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Fragile X–Associated Tremor/Ataxia Syndrome

An Aging Face of the Fragile X Gene

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Fragile X–associated tremor/ataxia syndrome (FXTAS) is a late-adult–onset neurodegenerative disorder affecting primarily male (and occasionally female) carriers of a premutation expansion (55-200 CGG repeats) of the fragile X mental retardation 1 gene (*FMR1*). FXTAS is principally characterized as a movement disorder with progressive intention tremor and gait ataxia, with more variable associated features of parkinsonism, dysautonomia, peripheral neuropathy, and dementia. The pathogenic basis of FXTAS is overexpression of the "toxic" expanded CGG repeat *FMR1* RNA, which leads to neural cell dysregulation, formation of intranuclear inclusions in neurons and astrocytes, and disruption of the nuclear lamin architecture. By contrast, larger CGG repeat expansions (>200 CGG repeats, full mutation) generally result in *FMR1* silencing and absence of *FMR1* RNA and protein (FMRP). The lack of FMRP is the pathogenic basis of the developmental disorder fragile X syndrome, the leading heritable form of mental impairment. Thus, the same gene presents 2 opposing faces: a neurodegenerative syndrome (FXTAS) in older adults, caused by excess gene activity and production of a toxic RNA, and a childhood-onset disorder (fragile X syndrome), caused by absence of gene activity. This review will focus on FXTAS, the aging face of the fragile X gene.

FXTAS is a late-onset neurodegenerative disorder with core features of intention tremor and gait ataxia with associated neurological and nonneurological features.[1-3] FXTAS affects carriers of premutation expansions (55-200 CGG repeats)[4] of the fragile X mental retardation 1 gene (*FMR1*) (Online Mendelian Inheritance in Man [OMIM] *309550). Larger expansions (>200 CGG repeats, full mutation) of the same gene give rise to the neurodevelopmental disorder fragile X syndrome, the leading inherited form of mental impairment. Fragile X syndrome results from the transcriptional silencing of *FMR1*, with consequent deficiency/absence of the *FMR1* protein (FMRP).

Fragile X syndrome has been recognized for more than a quarter of a century, and the causative gene (*FMR1*) was identified 17 years ago.[5] However, FXTAS was not recognized until nearly 10 years after the discovery of *FMR1*.[1] There were 2 basic reasons for the delayed recognition of FXTAS. First, geneticists who were studying fragile X syndrome were focused on a developmental disorder (ie, a childhood condition) affecting cognition. Because the gene was unknown before 1991, it was nearly impossible to establish any association with late-onset problems in adults (carriers) who had been essentially normal in childhood. Furthermore, the grandfathers of children with fragile X syndrome rarely came to the pediatric clinics, so their own age-associated symptoms were generally not recognized as being linked to their carrier status. With the discovery of *FMR1* in 1991, there arose a different problem: the pathogenic mechanism of fragile X syn-

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drome was gene silencing (ie, absence of the *FMR1* protein FMRP) due to hypermethylation of the *FMR1* promoter, and this only occurred for alleles with more than 200 CGG repeats. Therefore, clinical abnormalities were not expected among carriers of premutation alleles.

The second reason for the delay in recognition was that adult neurologists, geriatricians, and psychiatrists who were treating the carriers (unidentified as such) were generally unaware of fragile X syndrome, a childhood-onset disorder. Thus, cases now known to be FXTAS were generally regarded as being any one of a number of sporadic neurological disorders in older adults, with no obvious genetic basis.[6]

The first clue to any form of clinical involvement in carriers came about through discussions with mothers and grandmothers of the fragile X syndrome probands, who themselves were premutation carriers and who often described their own problems with premature ovarian failure (POF) (cessation of menses before age 40 years).[7] Premature ovarian failure is now known to occur in approximately 20% of female premutation carriers, and the prevalence of POF is correlated with the number of repeats within the premutation range.[8] Recognition of a premutation-associated syndrome (POF) set the stage for the later recognition of the neurodegenerative disorder in the carrier grandfathers, in this instance through the expressed concerns of mothers of the children with fragile X syndrome regarding their own fathers.[1]

