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Case report

An adult case of acute encephalopathy associated with general anaesthesia and the m.11232T > C *MT-ND4* variant

Encefalopatía aguda asociada a anestesia general en un paciente adulto portador de la variante m.11232T > C en el gen MT-ND4

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ABSTRACT

We report the case of a 20-year-old woman who developed acute encephalopathy after uneventful general anaesthesia with sevoflurane, propofol, and opioids. The patient presented neurological impairment followed by metabolic acidosis and hyperlactatemia and neuroimaging findings involving the basal ganglia, brainstem, and cerebellum. Genetic testing confirmed the mitochondrial variant m.11232T > C in the *MT-ND4* gene, previously described only in paediatric patients. This case could be one of the first cases described in the literature of acute encephalopathy associated with this mutation in an adult patient, possibly precipitated by exposure to volatile anesthetics. The patient's favorable clinical and radiological evolution after intensive neuroprotective management and suboccipital decompressive craniectomy highlights the importance of early diagnosis and individualized treatment. Mitochondrial dysfunction should be considered in atypical neurological presentations following general anesthesia, especially when accompanied by lactic acidosis and unusual neuroimaging findings.

RESUMEN

Se presenta el caso de una mujer de 20 años que desarrolló encefalopatía aguda tras anestesia general con sevoflurano, propofol y opioides, sin incidencias intraoperatorias. La paciente presentó deterioro neurológico severo seguido de acidosis metabólica e hiperlactacidemia y hallazgos radiológicos compatibles con afectación de ganglios basales, tronco del encéfalo y cerebelo. El estudio genético confirmó la presencia de la variante mitocondrial m.11232T > C en el gen *MT-ND4*, previamente descrita únicamente en población pediátrica. Este caso podría ser uno de los primeros casos descritos en la literatura de encefalopatía aguda asociada a esta mutación en un paciente adulto, posiblemente precipitada por exposición a anestésicos volátiles. La evolución clínica y radiológica favorable tras neuroprotección intensiva y craneotomía descompresiva suboccipital respalda la importancia del diagnóstico precoz y del manejo individualizado. Es importante considerar la disfunción mitocondrial ante cuadros neurológicos atípicos tras anestesia general, especialmente en pacientes con hiperlactacidemia y antecedentes familiares compatibles.

Introduction

Clinicians in Spain recently reported 2 cases of paediatric patients of Venezuelan ancestry who developed serious neurological injury with involvement of the basal ganglia on neuroimaging scans after undergo-

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ing uneventful general anaesthesia. A mitochondrial DNA mutation was identified in both cases.¹

Mitochondrial diseases are caused by adenosine triphosphate (ATP) synthase deficiencies.² The mitochondrial respiratory chain consists of 5 enzyme complexes located on the inner mitochondrial membrane, of which I, III, and IV are responsible for creating the electrochemical gradient used by complex V to create ATP.³

The m.11232T > C variant affects the *MT-ND4* gene that encodes a structural subunit of respiratory complex I (ubiquinone oxidoreductase [NADH]),¹ the entry point of the mitochondrial electron transport chain.

Patients with mitochondrial diseases have a reduced capacity to generate and use ATP as an energy source, especially in organs that are most dependent on mitochondrial energy such as the nervous system, cardiac muscle, and skeletal muscle.²

We report the case of an adult patient carrying the mitochondrial m.11232T > C variant in *MT-ND4* who developed acute encephalopathy after general anaesthesia.

Case report

A 20-year-old woman, habitual smoker, originally from Venezuela, whose medical-surgical history was only significant for a miscarriage, and who was not receiving chronic medication.

The patient was scheduled for surgery. Anaesthesia was induced with 150 µg fentanyl, 180 mg propofol, 60 mg lidocaine and 20 mg rocuronium, and maintained with sevoflurane (0.7–1 MAC) and remifentanyl (0.05–0.15 µg/kg/min). Intraoperative analgesia consisted of fentanyl (total 300 µg), 1 g paracetamol and 50 mg dextetopropfen, antiemetic prophylaxis consisted of dexamethasone and ondansetron, and antibiotic prophylaxis consisted of 2 g cefazolin. The patient remained haemodynamically stable with stable breathing throughout surgery, and no medical or surgical complications were observed.

