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Clinical case

Maximal and submaximal treadmill tests in a young adult with fragile-X syndrome

Épreuves d'effort maximal et sous-maximal chez un jeune adulte X-fragile

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Abstract

Fragile X syndrome is associated with expansion of a CGG triplet repeat in the *FMR1* gene, which abolishes production of the FMRP protein. This abnormality is expressed as a number of neuro-endocrine disorders (the adrenal axis, macroorchidism) and the emergence of significant behavioural stress. Here, we report on the hormonal status of a young adult with fragile X syndrome, with a focus on catecholamine and cortisol changes during a submaximal treadmill test. The patient showed abnormally high epinephrine and norepinephrine concentrations. During a submaximal incremental test, cortisol levels were higher than the laboratory reference range. Although the submaximal incremental test has a significant ''stressful'' effect, this young adult was able to complete the entire protocol without any maladaptive behaviour or withdrawal.
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Résumé

Le syndrome de l'X-fragile est lié à l'expansion d'une séquence de triplets CGG du gène *FMR1*, d'où une absence de production de la protéine FMRP. Les conséquences de cette anomalie s'expriment dans des troubles neuroendocriniens (axe surrénalien/macro-orchidie) et dans l'apparition d'importants comportements de stress. Nous rapportons des valeurs de catécholamines et de cortisol élevées chez un jeune homme X-fragile durant une épreuve d'effort sous-maximale de 40 minutes. Bien qu'il existe un réel effet « stressant » de l'épreuve d'effort, ce jeune adulte est parvenu à réaliser la totalité du test sans aucun comportement de mal-adaptation ou de retrait.
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Keywords: Fragile X; Physical test; Hormonal and metabolic responses

Mots clés : X-fragile ; Épreuve d'effort ; Réponses hormonales et métaboliques

1. English version

1.1. Introduction

Fragile X syndrome (FraX), an X-linked dominant disorder with reduced penetrance, is associated with cognitive dysfunction and aberrant behaviours, that are the hallmarks of childhood neurodevelopmental disorders. Described for the first time in 1969, under the term of Martin Bell syndrome, the gene responsible for its expression was eventually discovered in 1991. FraX is caused by a mutation in the *fragility mental retardation 1* (*FMR1*) gene on chromosome X (locus q27.3). The molecular abnormality consists of an unstable expansion of a CGG trinucleotide repeat within the 5′ untranslated region of *FMR1* gene [7]. In the normal population, there are between six

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and 50 repeats tract, 30 of them being the most common (normal or common alleles). From 51 to 199 repetitions, we speak about premutation, without specific clinical manifestation [7,23]. Full mutations, which cause FraX, have over 200 copies of the CGG trinucleotides, involve in hypermethylation of the gene promoter, lead to transcriptional silencing of the gene resulting in diminished levels or total loss of FMR1 protein (FMRP) [7,23]. FMR protein is in abundant quantity in many cells, regulates the translation of numerous proteins critical for brain maturation and function [26]. The lack of FMRP leads to dendritic spine dysmorphogenesis and impaired synaptic plasticity [26]. Then, with the *FMR1* full mutation, there is an aberrant brain development and function [8]. In addition to cognitive impairment, individuals with fragile X typically presented a neurobehavioural phenotype that included stress-related symptoms such as hyper-arousal, hyper-responsivity to sensory stimuli, hyperactivity, impulsivity, gaze aversion, social anxiety and withdrawal [6,14].

On the other hand, the physical characteristics of FraX are relatively common, with a great size, a great face with prominent ears, and joint hypermobility [12]. Physical features include, in males, macroorchidism that is apparent just prior to puberty, with an abnormal testicular volume (> 25 mL) [10,21]. Moreover, in FraX patients, the neuro-endocrine system is disturbed, especially the function of hypothalamic-pituitary adrenal (HPA) axis which is altered [14,25]. This HPA axis is involved in the regulation of the physiological and behavioural responses to stress through the secretion of adrenal glucocorticoid hormones and feedback mechanisms within the hypothalamus, pituitary, hippocampus and frontal cortex [8,25]. Thus, the HPA response to stress is adaptative in that it prepares the subject for coping with the source of the stress [6,13]; however chronic elevations or disruptions in the typical rhythm of cortisol secretion can lead to medical problems associated with immune suppression [18] and adverse effects on the brain that interfere with learning and memory [22].

