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Mitochondrial dysfunction in a family with psychosis and chronic fatigue syndrome

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ABSTRACT

Mitochondrial impairment is hypothesized to be involved in chronic fatigue syndrome (CFS) and schizophrenia. We performed a clinical, genetic and functional mitochondrial study in a family consisting of a female presenting schizophrenia in addition to CFS symptoms and her mother and older sister, both presenting with CFS. The three family members showed higher blood lactate levels, higher mitochondrial mass, lower mtDNA content and overall lower mitochondrial enzymatic activities and lower oxygen consumption capacities than healthy women. This family presented mtDNA depletion; however, no mutation was identified neither in the mtDNA nor in the nuclear genes related with mtDNA depletion, even though C16179A and T16519A variants should be further studied.

1. Introduction

Chronic fatigue syndrome (CFS) is a complex illness with an estimated prevalence of 0.8% (Johnston et al., 2013). Diagnosis consists of a list of symptoms that are often, but not always, present and that occur with varying degrees of severity. For a CFS diagnosis, a patient might self-report persistent or relapsing fatigue for at least six consecutive months or longer not caused by another medical condition and four or more of the following symptoms: post-exertional malaise, impaired memory or concentration, unrefreshing sleep, muscle pain, multi-joint pain without redness or swelling, tender cervical or axillary lymph nodes, sore throat or headache (Fukuda et al., 1994). Alterations in immune, gastro-intestinal, genitourinary and autonomic function may be associated with this syndrome. Although the causes and pathophysiology of CFS and the effectiveness of the few currently available treatments remain unknown, the central nervous system is most likely involved (Holgate et al., 2011).

Schizophrenia is also a complex illness with a prevalence of approximately 0.30–0.66% (McGrath et al., 2008). Schizophrenia is characterized by delusions, hallucinations, disorganized speech and behavior, and other symptoms that cause social or occupational dysfunction. Cognitive deficits and negative symptoms as social withdrawal, loss of motivation and initiative, self-neglect, emotional blunting, and paucity of speech are frequently present. Medical illness is highly prevalent in schizophrenia patients, and the mortality rates from medical illnesses are elevated in comparison to the general population for a number of disease categories, including infectious, respiratory, endocrine, gastrointestinal, and cardiovascular diseases (Leucht et al., 2007). The etiology

Abbreviations: ATP, adenosine triphosphate; C10orf2, chromosome 10 open reading frame 2; CI, mitochondrial complex one; CII, mitochondrial complex two; CIII, mitochondrial complex three; CIV, mitochondrial complex four; cDNA, complementary deoxyribonucleic acid; Cellox, global endogenous substrate consumption; CFS, chronic fatigue syndrome; CPK, creatine phosphokinase; CS, citrate synthase; DGUOK, deoxyguanosine kinase; DNA, deoxyribonucleic acid; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; EDTA, ethylenediaminetetraacetic acid; G3Pox, glyceraldehyde 3-phosphate oxidation; GMox, glutamate malate oxidation; GUSB, glucuronidase beta; HPRT1, hypoxanthine phosphoribosyltransferase 1; IPAQ, International Physical Activity Questionnaire; MPV17, MpV17 mitochondrial inner membrane protein; MRC, mitochondrial respiratory chain; MRI, magnetic resonance imaging; mtDNA, mitochondrial DNA; MT-ND1, mitochondrially encoded NADH dehydrogenase 1; MT-ND4, mitochondrially encoded NADH dehydrogenase 4; nDNA, nuclear DNA; PBMCs, peripheral blood mononuclear cells; PGM, personal genome machine; PMox, pyruvate malate oxidation; POLG, polymerase (DNA directed), gamma; qPCR, quantitative polymerase chain reaction; RNA, ribonucleic acid; RNAse P, ribonuclease P; RPPH1, ribonuclease P RNA component H1; RRM2B, ribonucleotide reductase M2 B; SCAN, Schedules for Clinical Assessment in Neuropsychiatry; SD, standard deviation; SEM, standard error of the mean; Sox, succinate oxidation; SPECT, single-photon emission computed tomography; TK2, thymidine kinase 2, mitochondrial; YWHAZ, tyrosine 3-monooxygenase.

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of schizophrenia is poorly understood; however the heritability has been estimated at 0.8 reflecting high genetic influence that interacts with environmental factors such as early life adversity, growing up in an urban environment, minority group position and cannabis use (van Os et al., 2010).

Mitochondria are key organelles necessary for energy production, and their proper function is therefore crucial for tissues with high metabolic demand, such as the nervous system and skeletal and cardiac muscles. Interestingly, mitochondria have their own genome, mitochondrial DNA (mtDNA), a 16,569-bp, double-strand, circular molecule that contains the genetic information necessary for the synthesis of 13 essential polypeptides of the mitochondrial respiratory chain (Verge et al., 2011). Mitochondrial dysfunction and mtDNA alterations have been hypothesized to be involved in both CFS (Myhill et al., 2013; Myhill et al., 2009; Vecchiet et al., 1996; Zhang et al., 1995) and schizophrenia (Anglin et al., 2012; Ben-Shachar, 2002; Sequeira et al., 2012; Torrell et al., 2013; Verge et al., 2011).

Here, we present a three-member family consisting of a proband presenting schizophrenia and symptoms compatible with CFS and her mother and older sister who present CFS, among multiple other conditions. We hypothesized that mitochondrial dysfunction and mtDNA alterations are present in this family as an underlying mechanism involved in both CFS and schizophrenia.