At the end of the procedure, sedation was withdrawn, neuromuscular blockade was reversed with sugammadex, and the patient was extubated. After extubation, she did not obey verbal commands or respond to stimuli despite a bispectral (BIS) index of 80 with 0 suppression rate. Despite flumazenil and naloxone, her Glasgow score remained at 3; her pupils were isochoric and reactive. She was diagnosed with delayed awakening, so orotracheal intubation was performed and she was trans-

ferred to the Intensive Care Unit (ICU). Her lab tests were significant for metabolic acidosis with hyperlactataemia (9 mmol/L) and base excess of -13. An urgent cranial computed tomography (CT) scan showed mild cerebellar hypodensity but no other findings.

At 24 h, a second attempt at extubation failed due to her fluctuating level of consciousness. Further lab tests showed that the metabolic acidosis had resolved and lactate levels had normalised. A second cranial CT showed extensive areas of hypodensity in the brainstem, cerebellum and globi pallidi, which was interpreted as hypoxic-ischaemic encephalopathy; a CT angiogram was normal. The electroencephalogram (EEG) showed moderately diffuse encephalopathy with no epileptiform activity or subclinical seizures.

Forty eight hours later, she was transferred to the neurocritical unit, where sedoanalgesia was maintained with midazolam and propofol, and neuroprotective measures were applied. Neurological tests performed during the sedation window showed slight anisocoria with slowly reactive pupils, response to pain in the right upper extremity and beginning of flexion in the left. The study was completed with brain magnetic resonance imaging (MRI), which showed bilateral, symmetrical hyperintense lesions in lenticular nuclei, thalami, hippocampi and cerebellar cortex in T2 weighted Fluid-Attenuated Inversion Recovery (FLAIR), with restricted diffusion (Fig. 1). Mass effect on posterior fossa and brainstem, obstruction of the fourth ventricle and supratentorial hydrocephalus and tonsillar descent. In light of the neuroimaging findings, the radiology service ruled out a hypoxic-ischaemic aetiology and suggested a *prior* an acute toxic aetiology, possibly related to opioid administration. The primary diagnosis was cerebellar, hippocampal, and basal nuclei transient oedema with restricted diffusion (CHANTER) syndrome.

Given the radiological findings and the clinical situation, emergency suboccipital decompressive craniectomy and C1 laminectomy were performed. During the intervention, asymmetric cerebellar herniation was observed, with recovery of cerebellar pulse after decompression (Fig. 2). Given the suspicion of CHANTER syndrome, anaesthesia was maintained with a multimodal opioid-free strategy using target-controlled infusion (TCI) of sevoflurane and propofol. Following surgery, the patient presented a further episode of metabolic acidosis with hyperlactataemia (5 mmol/L), which normalised again within 24 h.

These findings support the hypothesis of acute metabolic dysfunction, probably secondary to mitochondrial genetic dysfunction, with