CLINICAL PHENOTYPE AND SPECTRUM OF INVOLVEMENT IN FXTAS

FXTAS represents the most severe form of clinical involvement associated with premutation *FMR1* alleles; its core features are intention tremor and/or ataxia, with lower extremity neuropathy, autonomic dysfunction, and gradual cognitive decline beginning with memory and executive function deficits.[1,3,9] Psychiatric features, including anxiety, disinhibition, depression, and apathy, are also common problems.[10] In an initial longitudinal study of 55 male premutation carriers, the major motor signs of FXTAS had a median onset of approximately 60 years of age.[11] Although intention tremor preceded the onset of gait ataxia in the majority of cases, either tremor or ataxia could be the presenting feature. A typical presentation is a progressive intention tremor that interferes with handwriting, followed by interference with other activities of daily living (use of eating utensils, pouring liquids, dressing) and progressive problems with balance. From the onset of the initial motor sign, median delay of onset of ataxia was 2 years; onset of falls, 6 years; dependence on a walking aid, 15 years; and death, 21 years. Preliminary data on life expectancy are variable, ranging from 5 to 25 years. The age at onset of FXTAS correlates with the CGG expansion within the premutation range; the higher the repeat, the earlier the tremor or ataxia.[12]

Associated features include a neuropathy, usually in a stocking distribution[3,13]; psychiatric problems, including reclusive behavior, anxiety, mood instability, depression, and apathy[10]; and autonomic dysfunction, including orthostatic hypotension, impotence, and eventually urine and stool incontinence.[3] Relatively mild parkinsonism (bradykinesis, masked facies, and resting tremor) is common, with approximately 30% demonstrating a resting tremor in addition to the intention tremor.[3] A head-bobbing tremor and slurring of speech may also been seen in occasional cases of FXTAS.

As more cases are described, it has become evident that presenting features may include not only intention tremor and ataxia, which would direct these individuals to movement disorders clinics, but also neuropathy or cognitive problems, including dementia, which might result in initial visits to neuropathy, pain management, or psychiatric clinics.[14,15] We recently performed a survey of 56 patients with FXTAS who were given 98 prior diagnoses by adult-practice physicians (primary care, 26%; general neurologists, about 70%; movement disorders specialists, 4%).[6] None of those diagnoses recognized an association with the fragile X gene (parkinsonism, 24%; tremor, 20%; ataxia, 17%; dementia, 13%; cerebrovascular disease, 10%; miscellaneous, 16%).

Women also present with FXTAS, although the movement disorder is less common in female carriers compared with male carriers presumably because of the protective effect of the second X chromosome.[4,16-18] As discussed later, the penetrance of FXTAS is incomplete, suggesting that second-gene and/or environmental factors may influence penetrance. In 1 intriguing case report,[19] a female premutation carrier experienced a dramatic worsening of clinical and magnetic resonance imaging (MRI) features of FXTAS while receiving cancer chemotherapy (carboplatin/docetaxel), with substantial improvement of FXTAS symptoms following cessation of chemotherapy.

The MRI features of FXTAS include global brain atrophy; white matter disease in the subcortical, middle cerebellar peduncle (MCP), and periventricular regions; and dilated ventricles.[2,3,20] A bilateral increased signal intensity in the MCPs on T2-weighted MRI (MCP sign) is a relatively distinct, although not unique, radiological feature of FXTAS found in approximately 60% of male carriers with neurological involvement; it is currently used as a supporting diagnostic feature (**Table**). In a study of 36 male premutation carriers, the CGG repeat within the premutation range correlated with reductions in both IQ and cerebellar volume, increased ventricular volume, and volume of whole-brain white matter disease.[20]

