Mitochondrial Cardiomyopathies Associated With the m.3243A>G Mutation in the MT-TL1 Gene: Two Sides of the Same Coin

Miocardipatias mitocondriales asociadas a la mutación m.3243A>G en el gen MT-TL1: dos caras de la misma moneda

To the Editor,

We report 2 patients diagnosed with cardiomyopathy caused by a single genetic defect in the mitochondrial DNA. Both patients illustrate the importance of integrating clinical information when establishing a diagnosis, and allow us to discuss the unique characteristics of reproductive counselling for this type of genetic disease.

The first patient was a black Angolan man aged 47 years, who had moved to Spain to study ophthalmology. His clinical history included long-standing diabetes mellitus, recurrent tuberculosis, and bilateral sensorineural hearing loss. He was admitted for fever and acute respiratory failure. The echocardiogram (Figure) showed concentric left ventricular hypertrophy and severe systolic dysfunction. The cardiologic study was complemented with magnetic resonance imaging (absence of late-enhancement) and coronary angiography (normal). Other findings included marked cachexia, with steppage gait and renal failure with microalbuminuria. His mother had died of heart problems, his children were healthy, and a sister had an unspecified heart disease. Mitochondrial disease was suspected, specifically MIDD syndrome (maternally inherited diabetes and deafness) (Table). Sequencing of mitochondrial DNA from a blood sample revealed an m.3243A>G mutation in the MT-TL1 gene encoding mitochondrial tRNALeu, with 50% heteroplasmy. The patient was discharged with treatment for heart failure and returned to his home country.

The second patient was a 36-year-old woman with multiple brain microbleeds identified during a study for hearing loss, and in whom cardiac evaluation revealed a possible noncompaction cardiomyopathy (Figure). The patient had had type 1 diabetes since the age of 24 years, and had short stature and low body mass index. There was no family history of heart disease, myopathy, or sensorineural problems. The patient reported frequent migraines. She was in New York Heart Association functional classes II-III for exercise intolerance, had normal levels of creatine kinase and the amino terminal fraction of brain natriuretic peptide, and oscillating lactate levels (>2.5 mmol/L in several readings).

No further treatment was indicated, as ventricular function was normal. In this patient, the suspected clinical phenotype was MELAS (mitochondrial encephalomyopathy, lactic acidosis, and stroke–like episodes) (Table). Muscle biopsy showed 8% ragged red fibers, mostly cyclooxygenase-positive (Figure), and the genetic study again revealed the m.3243A>G mutation in MT-TL1, with 87% to 91% heteroplasmy in the muscle biopsy.

Mitochondrial diseases are characterized by dysfunction of the respiratory chain, leading to cellular energy deficit. The most commonly affected organs are those with the highest metabolic demand, such as the nervous system and muscle. Common manifestations include encephalopathy, myopathy, diabetes, and hearing loss. The simultaneous involvement of several of these organs without an apparent common cause or manifestations early in life, such as diabetes or stroke before age 40 years, should serve as a guide to this diagnosis. These syndromes may present with widely different percentages of cardiac abnormalities (from 3%–81%, depending on the series) and in the form of both cardiomyopathies (usually hypertrophic or dilated) and conduction disorders (Table). The m.3243A>G mutation in mitochondrial tRNALeu is one of the most common, and can result in different syndromes such as MIDD (case 1) and MELAS (case 2), with considerable variation in cardiac manifestations. It is common to observe onset or worsening of symptoms after stressful situations (in the first patient, the hearing loss attributed to tuberculosis drugs had actually started years earlier, following an episode of malaria). In the presence of a classical clinical syndrome, the diagnosis can be confirmed by genetic analysis. Treatment is symptomatic, and should avoid drugs such as metformin (risk of lactic acidosis) or statins (worsening myopathy). Antioxidants or alternative therapies with coenzyme Q10 and L-carnitine are used, although there is controversy about their beneficial effects. Anesthesia should be used with special caution due to the risk of respiratory failure, with avoidance of nondepolarizing muscle relaxants and barbiturates.

Following diagnosis, the patient in case 2 expressed a desire to have children without this disease. Providing genetic counseling is one of the tasks facing cardiologists managing patients with familial heart disease.

Mitochondrial genetics has a number of peculiarities to be taken into account when giving reproductive advice. Since zygote mitochondria come from the oocyte, inheritance is matrilineal, with women transmitting to all their descendants. The coexistence of more than one type of mitochondrial DNA molecule is called heteroplasmy. A minimum percentage of mutated DNA is necessary for symptoms to become evident (threshold effect). In cell division, the distribution of mitochondria is random, and daughter cells do not necessarily receive the same amount of mutated DNA. Mitochondrial DNA continues to replicate independently of cell division, such that initially healthy tissues may develop signs of disease over time. These features explain the phenotypic variation and clinical expression of these disorders, as well as the difficulty in preventing them by using assisted reproduction techniques. The reproductive options that guarantee the absence of disease transmission to offspring are adoption, gestation of an embryo from another couple, or fertilization of a donated egg. All have the disadvantage that the genetic link to the mother is lost.