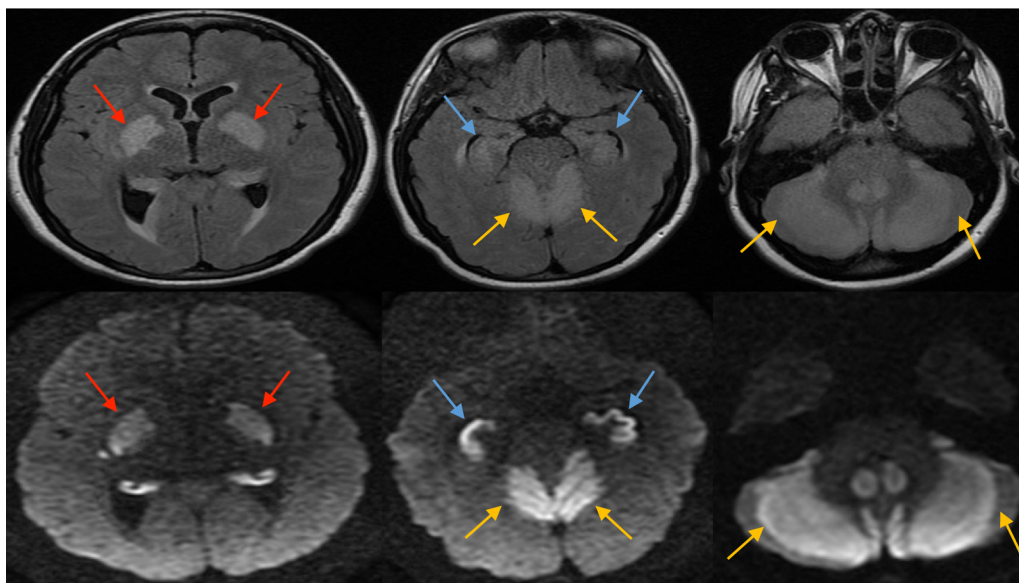


Figure 1. Axial T2-weighted FLAIR images (top) and their complementary diffusion image (bottom) in the acute phase of diagnosis. Note the extensive T2-weighted FLAIR signal alteration with diffusion restriction affecting bilaterally and symmetrically the lenticular nuclei (red arrows), hippocampal system (blue arrows) and cerebellar hemispheres (yellow arrows), in relation to areas of subacute cytotoxic oedema. This significantly restricts the available space, causing almost total collapse of the fourth ventricle, supratentorial hydrocephalus, obliteration of the basal cisterns, and mild herniation of the cerebellar tonsils.

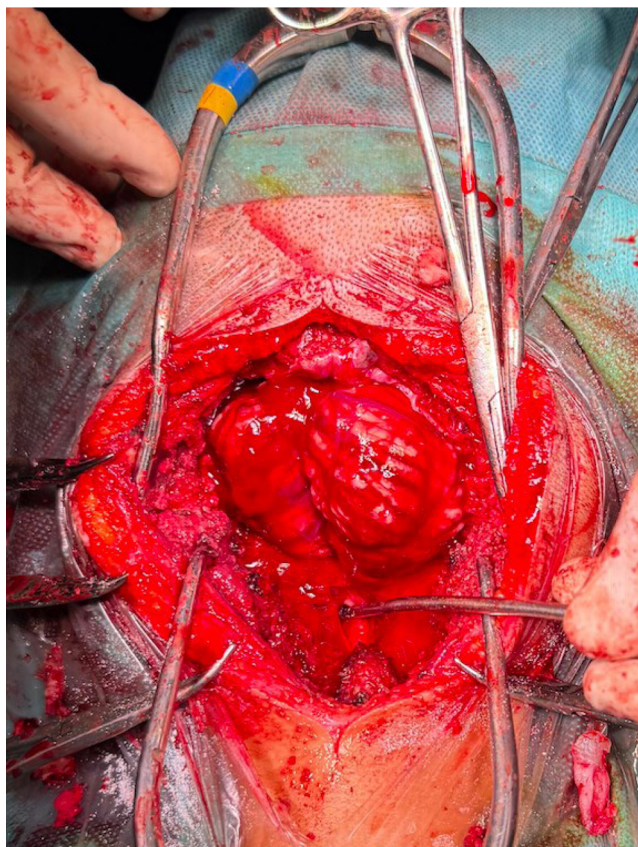


Figure 2. Suboccipital decompressive craniectomy and C1 laminectomy. Asymmetric cerebellar herniation.

opioid toxicity as a contributing factor. In this context, genetic testing confirmed the presence of the m.11232T > C variant in the *MT-ND4* gene and its germinal segregation in the mother and the maternal family.

During her stay in the ICU, the patient continued to receive neuroprotective measures under deep sedation with propofol and midazolam without halogenated drugs and opioids. Brain activity was monitored with continuous four-channel EEG, and serial pupillometry was performed, which showed slight anisocoria and altered reactivity, with a neurological pupillary index (NPI) < 3. Five days later, a new cranial CT scan was performed that showed improvement in the signs of hydrocephalus and the expansive process, definition of the cerebellar sulci and basal cisterns, with persistent hypodense areas in basal nuclei and cerebellar hemispheres. At that moment, sedation was again interrupted and the patient was observed to perform spontaneous eye opening with improvement in pupillary reactivity (NPI > 3), obey simple commands, and initiate contraction of the right upper limb.