At the time individuals present with motor symptoms, they usually already have mild cognitive features, including memory problems and executive function deficits. These problems progress over time and, in about 50% of cases, lead to a frontal subcortical dementia with relative preservation of verbal abilities, at least initially, but with gradual development of behavioral dysinhibition.[10,21,22] The memory decline may reflect early, or more extensive, involvement of the hippocampus, since expression of *FMR1* messenger RNA (mRNA) is highest in the hippocampus, and the numbers of intranuclear inclusions, which are found in all postmortem premutation cases analyzed to date (see later), are highest in hippocampal neurons and astrocytes.[23-25] The psychiatric problems that frequently occur in carriers during adulthood and before the onset of FXTAS may also relate to

Table. Diagnostic Criteria for FXTAS[a]

Definite FXTAS	Probable FXTAS	Possible FXTAS
Intention tremor *or* gait ataxia *and* MCP sign[b] *or* intranuclear inclusions on postmortem examination	Intention tremor *and* gait ataxia *or* MCP sign *and* a minor clinical feature: parkinsonism, executive function deficits, moderate short-term memory deficiency	Intention tremor *or* gait ataxia *and* White matter lesions in the cerebrum *or* moderate generalized brain atrophy

Abbreviations: FXTAS, fragile X–associated tremor/ataxia syndrome; MCP, middle cerebellar peduncle.
[a] Must be premutation carrier (55-200 CGG repeats).[3,4]
[b] MCP sign: symmetric hyperintensities of the MCPs on T2-weighted or fluid-attenuated inversion recovery magnetic resonance imaging.[2]

the effects of elevated mRNA levels in the hippocampus, an important component of the limbic system. In our studies of adult carriers, we found a significant positive association between the psychiatric problems in men, including obsessive-compulsive behavior on Symptom Checklist–90 (a psychiatric questionnaire), and the level of *FMR1* mRNA.[26] This was most pronounced in men who did not have FXTAS; it was also seen in female carriers in whom the majority of cells had the premutation allele as the active allele. These findings suggest that RNA toxicity in the limbic system may be responsible for the psychiatric problems seen in some carriers.

The premutation is also the most common known cause of POF in women in the general population, with approximately 2% to 14% of women with POF demonstrating the premutation.[8] In women with the premutation, approximately 20% will develop ovarian failure before age 40 years and an additional 20%, before age 45 years.[8] Even female carriers who are cycling have elevations of their follicle-stimulating hormone compared with controls.[27] It has been hypothesized that the ovarian dysfunction in female carriers may also be related to RNA toxicity in the ovum,[8,28] although a direct mechanistic link has yet to be established.

EPIDEMIOLOGY

Studies of the penetrance of FXTAS among adult premutation carriers, ascertained through families with known probands with fragile X syndrome, revealed that approximately 40% of male (premutation) carriers older than 50 years presented with both intention tremor and gait ataxia.[15,18] The penetrance of the movement disorder increased with age, with more than one-half of male carriers older than 70 years displaying features of the disorder.[18] Estimates of the number of males in the general population who carry a premutation allele (1 in 259[29] and 1 in 813[30]) suggest that an upper bound in excess of 1 in 2000 males in the general population would have a lifetime risk of developing FXTAS. However, this upper-bound estimate is biased by the ascertainment of FXTAS cases within known fragile X syndrome families, where transmission of full-mutation alleles (fragile X syndrome probands) is highly biased toward larger CGG repeats in the premutation range.

The magnitude of this bias can be gauged from epidemiological studies demonstrating that the penetrance among carriers of larger premutation alleles is greater than among carriers of smaller premutation alleles.[31] In particular, 86% of persons with FXTAS, ascertained either through a family history of fragile X syndrome or from populations with movement disorders, but without known family history of fragile X syndrome, had alleles with 70 or more repeats.[31] This result differs significantly ($P < .001$) from the general population where only about 22% of premutation alleles are 70 or more repeats. A simple correction for this size bias would reduce the expectation for lifetime risk among males in the general population to about 1 in 3000 to 6000. This number is much lower than Parkinson disease or essential tremor and similar in prevalence to inherited ataxia, progressive supranuclear palsy, multiple system atrophy, and amyotrophic lateral sclerosis.[32]

