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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.

Keywords

Fragile X-associated tremor/ataxia; syndrome; Industrial chemical exposure; Premutation; FMR1; Hexachlorocyclopentadiene; Agent Orange

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Conflict of interest

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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).

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; subsequently, she developed type 2 diabetes mellitus. At the age of 45, she started having pains in her muscles and tendons and was diagnosed with fibromyalgia. She also began having intention tremors in the right hand at age 49. An MRI was done at age 50 and revealed significant white matter disease and atrophy. She also had some symptoms of 8th cranial nerve involvement with dizziness and vertigo, and was treated with meclizine. The ataxia continued to worsen, leading to multiple fractures in her legs due to several falls. She subsequently needed a cane to walk more than one block. She also started having progressive difficulty with memory at the age of 53 years.

Bladder and bowel incontinence, especially upon coughing or laughing, were reported beginning at age 54 years. She also reported evidence of choking spells with swallowing; her husband had to perform the Heimlich maneuver when she was 53 years old.

Examination at 55 years of age revealed intention tremor in her hands and nystagmus, in addition to mild weakness in the right arm and leg. She also had some difficulties with tandem walking, as she was unable to walk for more than four tandem steps. DTRs were 2+ in right upper and lower extremities and 3+ on left side. MRI showed mild volume loss and scattered white matter changes on T2 and FLAIR imaging, but her middle cerebellar

peduncles (a location in the brain particularly susceptible to white matter changes in FXTAS) appeared normal.

Formal psychiatric interview (SCID) revealed a diagnosis of major depressive disorder, recurrent, panic disorder with agoraphobia, social phobia, and generalized anxiety disorder.

2.4. Patient 4

Patient 4 was a 62-year-old male with the premutation (110 CGG repeats) and was the brother of Patient 3. The subject had exposure to the same chemicals emitted by the chemical plant, including TDI.

Patient 4 developed neurological symptoms at the age of 46 years, with ataxia that progressed and led to frequent falls. He eventually required a walking stick for ambulation. He reported being hyperactive as a child with mild attention problems. The patient tried stimulants at age 50 and found them helpful for improving attention. At age 52, he displayed intention tremors and occasional resting tremors, which worsened over time. During this period he also reported some hearing loss with tinnitus. He also had memory problems, choking spells, and difficulty in swallowing, starting at the age of 57 years. He had dizzy spells associated with nausea and headaches, and reported some pain in his muscles and joints. He also noted impotence and the neuropathic symptoms of numbness and tingling in the lower extremities, in his late 50s. He also had loss of appetite, weight loss, insomnia, psychomotor agitation and fatigue in his late 50s.

On exam at 62 years of age, he was unable to maintain an erect posture without assistance and he stumbled frequently during the testing, despite the aid of a walking stick. He had severe tremors with finger to nose touching that was worse on the left side. The tremors were also seen on positioning and occasionally at rest as well. The DTRs were 1+ in upper extremities and 1 to 2+ in lower extremities. He had snout, glabellar and jaw jerk reflexes. He had vibration loss in his toes and absent ankle reflexes consistent with neuropathy. He had slightly broad-based gait and listed to the right side when he walked. He was unable to tandem walk. His exam was consistent with FXTAS. Formal psychiatric interview with the SCID revealed a diagnosis of major depressive disorder, single episode.

3. Discussion

In this study, we have reported four patients from two different families who were raised or lived near chemical plants that were closed because of the release of – and the widespread environmental contamination with – known chemical toxicants resulting from plant operations. One family (Patients 1 and 2) lived within proximity of a chemical plant. The plant was in operation between 1954 and 1983 during which time the plant manufactured chlorine, sodium hydroxide and hydrochloric acid. Of greatest concern to human health was, from 1956 to 1977, the production of 25,000 tons per year of hexachlorocyclopentadiene, a synthetic precursor to the manufacturing of a group of related chlorinated cyclodiene pesticides (e.g., chlordane, dieldrin, endosulfan, and mirex). Improper disposal contaminated the atmosphere, ground and surface waters (including an aquifer used for drinking water by local residents), and soil on and off the 900-acre site with C56 and chlorinated organic degradation products (Federal Register 1985). Occupational exposure to C56 produces eye irritation, headaches and throat irritation as primary acute effects. Subsequently, proteinuria and elevation of serum lactic dehydrogenase levels are observed within days of exposure, but do not persist (Morse et al., 1979). Animal studies have found that high-level exposure to C56 causes lung, liver, kidney, brain, and heart damage, although the nature of these effects have not been studied in detail (Abdo et al., 1984; Rand et al., 1982a, b).

