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Case report

Early onset of neurological symptoms in fragile X premutation carriers exposed to neurotoxins

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ABSTRACT

We present four cases of fragile X premutation carriers with early neurological symptoms, including symptoms consistent with multiple sclerosis (MS) and fragile X-associated tremor/ataxia syndrome (FXTAS). Each patient had significant exposure to one or more environmental neurotoxicants that have documented neurotoxicity (i.e. hexachlorocyclopentadiene or C56, Agent Orange, and 2,4- or 2,6-toluene diisocyanate and dichlormate). We hypothesize that premutation carriers are a vulnerable group to neurotoxins because elevated mRNA in the premutation can lead to early cell death and brain disease, leading to neuropsychiatric and neurological symptoms consistent with FXTAS.

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1. Introduction

Carriers of the premutation of the fragile X mental retardation 1 gene (FMR1; 55–200 CGG repeats) are relatively common in the general population. Approximately 1:130–250 females and 1:250–810 males carry the premutation (Hagerman, 2008). Premutation carriers who are older than 50 years of age are at the highest risk to develop the fragile X-associated tremor/ataxia syndrome (FXTAS), characterized by intention tremor, ataxia, and later, often dementia. The syndrome typically appears when patients are in their 50s and 60s, and it increases with age, with a mean tremor onset at approximately 60 years and ataxia onset at 62 years in a study of affected men (Leehey et al., 2007). Psychiatric symptoms are common in FXTAS, especially as movement symptoms become prominent, with anxiety, mood, and cognitive disorders having been reported (Bourgeois et al., 2007, 2009). There is higher incidence of autoimmune diseases associated with the premutation in females, including fibromyalgia in 43% and hypothyroidism in 50% of women with FXTAS (Coffey et al., 2008). Many individuals with FXTAS also show signs of Parkinsonism, peripheral neuropathy, focal muscle weakness and autonomic problems.

Approximately 3 in 106 female premutation patients have been diagnosed with MS (Greco et al., 2008; Zhang et al., 2005). There is great variability in the severity of symptoms, disease progression, and MRI findings, even between sibling pairs affected with FXTAS (Capelli et al., 2007; Peters et al., 2006), suggesting possible environmental modifiers of the FXTAS outcome and illustrating broad intrafamilial variability in the expression of FXTAS symptoms. There is some evidence that exposure to neurotoxicants can promote symptoms of FXTAS in susceptible individuals, as exemplified by a woman with the premutation who developed symptoms after initiation of chemotherapy for breast cancer with the chemotherapeutic agent carboplatin (O'Dwyer et al., 2005). A higher prevalence of alcohol abuse is associated with men with FXTAS when compared to controls, although the contribution of alcohol consumption to the course and severity of the disorder is not known (Kogan et al., 2008).

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2. Case reports

2.1. Patient 1

Patient 1 was a 40-year-old female with the premutation (29, 87 CGG repeats; activation ratio = 0.8) who presented with symptoms consistent with possible FXTAS. In her childhood, she and her family lived near a chemical plant that began operating in 1956 and was closed in 1981 due to environmental toxicity from chemical waste. The plant manufactured pesticides in the 1950s and 1960s. The main chemical that was manufactured in the plant was hexachlorocyclopentadiene (HCCPD or C56). This was used as a raw ingredient in many herbicide and pesticide preparations.

Patient 1 was born in 1968 following a normal pregnancy. In her early years, she did well in school except for a few academic difficulties with mathematics. She did not require any special education programming. She finished two years of college and worked as an administrative assistant.

At 15 years of age the patient experienced numerous neurologic symptoms. These included multiple episodes of syncope with falls, migraine headaches, restless leg syndrome, and intermittent tremors. She also began to experience ataxia at 16 years of age, six months after having her initial onset of tremors and syncope. At age 32, the tremors worsened and began to also occur at rest. Beginning at age 37, she had severe handwriting problems with increased pain in her extremities with numbness and tingling sensations and weakness in her left upper extremity. Her motor symptoms progressed significantly in subsequent years, and when clinically evaluated for FXTAS at age 40, she had required the use of a walking stick for balance for several months.

Patient 1 experienced episodes of bilateral optic neuritis at age 15, with decreased visual function. She was treated with prednisone for almost a year at that time; her vision gradually recovered. At age 16, she was diagnosed with MS after multiple CSF fluid analyses. She had another episode of vision impairment at the age of 17 years, for which she resumed prednisone for another two months with improvement in her vision. In her early twenties an MRI was done and apparently the report said she had no white matter disease.

She also had a confirmed REM sleep disorder, experienced as night terrors that began at age 16 years. This included episodes of awakening at night with screaming, along with aggressive acting-out behavior. She was treated with amitriptyline 50 mg and gabapentin 600 mg every night for the sleep disturbance, with a partial response.