Another approach to assess the prevalence of cases of FXTAS is to screen movement disorders populations based on phenotypic overlap between FXTAS and other disorders with parkinsonism, tremor, and/or gait ataxia. Of the roughly 15 studies reported to date, no increase in premutation alleles was found in parkinsonism populations, and only about 2% to 4% of cerebellar ataxia cases were found to be carriers of premutation alleles.[31,33] However, as noted earlier, in a survey of patients with FXTAS, only 4% were seen in movement disorders clinics (the source for essentially all of the high-risk screens).[6] Thus, there remains a large disconnect between the populations being screened and the physicians actually seeing the patients with FXTAS. Clearly, better prevalence estimates are needed based on larger-scale screens of US populations.

NEUROPATHOLOGY

The principal feature of the neuropathology of FXTAS is the presence of ubiquitin-positive intranuclear inclusions in neurons and astrocytes (but not oligodendroglia) in broad distribution throughout the brain (**Figure 1**).[23,34] The inclusions are solitary and spherical and appear as nonmembrane-bound collections of granulofilamentous material by electron microscopy.[34]

Inclusion counts are highest in the hippocampus, having been observed in as many as approximately 40% of hippocampal neurons in some cases, with smaller numbers (approximately 5%-10%) present in cortical neurons. Inclusions are only rarely detected in Purkinje cells despite substantial cerebellar Purkinje cell dropout.[34] The observation of inclusions in neuronal nuclei within the hypoglossal cranial nerve nucleus may be a neuropatho-

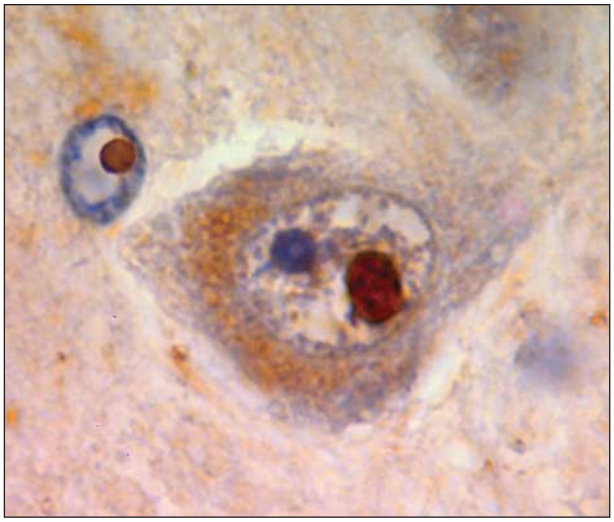

Figure 1. Micrograph of cortical neuronal (center) and astroglial (left) cells bearing intranuclear inclusions (brown, ubiquitin immunostaining). The separate nucleolus (blue) in the central neuronal nucleus is shown (original magnification ×1000).

logical correlate to the difficulties with swallowing experienced by individuals with late-stage FXTAS. Inclusions have not been identified in motor neurons of the spinal cord, although they are present in spinal autonomic neurons in the same region and astrocytic nuclei of the spinal cord.[34] Finally, the fraction of inclusion-bearing neurons and astrocytes is highly correlated with the number of CGG repeats in the *FMR1* gene,[23] further establishing the relationship between the length of the premutation expansion and disease formation.

Associated neuropathological changes include patches of subcortical white matter pallor and spongiosis, with axonal spheroids present to varying degrees in white matter, accompanied by loss of axons and myelin. The regions of patchy pallor correspond to areas of increased signal intensity on T2-weighted MRI in the same individuals. The MCP sign seen on MRI is generally more prominent than the mild degree of spongiosis of the MCPs at autopsy. Deep cerebellar white matter in the region of the dentate nucleus also shows some abnormalities, with spongiosis and axonal and myelin loss. The more severe FXTAS cases also possess markedly enlarged astrocytes containing cytoplasmic material that appears to have been phagocytosed.[23]