When Patient 1 developed several neurological symptoms in her mid to late teens, it led to a diagnosis of MS. However, her symptoms now, at age 40 years, are most consistent with early FXTAS. She is a premutation carrier with a son who has fragile X syndrome. She had much earlier onset of these neurological symptoms (tremors at age 15, ataxia at age 16) than the average onset of FXTAS symptoms of approximately 60 years of age (Leehey et al., 2007).

Though Patient 2, the father of Patient 1, developed neurological symptoms later in life than his daughter, the clinical onset was nonetheless earlier than that typically observed for male carriers (Leehey et al., 2007). He started having handwriting difficulties and tremors in his late 30s to early 40s. He was also exposed to the herbicide Agent Orange during his tour of duty in Vietnam and subsequently developed optic atrophy and ataxia. A known contaminant in Agent Orange is 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD; dioxin), although appreciable accumulation of TCDD in veterans would have required repeated long-term direct skin contact (Young et al., 2004). In individuals highly exposed to Agent Orange during the Vietnam War, there is an association with increased incidence of neurological deficits (Ambrus et al., 2004; Kim et al., 2003). However, in the general population the association between exposure to Agent Orange and neurological impairments in humans is not strong (Goetz et al., 1994). Nevertheless experimental animal models of TCDD exposure indicate that exposure causes polyneuropathy (Grehl et al., 1993) and alters the expression of synaptic proteins and synaptic transmission (Cho et al., 2002). Perhaps Agent Orange was additive to his earlier exposures and to his premutation status, causing earlier neurological symptoms of FXTAS.

Patient 3 was also distinguished based on the fact that her family lived in close proximity to an anthropogenic source of environmental chemicals and she presented all the neuropsychiatric manifestations related to FXTAS at a relatively early age. Especially notable was that she displayed neurological and psychiatric manifestations in her adolescence. The neurological symptoms consistent with FXTAS (tremor and ataxia) started in her early 40s, which is very early compared to the typical onset of symptoms in carriers (Leehey et al., 2007). Her brother (Patient 4) also presented with neurological symptoms early, starting at 46 years of age.

Although these two families were chronically exposed to different groups of chemical toxicants, the early onset of neurological impairments in the four cases (as compared to the age of onset in Leehey et al., 2007, $p < 0.011$) raises the intriguing question of whether fragile X carriers have increased susceptibility to adverse neurological outcomes with chronic exposures to chemicals with neurotoxicological potential. Results from a recent study of a 70-year-old carrier of the fragile X premutation treated with chemotherapy for breast carcinoma indicated that one or more chemotherapeutic agents aggravated her tremor and ataxia symptoms. These symptoms resolved after she ceased chemotherapy (O'Dwyer et al., 2005). Therefore, in subjects with the fragile X premutation, neurological and psychiatric symptoms may result from a potentiation of risk by chemical exposure. This hypothesis is reasonable since enhanced cell death or apoptosis has been reported in cells, including neurons, which express expanded CGG alleles (Arocena et al., 2005). A recent publication has confirmed that hippocampal neurons from knock in mice expressing CGG expansion repeats in the premutation range express elevated levels of stress-associated proteins and lose viability between 21 and 28 days in culture, to a much greater extent than neurons cultured from wild type littermates (Chen et al., 2010). Regarding psychiatric diagnosis, the SCID-validated diagnoses in all four cases were of psychiatric illnesses seen commonly in patients with FXTAS. Although the psychiatric illnesses in these patients may be attributed to other provocative factors (notably PTSD and combat service in Patient 2), the pattern of psychiatric illnesses in patients with the premutation, with or without FXTAS,

is an increasingly reported relationship (Bourgeois et al., 2007, 2009, in press; Roberts et al., 2009; Rodriguez-Revena et al., 2008). The model of neurodegeneration and concurrent progressive neurologic and psychiatric illnesses both being consequent to the premutation carrier state itself is becoming more widely accepted. This is quite similar to other more well-established neuropsychiatric illnesses, such as MS or Parkinson's disease. Ironically, cases later diagnosed as FXTAS are commonly initially diagnosed as MS or Parkinson's disease (Greco et al., 2008; Hall et al., 2005). It is a reasonable hypothesis that chemical exposure in patients with the premutation might thereafter exhibit accelerated neurotoxicity with its associated neurologic and psychiatric manifestations. At the very least, the evaluation of suspected FXTAS in patients should include a history of significant chemical exposure.

In summary, we reported four premutation carriers affected by FXTAS and presenting with neurological symptoms that started earlier than what has been previously reported (Leehey et al., 2007). We suggest that the early onset of neurological problems may be related, at least in part, to chronic exposures to environmental toxicants that may trigger earlier clinical expression of their FXTAS symptoms. We recommend that environmental exposure histories be included in the clinical workup of patients with FXTAS, as such information could address the hypothesis that carriers represent an especially vulnerable population to the adverse outcomes of known chemical exposures.

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