Following this, she made slow but favourable progress. She presented lower cranial nerve involvement (IX, X and XII), with sialorrhea, difficulty in managing secretions, upper airway oedema and alteration of oropharyngeal and neck and trunk muscle tone. An MRI showed some persistent alterations in the lenticular nuclei and both cerebellar hemispheres in T2 weighted FLAIR. The alteration of the hippocampal system signal had resolved and diffusion was no longer restricted, indicating improvement of the cytotoxic oedema (Fig. 3).

Tracheostomy was performed on day 13 of admission, and mechanical ventilation was disconnected on day 17. She received speech therapy and motor rehabilitation, at first passive and then progressively active. By the third week of admission, the patient presented symmetrical, coordinated limb movements, better control of neck and trunk tone, and better management of oral secretions, although dysphagia persisted. Gastrostomy was performed on day 23 of admission. Imaging studies

also showed good progress, with an MRI at 4 weeks showing significant improvement in the areas of hyperintensity in T2 weighted FLAIR, mainly in both thalami, hippocampal system and cerebellum, and normalization of the areas of diffusion restriction observed the previous study (Fig. 4).

The patient was discharged from the ICU on day 48 of admission, presenting with residual cerebellar syndrome and mild generalized hypotonia and slight ataxia of all 4 limbs. This predominantly affected the lower cranial nerves, which caused significant otorhinolaryngological (ENT) symptoms, particularly severe dysarthria, poor management of secretions, dysphagia, and paresis of the tongue and vocal cords.

One month after discharge from the ICU, she remains on a hospital ward awaiting transfer to a neurorehabilitation centre. She presents global bradykinesia, mild axial hypotonia, and hypotonia in the left upper extremity, together with weakness of the extensor muscles of the neck. She is able to stand upright, with lateropulsion to the left. In terms of ENT: tongue protrusion with slight lateralization to the right, posterior oral hyperreflexia, vocal cords of normal appearance, symmetrical, with good mobility. Severe lack of coordination of the pharyngolaryngeal muscles during phonation or swallowing.

Discussion

Complex I of the mitochondrial respiratory chain is a rate-limiting step in mitochondrial energy production⁴ that relies on subunits encoded by mitochondrial genes such as *MT-ND4* to function correctly.

The m.11232T > C variant in the *MT-ND4* gene appears to alter oxidative phosphorylation, which limits ATP production, particularly in tissues with high energy demand, such as the central nervous system (CNS).¹

Respiratory complex 1 is inhibited by volatile anaesthetics such as halothane, isoflurane, and sevoflurane.⁵ This leads to an increase in lactate⁶ and a decrease in ATP production, and creates an environment of low metabolic activity that could contribute not only to the observed neurotoxicity but also to the intended pharmacological effects of anaesthetics, although the exact mechanism still requires experimental confirmation.

In patients with reduced bioenergetic response, the stress, fasting and catabolism associated with surgery increases cerebral metabolic demand, a process that is compounded by exposure to volatile anaesthetics, which alter the function of the mitochondrial transport chain⁷ and promote anaerobic metabolism and lactate accumulation. The combination of these factors maximises the patient's vulnerability to neurological damage and could precipitate serious neurological injuries in nuclei with high synaptic activity, such as the basal ganglia.⁸

This case could be one of the first descriptions in the literature of acute encephalopathy associated with the administration of anaesthetic drugs in an adult patient carrying a variant in the *MT-ND4* gene. Although the global prevalence of this variant is unknown, there are reports in Spain of two paediatric patients, both of Venezuelan origin, who developed severe neurological lesions in the basal ganglia after general anaesthesia with sevoflurane, propofol and fentanyl. Both patients carried the same *MT-ND4* gene variant.¹

Given the need for a second urgent surgical intervention, and the suspicion of opioid-related Chanter syndrome, the treating team decided to perform opioid-free anaesthesia with sevoflurane and propofol. Lab tests on admission to the ICU after surgery again showed metabolic acidosis with hyperlactataemia; however, during her stay in the ICU the patient received propofol and midazolam without incident. The timing of these clinical manifestations suggests that sevoflurane could be culprit, but it is impossible to establish a definitive causal relationship.