The diagnostic criteria for FXTAS outlined in the Table, originally published in Jacquemont et al,[3] have been modified to include the presence of inclusions when brain tissue is available.[4] More recently, inclusions have also been observed in other tissues, including both the anterior and posterior pituitary,[35] and in the Leydig and myotubular cells of the testes of 2 males with FXTAS.[28] Because the Leydig cells produce testosterone, we routinely measure testosterone levels in patients with FXTAS. Testosterone levels are often deficient, and replacement therapy has been helpful anecdotally in several patients.[28]

MOLECULAR PATHOGENESIS

There are several lines of evidence that support an RNA "toxic" gain-of-function model for FXTAS (**Figure 2**).[4,36] First, the disorder appears to be confined to carriers of active premutation alleles of *FMR1*; that is, FXTAS has not been reported among older adults with fragile X syndrome, for whom the gene is generally silent.[4] The absence of FXTAS among older individuals with fragile X syndrome also argues against deficiency of the *FMR1* protein (FMRP) as part of the pathogenic mechanism, since such individuals generally have little or no FMRP as a consequence of gene silencing. Moreover, absence of FXTAS in those with full-mutation alleles also argues against DNA level effects (eg, protein-DNA interactions), since full-mutation alleles are generally many times larger than alleles in the premutation range. Therefore, *FMR1* must be transcriptionally active to give rise to FXTAS. Thus, the pathogenesis of FXTAS (RNA toxicity) is completely distinct from the pathogenesis of fragile X syndrome (protein deficiency).

Second, *FMR1* expression is abnormal in at least 3 respects for alleles in the premutation range: (1) *FMR1* mRNA levels are elevated by as much as 8-fold for premutation alleles over the levels found for normal alleles; (2) the mRNA itself is altered because of the presence of the expanded CGG repeat in the 5′ noncoding region of the message; and (3) the start site for transcription is altered (shifted upstream) by the presence of the expanded repeat, such that the 5′ end of the message is extended by about 50 nucleotides.

Third, both mouse and *Drosophila* (fly) models that harbor the CGG repeat expansions in the premutation range (approximately 90-100 CGG repeats) manifest features of the neuropathology of FXTAS.[37,38] Furthermore, the knock-in mice with an expanded (approximately 100 CGG repeat) *FMR1* showed cognitive and behavioral impairment as well as ubiquitin-positive intranuclear inclusions.[37,39] In the case of the fly model, neuropathic features are present even when the expanded CGG repeat is transcribed upstream of an unrelated reporter gene.[38] Therefore, the expanded repeat, as RNA, is capable of inducing several features of the human disease.

Fourth, in direct support of an RNA-based pathogenesis for FXTAS, the *FMR1* mRNA is detected within the inclusions of patients with FXTAS.[24] This observation provides a clear parallel with the intranuclear foci of the myotonic dystrophies DM1 (*DMPK*, OMIM #160900) and DM2 (*ZNF9*, OMIM #602668), which contain the expanded CUG repeat (*DMPK*) or CCUG repeat (*ZNF9*) RNAs, respectively.[40-42] In this regard, the myotonic dystrophy model represents a useful framework for understanding the RNA gain-of-function pathogenesis of FXTAS, namely, that a normal interaction between 1 or more nuclear proteins and the repeat element, rendered abnormal by the expanded, and for FXTAS, overexpressed, repeat-containing RNA, is the inciting event for disease pathogenesis. For myotonic dystrophy, the RNA binding protein, muscleblind-like 1 (MBNL1), is sequestered by the large mRNA C(C)UG expansions; this sequestration is responsible, in part, for the altered splicing events associated with disease formation.[42]

Initial immunocytochemical studies of FXTAS inclusions demonstrated the presence of both ubiquitin and the small heat shock protein αB-crystallin, which is also found