2. Case report

Ms. Z is a 29-year-old woman who fulfills the DSM-IV criteria for schizophrenia. When she was 7 years old, she began presenting prejudice and paranoid delusional thoughts, behavioral disorder, and irritability, symptoms that were recurrently present until the date of this study. At age 8, she began ambulatory psychiatric treatment, and at 18, she was admitted for the first of five psychiatric hospitalizations. The patient's antipsychotic drug treatment resulted in significant side effects and was changed several times, always with a partial response. Ms. Z has a history of asthma, multiple allergies (penicillin, pollen, and mites), and food intolerances (lactose, legumes, and gluten). She used to swim regularly until she was 21 when she presented post-exertion fatigue, muscle stiffness, and pain, with a slow recovery after exercise. At the age of 23, Ms. Z presented an episode of ocular and vaginal mucosa dryness, difficulty in swallowing, respiratory distress, muscle cramps, generalized arthralgia, intense asthenia, persistent constipation, sickness, pollakiuria, sleep disturbances, and loss of memory. She was then examined in the Internal Medicine and Neurological Department at the hospital of Vall d'Hebron. Her electromyography activity, creatine phosphokinase (CPK), lactate, pyruvate, and electroneurogram were normal; therefore, muscle biopsy was not conducted. The electroencephalogram, magnetic resonance imaging (MRI), and polysomnography results were also normal. Brain perfusion single-photon emission computed tomography (SPECT) resulted in less uptake in the frontal left-side zone, with light extension to the right, suggesting a degenerative process or bilateral frontal atrophy. At 25 years old, she continued showing extreme asthenia, sickness, mucosa dryness, and cognitive problems, and extensive blood tests were performed, including an immunologic study that revealed antibodies against the zoster and Epstein-Barr viruses and a low percentage of T4, T8, and suppressor T8 lymphocytes. Although the electrocardiogram was normal, she presented presyncopal symptoms in the tilt test. Neurologic examination did not identify any acute focalities; however, she presented a moderate degree of dysexecutive syndrome, mild melokinetic apraxia, and some anomie. At the age of 28 years, a neuropsychological study identified a moderate cognitive deficit, with signs of cortico-subcortical dysfunction with frontal predominance. At the time of this study, she was an outpatient under pharmacological treatment consisting of 300 mg/day of clozapine and regularly attended the Institut Pere Mata day center facility for medical follow-up and rehabilitation work.

Ms. Z's mother is a 56-year-old woman who fulfills the Fukuda criteria for CFS and has a wide medical history. She was diagnosed with severe cervical dysplasia at 42 and Hashimoto thyroiditis at 47. The next year, she presented with loss of memory and sleep disturbances as well as sensibility and strength alterations, with a general slowdown; indeed, she presented slowing electroencephalographic activity. Multiple complementary tests, including muscular biopsy, electromyography, and routine blood tests, were within the normal ranges, whereas her viral serology and lymphocyte typing were not. She presented antibodies against Epstein-Barr, herpes simplex, varicella-zoster, cytomegalovirus, and *Mycoplasma pneumoniae* as well as a low percentage of T4, T8, and suppressor and cytotoxic T8 lymphocytes. MRI did not identify significant alterations; however, SPECT showed hypo-uptake areas in the left posterior frontal region that were suggestive of a neurodegenerative process. Cognitive tests revealed a mild cognitive impairment. After repetitive episodes, spanning over more than 10 years, of loss of consciousness and normal echocardiogram and Holter electrocardiography, a diagnosis of vasovagal syncope was made. Ms. Z's mother has multiple allergies (cereals, bees, wasps, and nickel) and several long-developing food intolerances, with sensitization to gluten, producing recurrent symptoms of weight loss, abdominal pain, and asthenia. She is also described as having Sjögren syndrome.

Ms. Z's sister is a 32-year-old woman who began to experience increased fatigue and generalized pain coinciding with a stress period at the age of 23 when she was diagnosed of CFS according to the Fukuda criteria. She was also diagnosed with fibromyalgia at 27 years and has multiple allergies and food intolerances.

Supplementary text 1 reports information regarding Ms. Z's father, maternal grandmother and maternal uncles and aunts.

3. Materials and methods

3.1. Subjects

We studied Ms. Z, Ms. Z's mother, and Ms. Z's sister and a control group of 18 healthy women aged 23 to 71 years old with no personal or familial antecedents of psychiatric symptoms or fatigue. Approval for this study was obtained from the Clinical Research Ethics Committee of Hospital Sant Joan de Reus. All participants except Ms. Z understood the purpose of the study in accordance with the requirements of the Declaration of Helsinki of 1975 (revised 1983) and provided written informed consent after full explanation of the benefits and risks of participation. Because Ms. Z is incapacitated, her mother provided consent for her participation in the study. The three case members and the control women did not present diabetes mellitus, acquired immunodeficiency syndrome, cardiac ischemia, seizures, or liver pathology that could alter their lactate values. Similarly, these individuals were not under pharmacological treatment consisting of valproic acid, glucocorticoids, anesthetics, salicylates, and oral contraceptives, which could alter mitochondrial function. The participants were not consuming drugs (tobacco, alcohol, cannabis, hallucinogens, cocaine, and opioids) before or at the time of the study, with the exception of a control individual who smoked approximately 5 cigarettes per day. Physical exploration did not identify any significant alterations.

3.2. Interviews and questionnaires

The three participants and the control group completed a structured clinical interview by a psychiatrist to provide clinical, socio-demographic and drug consumption data. A psychopathological examination was performed by the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) (Vazquez-Barquero et al., 1994). The diagnosis of schizophrenia was based on the DSM-IV criteria, and the diagnosis of CFS was based on the Fukuda criteria. Because muscular exercise greatly influences the anaerobic threshold and is related to mitochondrial function, only physically moderate or non-trained women as close to the three participants