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Case Report: Complications in ECT due to Fmr1-Premutation?

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ABSTRACT

After a short summary on Fragile-X-Syndrome and fmr1-premutation, we present a case report on a patient pre diagnosed with fmr1-premutation undergoing a series of 14 ECTs because of a treatment resistant major depressive episode. In the course of the series, several unexpected adverse incidents occurred. According to a literature research we did on PubMed, we concluded that these adverse incidents may be related to fmr1-premutation and associated abnormities in cerebral and other physical features.

Keywords

Fmr1-premutation, Fragile-x-syndrome, ECT, Adverse incidents in ECT, Treatment resistant major depression.

Abbreviations

FXS: Fragile-X-syndrome; fmrp: fmr1's gene product; ADHD: Attention Deficit Hyperactivity Disorder; POF: Primary Ovarian Failure; OCD: Obsessive-Compulsive Disorder; ECT: Electroconvulsive Therapy; HDS: Hamilton Depression Scale; FXTAS: Fragile-X-(premutation)-Related Tremor/Ataxia-Syndrome; OSAS: Obstructive Sleep Apnoea Syndrome.

Introduction

Fragile-X-syndrome is one of the main causes for inherited intellectual disability. Through x-linked recessive inheritance, FXS is caused by an unstable mutation on the fmr1-gene on Xq27.3 leading to more than 200 CGG-repeats in this area. As a result, the production of fmr1's gene product declines or is abandoned completely [1]. Affected individuals suffer from mental retardation; they are often affected by psychiatric disorders, especially autism or adhd, and different medical conditions, e.g. epilepsy or obesity [2].

Individuals with 55 up to 200 CGG-repeats are classified as premutations carriers. In this range, mutation leads to an increased production of fmrp [3]. Premutation carriers are at a higher risk regarding psychiatric disorders as non-carriers; 50% suffer from depression or anxiety, some show also mild cognitive deficits such as attention deficits or a delayed processing speed [4]. Furthermore, premutations carriers are likely to develop hypertension, thyroid disorders or several autoimmune diseases (e.g. rheumatoid arthritis, Raynaud's syndrome [5]. Additionally, premutations is associated with primary ovarian failure in female carriers [6] and tremor-ataxia-syndrome, especially in male patients [7], each of both rising again the risk of other pathologies (e.g. osteoporosis [8], epilepsy [9]. As the mutation is instable, there is the possibility of passing on premutations as well as full mutation to descendants while the risk of anticipation depends on the number of maternal CGG-repeats [10].

The diagnosis of FXS or fmr1-premutation is verified by polymerase chain reaction. To specify the result of full mutation further in order to facilitate a prediction concerning the proband's clinical prognosis, southern blot might be used to identify methylation status limiting fmrp's possibly remaining production further.

Electroconvulsive therapy (ECT) is a common treatment of major depression and other psychiatric diseases. Grand mal seizures are induced by the use of unilateral or bilateral electric stimulation of the brain while the patient is undergoing general anaesthesia.

Among others, possible side effects of ECT include headache, nausea, intermittent cardiac arrest, rise in blood pressure and

heart rate or negative influence on cognitive abilities. Especially cardiovascular reactions may depend on parasympathetic and sympathetic reaction to stimulation or convulsion. Side effects, especially cognitive ones, are supposed to occur more often and more pronounced after bilateral stimulation.

Case Report

A female 38 year old teacher with fmr1-premutation was admitted to psychiatric ward because of treatment resistant major depression (HDS: 34 points) with comorbid panic disorder and obsessive-compulsive disorder for ECT in January 2018.

Approximately four years earlier, human genetic analysis regarding FXS was run due to mental retardation of her niece and showed 100 CGG repeats in the patient´s sample, classifying her as premutations carrier. She was at a high risk for POF but not diagnosed with FXTAS which her father suffered from.

Additionally to being premutations carrier, the patient suffered from Crohn´s disease, primary thrombophilia, hypothyroidism, a hepatic haemangioma and obesity (BMI 32).

She was a married teacher and had a 2.5 months old son born after she had received an egg donation in order to avoid passing on the mutation.

The routine blood diagnostics before ECT revealed increased liver values (gamma-GT: 236U/l, ALT: 46U/l, AP: 122U/l), mild hypercholesterinaemia (221mg/dl) and –triglyceridaemia (281mg/dl). MRI showed unspecific periventricular and juxtacortical white matter lesions; there were no corresponding clinical symptoms found and neurological physical examination came off completely normal.

EEG recorded increased beta activity, probably due to medication with lorazepam. Heart rate and blood pressure were within normal range (87bpm, 120/70mmHg); ECG revealed no pathologies.