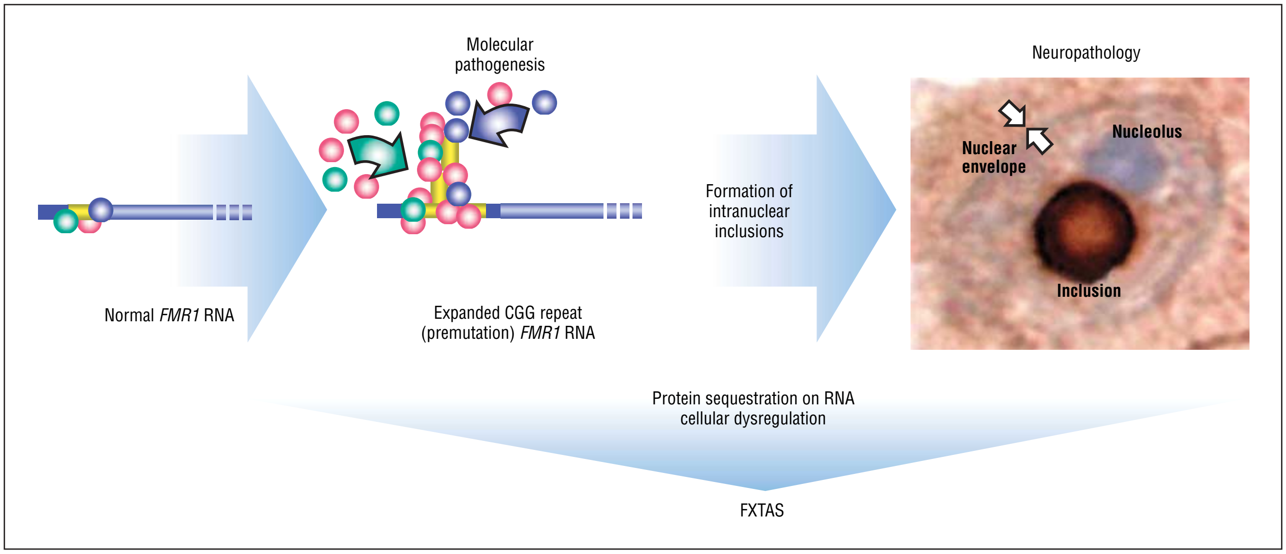

Figure 2. RNA "toxicity" model of fragile X–associated tremor/ataxia syndrome (FXTAS). Excessive accumulation of proteins to expanded CGG (gold) *FMR1* RNA leads to cellular dysregulation through protein depletion (myotonic dystrophy model [see "Molecular Pathogenesis" section of text]) and/or direct effects of the RNA-protein complex. Inclusions contain *FMR1* RNA and at least 30 proteins.

in the Rosenthal fibers of Alexander disease.[43] The inclusions were found to be negative for either α-synuclein or tau isoforms. Recently, we have been able to isolate microgram quantities of purified inclusions using a novel automated particle-sorting protocol with immunofluorescence-tagged inclusions. Mass spectrometric analysis of the protein complement of the inclusions has revealed the presence of more than 30 proteins.[44]

Several of these proteins are of potential interest to the pathogenesis of FXTAS, including 2 RNA binding proteins, heterogeneous nuclear ribonuclear protein A2 (hnRNP A2) and MBNL1, and the nuclear intermediate filament protein lamin A/C (A and C isoforms). MBNL1 is also associated with the pathogenesis of myotonic dystrophy, although the functional significance of MBNL1 in FXTAS inclusions is not known.

Expression of the expanded CGG repeat RNA in cultured neural cells results in the accumulation of lamin A/C within the intranuclear inclusions. This finding is in accord with the observation that lamin A/C is present within the neural cell intranuclear inclusions of patients with FXTAS. Furthermore, the expanded CGG repeat RNA leads to substantial disruption of the normal ringlike arrangement of lamin A/C at the nuclear periphery (**Figure 3**).[45] This second aspect of the altered distribution of lamin A/C, with associated changes in nuclear morphology, is far more widespread than the formation of inclusions per se.[45]

These observations, and the finding that lamin A/C is present in both the inclusions of patients with FXTAS and the inclusions in cell culture, suggest that lamin A/C dysregulation may be a component of the pathogenesis of FXTAS. In this regard, a significant clinical feature of FXTAS is a peripheral (axonal) neuropathy[13] that is similar to a form of type 2 Charcot-Marie-Tooth disease that is caused by mutations in the *LMNA* gene. On the basis of our current and previous findings, we hypothesize that FXTAS may represent a functional laminopathy; that is, abnormal lamin A/C function, induced by the expanded CGG repeat RNA, leads to many of the downstream effects involving both the central nervous and peripheral nervous systems.