Furthermore, other endocrine disruption has been described in relation with this hypothalamic-pituitary dysfunction, such as precocious puberty and elevated gonadotrophin levels [4], normal Thyroid Stimulating Hormone (TSH) level although the response is blunted after Thyrothropin Releasing Hormone stimulation [1]. Salivary cortisol was strongly increased especially during cognitive testing and social demands, and higher levels of this hormone were independently associated with the severity of behaviour problems in FraX patients [15].

1.2. Case report

A 24-year-old male named HY (185 cm – 62.5 kg – Body Mass Index: 18.3 – Fat mass: 10.1%) volunteered for participating to a clinical research, approved by the local ethic committee of the Grenoble Hospital (No.9-03CMJL1). All the methodology and dosage techniques of metabolic and hormonal variables were detailed as previously published [2].

The diagnosis of FraX syndrome was made during his childhood with a mutation transmitted by his grandmother, and his family medical history was unremarkable. He acquired late walking (18 months) with a significant hypotonia. During his childhood, HY was schooled in a classical structure, and then entered into a specialized establishment where he acquired reading and writing. HY practises sports activities: swimming (90 min/wk).

A primary medical examination was made, and we noticed:

- cardiovascular examination at rest:
  - heart rate (HR): 65 b/min,
  - blood pressure: 120/90 mmHg,
  - cardio-pulmonary auscultation normal;
- osteo-articular examination: there is a pectus excavatum, bilateral hollow feet, calcaneal varus, diastasis C1-C2 (4 mm) and lumbar canal stenosis;
- neurological examination: substantial difficulties of coordination;
- endocrinological examination:
  - cortisolemia at rest followed a normal kinetic: 685 nmol/L at 8:30 AM; 579 nmol/L at 9:10 AM; - 443 nmol/L at 9:40 AM; - 370 nmol/L at 10:40,
  - thyroid function: echography examination without significant anomaly. TSH: 1.48 mUI/L, free triiodothyronin: 4.1 pmol/L; free thyroxin: 18.4 pmol/L,
  - gonadic function: length of verge: 10 cm; circumference: 9.5 cm. Testicular volume: right: 39.1 ml – left: 45.5 ml (normal value: 25 ml).

In addition, the blood test rest showed no disturbance of the hemogram, ionogram and lipid balance sheet. Different markers and antibodies were normal.

Two different exercise tests were conducted on two separate days.

"The first test" was a maximal treadmill exercise conducted on a treadmill (Gymrol Super 2500, Andrézieux, Bouthéon, France). For this maximal test, the subject started walking at a slow speed for one minute. Thereafter, the slope and the treadmill speed were alternately increased every minute until exhaustion. The test was over when the subject could not longer keep up with the treadmill speed or showed signs of volitional fatigue. During this maximal test, gas exchanges were measured on an automated ergospirometer (Brainware, Toulon, France). Heart Rate was monitored continuously and displayed on an ECG (Nihon Kohden Lifescope 6).

Secondly, a submaximal incremental test was conducted. Three stages were imposed:

- 30% of VO_{2max} during 10 min;
- 50% of VO_{2max} during 10 min;
- 75% of VO_{2max} during 20 min.

During this test, gas exchange and heart rate were continuously monitored. Thirty minutes before the beginning of the test, a venous catheter was put in place from which blood samples were collected at seven different times (T-1/T0/T1/T2/T4/T5/T6) for the biological measurements (metabolic and hormonal variables) as indicated in Table 1.

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