Researchers from the *Oxphos* project led by Dr. Eduardo Ruiz have hypothesized that exposure to halogenated anaesthetics, especially sevoflurane, could significantly alter mitochondrial oxidative phosphorylation. The preliminary results, pending publication, confirm this

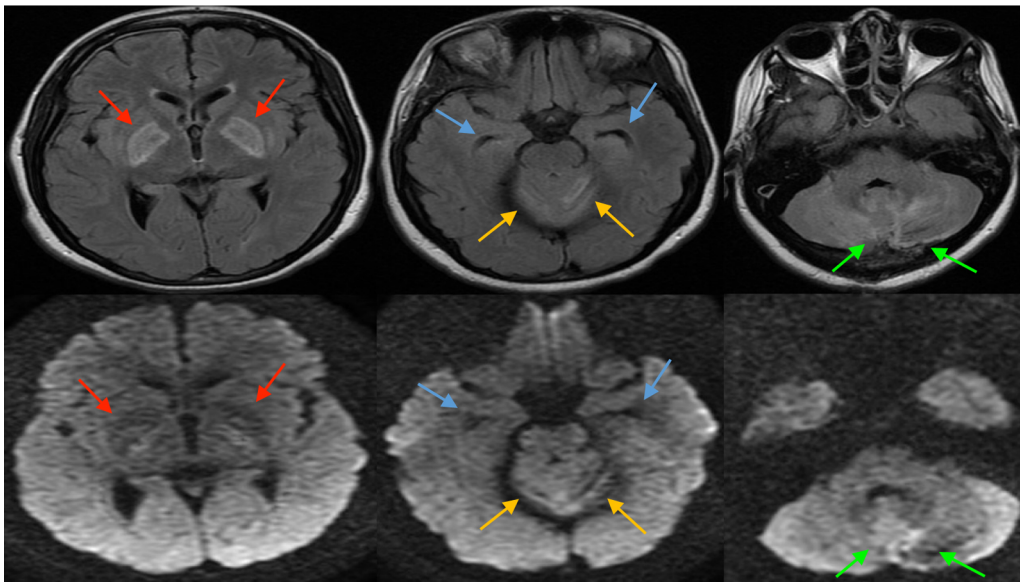


Figure 3. Axial T2-weighted FLAIR images (top) and their complementary diffusion image (bottom) 2 weeks after the previous MRI showing good radiological evolution of the previously identified lesions. There is some alteration of the T2-weighted FLAIR signal in the lenticular nuclei (red arrows) and both cerebellar hemispheres (yellow arrows). The alteration of the hippocampal system signal had resolved and diffusion is no longer restricted, indicating improvement of the cytotoxic oedema (Fig. Clear improvement of the mass effect on the ventricular system and brainstem. Note the areas of gliosis and cerebellar microbleeds secondary to decompressive craniectomy (green arrows).