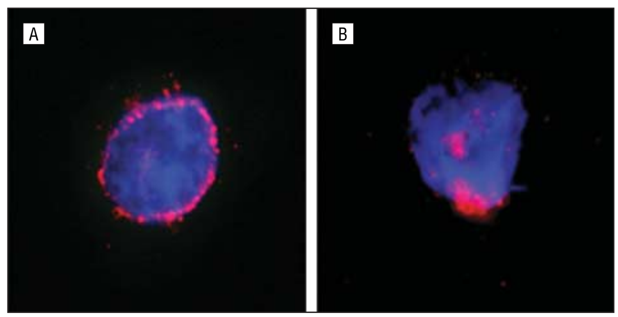

Figure 3. Disruption of lamin A/C nuclear architecture in cultured human neural cells by expanded CGG repeat RNA. A, Normal lamin localization (red, antilamin) with control reporter plasmid. B, Collapse of lamin architecture with expanded-repeat (CGG_{88}) reporter.[45] Nuclear (4′,6-diamidino-2-phenylindole [DAPI]) counterstain (original magnification ×1000).

TREATMENT OPTIONS

There is no single therapeutic agent that is effective for all of the neurological features of FXTAS; current treatment approaches for symptomatic relief in FXTAS have focused on the use of existing agents that have shown some degree of efficacy in other movement disorders. A recent survey of medication use in 56 patients with FXTAS indicated that 40% were taking some form of medication for tremor/ataxia, parkinsonism, or cognitive decline, and most of these patients reported some improvement with various treatments.[46] Although the numbers of patients treated are quite small, with results accordingly regarded as anecdotal, some improvement in the core movement disorder was reported with use of primidone (3 of 6 patients), β-blockers (3 of 8 patients), memantine (1 of 1 patient), or benzodiapines (2 of 8 patients). Parkinsonism improved while taking carbidopa/levodopa in 2 of 9 patients. Family members reported slowing of cognitive decline in 2 of 6 patients with FXTAS taking venlafaxine hydrochloride and 3 of 9 patients taking acetylcholinesterase inhibitors. Reduced anxiety was also reported in 2 of 6 patients with FXTAS taking venlafaxine and 5 of 8 patients taking benzodiazepines. An additional caveat with this initial survey was the questionnaire study design itself, which may have underestimated reported effectiveness in part because of the small sample sizes, cognitive impairment of the respondents, and lack of insight into some of the symptoms of the disease.[46] Another anecdotal report noted that gabapentin appeared to be helpful for neuropathic pain in some patients with FXTAS.[47]

Both anxiety and depressive disorder in FXTAS may respond to antidepressant medications, such as selective serotonin reuptake inhibitors or serotonin-norepinephrine reuptake inhibitors. The association of FXTAS with dementia indicates that benzodiazepines (associated risks to cognitive function) and tricyclic antidepressants (anticholinergic, possibly exacerbating cognitive impairment in some patients with FXTAS)[48-52] should be used only with caution and careful follow-up.

Clearly, what is needed at this point are large controlled trials with agents that have been reported to be of some benefit in the anecdotal reports. Hypertension, often observed in patients with FXTAS,[47] should be treated aggressively to avoid the added deleterious effects of hypertensive vascular disease on the white matter disease associated with FXTAS. Furthermore, since the pathogenic trigger is known (*FMR1* RNA), it is hoped that targeted intervention involving knock down of the RNA itself may become a viable approach to therapeutic intervention in the near future.

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