She had transient hypothyroidism between 17 and 19 years of age, which was treated with thyroid hormone replacement therapy. She also had a history of cardiac arrhythmias in her 20s, which was treated with cardiozyme for three years.

In her mid-20s, Patient 1 also was diagnosed with fibromyalgia (at the age of 24 years). At age 26 she had a hysterectomy and oophorectomy to treat ovarian cysts and endometriosis. She was on hormone replacement therapy until age 29. Her history also included hypertension, diagnosed at the age of 38, and bladder incontinence especially upon laughing or coughing.

Her physical exam at age 40 revealed an intention tremor on finger to nose touch testing, and also postural tremors. Resting tremors were seen intermittently, particularly in forefingers bilaterally. Gait and station exam revealed difficulty with tandem walking. Cranial nerves were intact except for non-sustained horizontal nystagmus bilaterally. Her muscle tone was normal and reflexes were 2+ and symmetric in all four extremities. The exam was consistent with possible FXTAS, although her MRI was normal. Formal psychiatric interview with the Structured Clinical Interview for DSM-IV (SCID) revealed a diagnosis of major depressive disorder, single episode, in remission.

2.2. Patient 2

Patient 2 was a 67-year-old male with the premutation (68 CGG repeats) and was the father of Patient 1. He was born in 1941. The patient lived near the same chemical plant as Patient 1, from 1966 to 1981 (from the age of 25–40 years). While serving in the Vietnam War, he was exposed to Agent Orange, a wide spectrum herbicide that is a 50:50 mixture of 2, 4-dichlorophenoxyacetic acid and 2,4,4-trichlorophenoxyacetic acid.

Following his service in Vietnam, he developed nightmares, flashbacks, social detachment, hyperarousability, and mood symptoms consistent with post-traumatic stress disorder (PTSD). The patient developed intention tremors and handwriting difficulties at the age of 46 years, several years after returning from Vietnam. His tremors progressed in intensity to where they significantly interfered with his eating and other activities of daily living. Propranolol improved his tremors. He began having symptoms of ataxia at age 61.

Patient 2 also had severe optic nerve atrophy bilaterally beginning at age 46 years. He lost his peripheral vision, and was legally blind by the age of 49. MRI confirmed optic nerve atrophy in 1990. He had the onset of high blood pressure in his late 40s and impotence beginning at the age of 61. He also reported problems with his short-term memory, as well as choking and swallowing problems, beginning at the age of 63.

On physical examination, he had masked facies and mild intention and postural tremors. Cranial nerves were normal except for tunnel vision (loss of peripheral vision) in the left eye and the need for hearing aids bilaterally. Deep tendon reflexes (DTRs) were decreased (1+) in the right upper extremity. Vibratory and temperature senses were normal and intact in both upper and lower extremities. He could not perform a tandem-walking test for more than two steps due to his ataxia. His MRI at the age of 68 years demonstrated mild enlargement of lateral and third ventricles, mild thinning of the corpus callosum and mild cerebral cortical volume loss. There was no alteration in white matter signal intensity. Formal psychiatric interview with SCID revealed a diagnosis of PTSD.

2.3. Patient 3

Patient 3 was a 55-year-old female with the premutation (42 and 95 CGG repeats) with an activation ratio of 0.9, and was affected by mild tremors and ataxia. During childhood she lived next to a chemical plant, which emitted chemicals related to the manufacture of polyurethane foam for the bedding and furniture industries (ATSDR Report, 1997). These chemicals included 2,4- or 2,6-toluene diisocyanate (TDI) and dichloromethane, compounds known to exacerbate or cause a host of sensitization reactions resulting in obstructive airway disorders (Ott et al., 2003) and neurotoxicity (Singer and Scott, 1987; Winneke, 1981).

Patient 3 had a long history of anxiety and depression, with onset at 13 years of age. At that time she had academic difficulties, shyness, and irritable mood. In her 20s, she had panic attacks without agoraphobia. She was treated by a psychiatrist on a weekly basis and was on medication intermittently; she did not recall the specific medications used. When evaluated at age 55, she was being treated with a serotonin–norepinephrine reuptake inhibitor (SNRI; Duloxetine, 60 mg per day).

She had a history of three febrile seizures in her childhood and a generalized tonic/clonic seizure at the age of 36. She had two more seizures in her 40s; an EEG revealed a spike wave pattern.

Patient 3 reported having ataxia with frequent falls along with weakness at the age of 41 years. These symptoms were initially attributed to MS. However, a lumbar puncture and CSF analysis was not consistent with a diagnosis of MS because of the absence of oligoclonal bands. Hypothyroidism was diagnosed at age 47;

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