As psychiatric medication, she initially took fluoxetine (40mg), risperidone (2mg), quetiapine (600mg) and lorazepam (4.5mg); additionally, cortisone (30mg) was applied and thyroid hormone (12.5µg) substituted. In the course of the treatment, medication was switched from risperidone to aripiprazole (20mg); the dose of quetiapine was reduced to 25mg due to increased liver values, the dose of fluoxetine to 30mg because of excessive serum levels. The dose of lorazepam was reduced to 3.25mg before the first ECT session.

According to guidelines [11], the patient received a series of 14 ECTs with two sessions per week; anaesthesia was performed with propofol (dosage adjusted to body weight). During the first 9 sessions, unilateral stimulation was performed (max. 100%).

After a slight reduction of lorazepam (-0.25mg, leaving in total 3mg/d) after the fifth session, she showed a hyperactive hemodynamic response after the sixth stimulation in the postictal episode with a heart rate up to 160 bpm and a systolic blood pressure up to 220mmHg. Furthermore, she presented a spontaneous second convulsive seizure in the postictal episode ceasing spontaneously after approximately ten seconds.

Subsequently, the dose of lorazepam was increased again to avoid further unscheduled seizures. Additionally, a long-term surveillance of blood pressure was run; as it revealed mild hypertension (average: 132/83mmHg), low-dose Ramipril (2.5mg) was given to prevent further cardiovascular complications. Under the medication with Ramipril, blood pressure descended to normal range.

The next three sessions of ECT were performed without any incidents.

As the depression did not respond sufficiently to unilateral stimulation, a switch to bilateral stimulation was performed in session 10 (20%). The patient developed a severe hyperactive hemodynamic response in the postictal period (heart rate up to 180 bpm, 240/160mmHg; approximately 200% compared to baseline values) which declined only after she was given urapidile intravenously (dose unknown). Hereinafter, decision to go back to unilateral stimulation was made. She received further three sessions of unilateral ECT as well as a single maintaining session four weeks after having completed the series without any additional adverse incidents. The score in HDS receded to 13 points.

Discussion

To our best knowledge, this is the first published case of an fmr1-premutation carrier receiving ECT as a treatment of severe depression.

Regarding the observed side effects during the series, the question of underlying reasons for the patient's vegetative sensibility to ECT arose as the incensement of blood pressure and heart rate seems to be rather pronounced compared to the average cardiovascular reaction to ECT [12].

It is known that a hyperactive cardiovascular reaction may occur in the postictal phase; the average postictal enlargement seems to be about more or less 150% of the baseline values. The severity of sympathetic reaction may depend on individual biological factors and might be more pronounced in patients with essential hypertension due to a diminished elasticity in the vessels' walls [13].

Besides the mild essential hypertension diagnosed and treated in the course of the series and possibly having influence on the cardiovascular reaction to stimulation, we wondered if there might be another, premutation-associated contributory factor complicating the course.

We found case reports addressing the possible influence of untreated obstructive sleep apnoea syndrome on general anaesthesia during ECT including cardiovascular complications [14] similar to

our patient's reaction. As the risk OSAS might be elevated in premutation carriers [15] and as the patient had other risk factors (overweight, medication with lorazepam, snoring), suspicion of OSAS was raised; evaluation through cardiorespiratory polygraph was run but came off negative.

Another factor relevant to the regulation of the cardiovascular reaction is the autonomic nervous system including both the parasympathetic and the sympathetic part. There is evidence that fmr1-premutation carriers' vagal tonus is diminished compared to normal population [16]. This might be an explanation for the patient's rather attenuated physical reaction to ECT; corresponding to the diminished vagal tonus, the sympathetic nervous system's influence on blood pressure and heart rate may be stronger than in non-fmr1-affected individuals. Thus, it might take longer to regulate blood pressure and heart rate down again after the sympathetic reaction to the stimulus.

Furthermore, we hypothesize that the patient's central nervous system might be more sensitive to electric stimulation than a non-premutations-carrier's one. As some fmr1-premutation carriers are generally at a higher risk for seizures, we attribute the additional seizure after the sixth session of ECT to the previous minimal reduction of lorazepam seemingly leading, in this case, to a significant lower seizure threshold.

As a result, we conclude that it may be useful to be more sensitive regarding possibly elevated cardiovascular risks in fmr1-premutation carriers undergoing ECT.

Subsequently, routine long-term surveillance of blood pressure and heart rate might be recommendable as well as an up titration of low-dose antihypertensive medication pre-intervention ally, maybe even in patients with baseline values within normal range. Furthermore, one should consider a possibly increased probability of ECT-induced unscheduled seizures before reducing antiepileptic drugs during the course of ECT.

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