography (EEG). The EEG shows diffused signs of severe encephalopathy, with an irregular, continuous, severe and slowing diffused pattern with a predominance of theta and delta activity.14–16

A case of a patient who underwent awake craniotomy for language mapping is reported, in whom the presence of ammonia encephalopathy contributed to the appearance of respiratory depression, a fact that forced the neurosurgeon to abort the language mapping.

Case report

We present a 47 year old male, 87 kg, 180 cm, ASA grade II, without toxic habits with a brain MRI showing a left frontotemporinsular tumor suggestive of high-grade glioma. He debuted with a tonic-clonic seizure, followed by partial-complex and generalized seizures. He was treated with levetiracetam (1500 mg/12 h), valproic acid (1000 mg-500 mg-500 mg), and clobazam (10 mg/12 h). Liver function was normal. The preoperative neuropsychological assessment confirmed a slight expressive aphasia, and impaired verbal memory. The patient also complained of fatigue
for several months, and the examination revealed a mild
bradypsychia. We attributed the symptomatology to
the tumor size and location.

The strategy was to carry out the surgery in two surgi-
cal procedures. The first one consisted in a frontotemporal
craniotomy and temporal lobe resection under general anes-
thesia. One week after, a second surgical procedure took
place, under conscious sedation and language mapping, to
remove insular and frontotubaral tumor.

On arrival at the operating room, the patient was con-
scious and oriented with a GCS of 15. The left radial artery
was canialized and an arterial gasometry was taken. Par-
tial pressure of carbon dioxide in the arterial blood (pCO₂)
was 38 mmHg. In addition, ECG and pulse oximetry were
monitored. Three liters per minute of oxygen was admin-
istered via a nasal cannula with capnography to register the
etCO₂ in spontaneous ventilation. 1 mg/kg/h Propofol and
0.025 g/kg/min remifentanil infusions were initiated, while
the scalp, the trigeminal branches, occipital nerves, and the
points for Mayfield head-holder placement were infiltrated
with a total dose of 40 ml of 0.25% bupivacaine without
epinephrine. When the duramater was opened, remifen-
tanil infusion was interrupted in order to maintain the
patient alert and cooperative. Ten minutes later, the patient
remained drowsy. In this moment, the etCO₂ was 55 mmHg,
and respiratory rate decreased to 8 breaths/min. Then,
propofol (60 mg) and cisatracurium (10 mg) were admin-
istered, and airway control was achieved by a laryngeal fast
track mask without difficulty, and mechanical ventilation
was initiated. The anesthetic maintenance was done with
an infusion of propofol plus remifentanil titrated to main-
tain a value of bispectral index (BIS) between 45 and 60.
Mechanical ventilation was adjusted to achieve and main-
tain normocarbia. After waiting for 30 minutes, the surgical
team decided to stop the propofol infusion, to assess if the
patient was prepared for language mapping. The patient
was awakened and extubated, he went on breathing spon-
taneously with pulse oximetry values around 96%, but the
latency of his speech made it impossible to undergo a cor-
correct language mapping. The surgery was finished at that
point. The patient was moved to the postsurgical resus-
citation unit for 24 hours observation, and later to the
neurosurgical ward. In the first 48 hours of the postop-
erative period, the patient remained bradypsychic and at
72 hours after surgery he suffered flapping. The consulting
neurologist suggested ruling out ammonia encephalopathy
due to valproic acid. We measured valproate level, which
was 98.20 mcg/ml (normal range 50-100), but serum ammno-
ania level was 106 mcg/dl (normal range: 25-94). Liver and
renal functions, and albumin level, were normal. Taking
into account these results, we initiated treatment with
L-carnitine and we interrupted valproic acid treatment.
72 Hours after the treatment modification, the tiredness,
tremor and bradypsychia disappeared. The plasma level of
valproate was 73 mcg/dl and serum ammonia level was
63 mcg/dl.

Discussion

The patient’s symptomatology, fatigue and mild bradypsychia,
was usual in our clinical practice, in patients that
have a extensive glioma in the frontotemporinsular lobes.
Bradypsychia and fatigue were attributed to the tumor size,
location (frontotubaral tumors may produce cognitive symp-
toms frequently) and to the antiepileptic treatment. Some
antiepileptics, like levetiracetam, may produce, among
other symptoms, fatigue.19,20

After the first surgery (temporal lobe removal) the
patient worsened. He had a higher grade of bradypsychia,
but he could maintain a correct conversation that enabled
us to carry a good intraoperative language mapping. We
decided to perform the second surgery only 1 week after,
in order to prevent further neurological deficits. The his-
tological result was of grade III astrocytoma (malignant
glioma), and waiting for weeks for surgery in this kind
of tumor can drive a faster growth and not surgical possibil-
ity.