Preimplantation diagnosis for mitochondrial genetic disorders can only reduce the chances of disease by transferring embryos with low levels of heteroplasmy. Under current Spanish law, it is unlikely that this treatment would be authorized, since it does not ensure the use of embryos without genetic defects.

Although still in the experimental stage, the future of prevention for these diseases lies in mitochondrial replacement techniques. These techniques consist of creating embryos with...
nuclear DNA from the parents, and mitochondrial DNA from a donor (“3-parent babies”). The efficacy and safety of these techniques is supported by a recent British scientific document supports, which calls for their translation to humans, in the current context in which it is not possible to use genetically modified embryos. Following publication of this document, and following popular consultation showing that public opinion was in favor of these techniques, the UK government has proposed to amend its legislation.1

The patient in case 2 finally decided to undergo in vitro fertilization with donated oocytes.

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Early Prognostic Evaluation After Mild Therapeutic Hypothermia in Sudden Cardiac Arrest Survivors

Valoración pronóstica precoz de pacientes con muerte súbita recuperada sometidos a hipotermia terapéutica

To the Editor,

The presence of severe neurological sequelae following sudden cardiac arrest leads to heavy resource use. Therapeutic hypothermia is indicated to prevent severe brain damage (SBD) although this treatment and prognostic evaluation in this setting are controversial. Prognostic evaluation basically has 2 objectives: first, to inform the family of the possibilities of recovery and, second, to aid diagnostic and therapeutic decisions. A neurological evaluation using several variables is recommended from the third day after injury. In contrast, information on the early prediction of SBD has received much less attention.

The aim of this study was to design a model for predicting SBD using the admission data of consecutive patients who survived cardiac arrest of probable cardiac origin and who underwent therapeutic hypothermia.

Data from patients admitted to the cardiology intensive care unit at our center were collected between November 2009 and January 2014. Their clinical and analytical data were recorded, as well as their clinical course while in hospital. Hypothermia was applied using an Artic-Sun device (33°C 24-hour and rewarming at 0.25°C/h). Neurological outcome was measured using the Cerebral Performance Category (CPC) scale. Patients with a CPC 3 to 5 and those who died during hypothermia were considered to have SBD. In patients with no recovery of consciousness after completing hypothermia and withdrawal of sedation, an electroencephalogram was performed 72 to 96 hours after admission, as well as an evoked potentials test to determine the presence of the N20 wave, which indicates cortical response.

A model for predicting SBD was designed using various variables available early on. The analysis included the variables available at admission that showed a statistical association (P < .2) with the onset of SBD. The predictive model was obtained using binary logistic regression and ROC curve analysis (PASW Statistics 19.0; Chicago, Illinois, United States), prioritizing the simplicity of the measure and the reproducibility of its component variables, as well as the statistical criteria of the lowest Mallow’s Cp, the greatest area under the ROC curve (AUC), and maximum parsimony of the model.

Of the total number of patients treated (n = 100), 1 was excluded for being deemed unsuitable. The patient characteristics and their in-hospital clinical course are summarized in the Table.

The incidence of SBD was 57 of 99 (57.6%). The distribution by CPC categories at discharge was: CPC1, 34 of 99 (34.3%); CPC2, 8 of 99 (8.1%); CPC3, 5 of 99 (5.1%); CPC4, 38 of 99 (38.4%); and CPC5, 12 of 99 (12.1%); the 2 remaining patients (2.1%) died before reaching normothermia.

At admission, the variables associated with SBD were initial lactate level, metabolic acidosis, myoclonus, absence of motor activity, time to start of cardiopulmonary resuscitation, and age. Other variables associated with SBD were myoclonic status at the end of hypothermia, persistent metabolic acidosis, and the absence of cortical response in evoked potentials.

The technical aspects and complications associated with the treatment were not correlated to SBD.

The final predictive model, comprising 3 components (age, initial lactate, and myoclonus at admission) showed an AUC of 0.85 (95% confidence interval, 0.76-0.94). The Figure shows the ROC curve of the predictive model.

In patients undergoing therapeutic hypothermia, neurological recovery may be delayed by the effect of sedation or by therapeutic hypothermia in the brain. Current recommendations stipulate that neurological evaluation should be delayed for more than 72 hours and should be based on multiple predictors, as no individual variable can completely rule out a delayed recovery.

There is little information on early prognostic evaluation in patients with sudden cardiac arrest. Recently, Aschauer et al analyzed a series of 1932 patients with out-of-hospital sudden cardiac arrest and obtained a risk of death score at 30 days with 4 variables with a remarkable predictive capacity (AUC = 0.81). The main difference with our series was the objective variable. In our opinion, all-cause mortality (bleeding, infections, etc) and SBD are outcomes with significant conceptual differences and different socioeconomic consequences. In addition, some of the variables included, despite being powerful predictors (amount of adrenaline administered, minutes to recovery of spontaneous circulation), are sometimes difficult to measure accurately given the emerging nature of the event. In our series, priority was given to the...