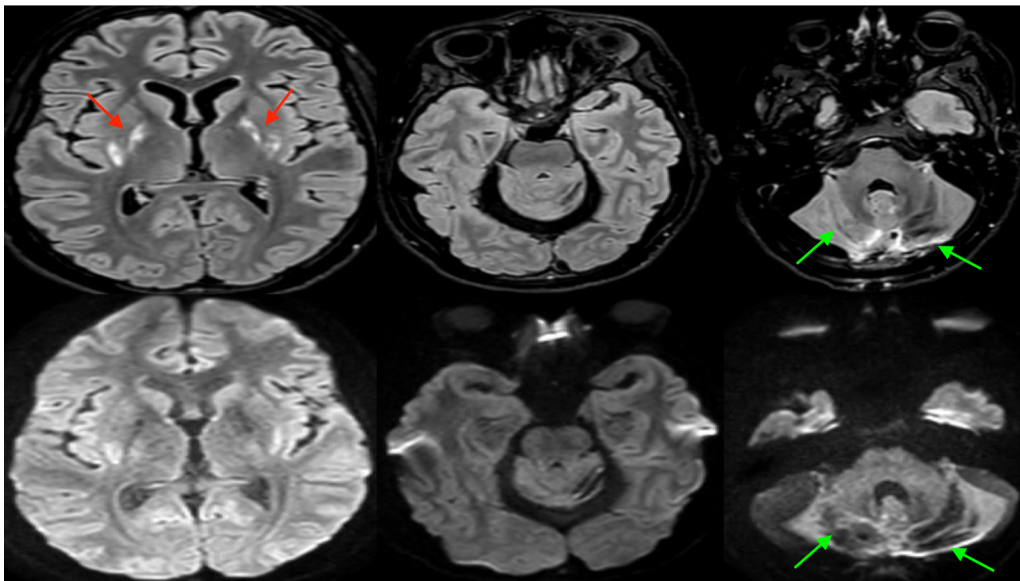


Figure 4. Axial T2-weighted FLAIR images (top) and their complementary diffusion image (bottom) 5 weeks after the previous MRI. Almost complete resolution of T2-weighted FLAIR signal alteration and diffusion. Only minimal residual hyperintensity persists in the posterior aspect of the lenticular nuclei (red arrows); there is absolutely no diffusion restriction. Note the areas of gliosis and cerebellar microbleeds secondary to decompressive craniectomy (green arrows).

bioenergetic dysfunction in samples from 6 patients of Venezuelan origin from 5 unrelated families who were carriers of the mutation in the *MT-ND* gene.¹

Neuroimaging plays a key role in diagnosis. Cranial CT scans usually show hypodensity in basal ganglia. MRI shows hyperintense lesions on T2-weighted FLAIR images in the same locations.⁹ This entity is characterised by cytotoxic oedema, which is identified on MRI by restricted diffusion similar to that observed in hypoxic-ischaemic lesions. Although the basal ganglia can be involved in hypoxic-ischaemic encephalopathy, this involvement rarely occurs in isolation and is usually accompanied by cerebral cortical lesions.¹⁰ In our patient, however, both cerebral hemispheres were normal, and only the basal ganglia on

both sides together with the cerebellum and brainstem were involved, all suggestive of toxic-metabolic encephalopathy.

On MRI, these lesions are hard to distinguish from those presented by other clinical entities associated with diffusion restriction, such as Chantier syndrome, a condition that presents with transient lesions in the cerebellum, hippocampus, and basal ganglia, usually associated with opioid¹¹ or cocaine¹² use. The pathophysiological mechanism is unknown; however, a possible culprit could be primary metabolic or mitochondrial failure of the grey matter.¹³

Finally, occipital decompressive craniectomy is a therapeutic option in cases of posterior fossa hypertension with risk of brainstem herniation. It has been shown to reduce mortality by 20%,¹⁴ and the functional

prognosis is favourable in more than 50% of cases.¹⁵ It is currently indicated in malignant cerebellar infarction with brainstem compression or obstructive hydrocephalus and in cerebellar haemorrhage with neurological deterioration and mass effect.¹⁶ In this case, however, early intervention was decisive in changing the patient's prognosis. Furthermore, the transient nature of the lesions and the favourable clinical evolution up to the time of writing, which contrasts significantly with cases reported so far, strongly suggests that it should be considered in patients with a similar clinical picture.

Conclusion

Unexpected events following general anaesthesia, such as delayed awakening, should prompt consideration of possible mitochondrial metabolic dysfunction, especially in the presence of metabolic acidosis, hyperlactataemia, and atypical neuroradiological findings for ischaemia. The prevalence of the m.11232T > C variant in the *MT-ND4* gene is unknown, and the evidence published so far is limited to the paediatric population.

This genetically confirmed case of an adult patient of Venezuelan origin extends the known age range and suggests that the condition could be underdiagnosed in the adult population. Although we cannot establish a causal relationship, the timing of clinical events in our case points to sevoflurane as the most likely culprit. We believe that the appropriate use of neuroprotective strategies, along with early neurosurgical management in selected patients, can help improve prognosis.

This case raises the need to investigate the true prevalence and causality of this entity so that researchers can develop specific protocols that promote early recognition and optimize perioperative management.

CRedit authorship contribution statement

All authors have made substantial contribution to this article.

Informed consent

The data presented do not violate patient privacy or confidentiality and cannot be used to identify the patient. Informed consent was obtained to use the clinical information.

Declaration of Generative AI and AI-assisted technologies in the writing process

Artificial intelligence has only been used solely for writing assistance.

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Declaration of competing interest

None of the authors have any conflicts of interest to declare.

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