During the postoperative period of the awake craniotomy,
high levels of serum ammonia were detected, L-carnitine
administration was initiated and the acid valproic treatment
was interrupted. The improvement of the neurological sta-
tus was evident, demonstrating that high levels of serum
ammonia caused a depression of the central nervous sys-
tem.

For awake craniotomy, we usually administered a
remifentanil infusion, which is stopped during the dura
mater opening, then, the patient is able to perform
various tasks including counting or naming objects.21,22
Remifentanilis a short acting opioid with a predictable
pharmacokinetic profile.23 Its context-sensitive elimination
half-life is approximately 3 min, and it is independent
of infusion duration. In our case, the propofol and the
small dose of remifentanil could induce hypoventilation
and hypercapnia that could have contributed to the respira-
tory depression, but the patient would have recovered after stop-
ning the opioid infusion.

In the literature we can find some publications about
how the absorption of a local anesthetic, particularly
bupivacaine, can produce some cognitive alterations. On
the other hand, Costello et al. demonstrated a relatively
fast rise of plasma levobupivacaine concentration without
evidence of cardiovascular or central nervous system
sequelae.3,24 In our experience with brain language map-
ing, we generally noticed that after 30-40 ml of 0.25%
bupivacaine infiltration, patients remained quiet and they
rarely need more sedation. In our patient, the absorption
of the local anesthetic could have aggravated the previous
neurological status.

Bezinover et al. reported an increased sleepiness
and impaired cognitive status in a patient with chronic
hyperammonemia induced by valproic acid, after a general
anesthesia. In these patients, a surgical procedure, gener-
ating a catabolic state, can have a negative influence on
the mental status.11

It has also been reported that a combination of
antiepileptic drugs such as valproic acid and levetiracetam
can elevate ammonia levels.15

The publication of Nossek et al. is the only one in the lit-
erature in which causes of failed awake craniotomies were
investigated.25 A retrospective study of 424 cases was per-
formed. In none of them the treatment with valproate was
found as a cause of failed awake craniotomy. The authors
found that patients (with a previous language disorder, and
without seizure treatment before surgery), who received intraoperative phenytoin, had more cognitive alterations and excessive sedation.

The relation between an antiepileptic and mild sedation with a hypnotic drug was investigated. Ishii et al. showed an interaction. Patients taking valproic acid who underwent dental procedure with a minimal sedation required smaller doses of propofol.26

Due to its high sensitivity, EEG in ammonia encephalopathy is very useful. Nevertheless, as different causes of encephalopathy show the same encephalographic pattern, it is scarcely specific. The EEG shows diffused signs of severe encephalopathy, with an irregular, continuous, severe and slowing diffused pattern with a predominance of theta and delta activity.14-16 However, cases of presence of periodic activity or triphasic waves have also been described.14,17 As far as the case being described in this paper is concerned, if an intraoperative EEG study had been indicated, it may have detected the encephalopathy, even though the most likely diagnosis would not have been ammonia encephalopathy.15

In this case, it was deemed that the most plausible cause of neurological impairment in the form of bradypsychia, asthenia and flapping in a patient treated with valproic acid was an ammonia encephalopathy, although ammonia level was not obtained prior to the second surgery. Flapping was the sign that raised the suspicion of ammonia encephalopathy. Encephalopathy is an infrequent but severe complication, originated due to an increase in the blood ammonia level and indirectly producing brain edema. Treatment with L-carnitine and valproic acid discontinuation is described in the literature.16,18

Conclusion

Preoperative ammonia levels should be obtained in patients treated with valproic acid scheduled to undergo an awake brain surgery and show a clinical state that may suggest ammonia encephalopathy, regardless how subtle it might be, and should be treated before surgery. Moreover, the sedative effect of minimum doses of intravenous anesthetics (like remifentanil or propofol) and/or local anesthetic absorption will probably be increased in patients suffering an ammonia encephalopathy.

Ethical approval

The authors have taken into account the ethical responsibilities of the journal.

Conflict of interest

No conflict of interest for anyone of the authors.

References

