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FRAGILE X-ASSOCIATED TREMOR/ATAXIA SYNDROME: ANOTHER PHENOTYPE OF THE FRAGILE X GENE

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Abstract

Objective—Neuropsychologists have an important role in evaluating patients with fragile X-associated disorders, but most practitioners are unaware of the recently-identified neurodegenerative movement disorder known as fragile X-associated tremor ataxia syndrome (FXTAS). The objective of this editorial is to orient the reader to FXTAS and highlight the importance of clinical neuropsychology in describing the fragile X premutation phenotype and the role practitioners may have in assessing and monitoring patients with or at risk for neurodegeneration.

Method—We issued a call for papers for the special issue, highlighting the primary objective of familiarizing clinical neuropsychologists with FXTAS, and with the neuropsychological phenotype of both male and female asymptomatic carriers.

Results—Eight papers are included, including an overview of the fragile X-associated disorders (Grigsby), a review of the neuroradiological and neurological aspects of FXTAS and how the disorder compares to other movement disorders (O'Keefe et al.), a perspective on the prominence of white matter disease and dementia in FXTAS (Filley), and a review of mouse models of FXTAS (Foote). There are four research papers, including one on self-reported memory problems in FXTAS (Birch et al.), and three papers focused on the neuropsychiatric aspects of the fragile X premutation, a review (Bourgeois), an examination of autism-related traits (Schneider), and a research paper on executive functioning and psychopathology (Grigsby).

Conclusions—The issue highlights the importance of awareness of fragile X-associated disorders for neuropsychologists, an awareness that must reach beyond neurodevelopmental aspects related to fragile X syndrome into the realm of neurodegenerative disease and aging.

Keywords

FMR1 gene; FXTAS; dementia; movement disorder; executive function

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When they hear the term “fragile X,” non-pediatric neuropsychologists may find that their eyes glaze over, as they assume that the discussion concerns the neurodevelopmental disorder known as fragile X syndrome (FXS). FXS becomes evident in early childhood, and is characterized primarily by intellectual disability, attention problems, hyperactivity, anxiety, and autism spectrum symptoms. However, in recent years, it has become apparent that neuropsychologists who specialize in aging, movement disorders, and dementia should also pay close attention when fragile X is discussed. This is because in 1999, a team of researchers at the University of Colorado Denver and Children’s Hospital Colorado (Hagerman et al., 2001) discovered that carriers of the fragile X gene (*FMR1* or “fragile X mental retardation 1”) who are in their 50s and older, and who do not present with FXS, are at risk for a neurodegenerative movement disorder known as “fragile X-associated tremor ataxia syndrome” (FXTAS).

The term FXTAS may well be aptly named, but research focusing on carriers of the fragile X premutation in the past decade has shown that the phenotype is much broader than originally thought. Indeed, before its discovery in 1999, it was widely assumed that “carriers,” as the term implies, only pass on the mutation to succeeding generations, and are not themselves clinically affected. Subsequent to the discovery of FXTAS, action tremor, gait ataxia, parkinsonism, and cognitive decline were initially viewed as the primary symptoms of the disorder. Recent research on FXTAS has made it apparent that there was, and remains, much to be learned. Although the investigation of this disorder of late life is itself still in its youth, the effects of the fragile X premutation on the brain, behavior, and cognition reach beyond the realm of neurologists who specialize in movement disorders. It is important now that clinical neuropsychologists become knowledgeable about this fragile X-associated neurodegenerative disorder and its accompanying comorbid conditions.

These disorders—their penetrance and expression—are quite varied, both within and across affected individuals. In part for this reason, the research teams that have studied them are typically transdisciplinary, with both broad and deep experience of neuropsychology, neurology, psychiatry, epidemiology, molecular biology, and neuroimaging. In part this reflects the diverse impacts of the *FMR1* gene, and the fact that the trinucleotide repeats that characterize the gene’s mutations are themselves variable—CGG triplet repeats may range from as low as 6 to as high as several thousand (Leehey et al., 2008). In addition, these repeats may contain one or more AGG “interruptions” at different places (Yrigollen et al., 2014), and they may be expressed in different types of mosaicism. Other variables that influence the impact of *FMR1* include the mother’s age at the time of the child’s birth, the effects of other genes (both genomic and mitochondrial), possible environmental variables, and even perhaps such factors as the state of the gut microbiome, as appears to be the case in Parkinson disease (Scheperjans et al., 2015). The problem is more complex among female carriers, who have a second intact X-chromosome and a “healthy” *FMR1* gene that can compensate for problems associated with the defective gene. Finally, even younger premutation carriers who appear healthy may have a neurodevelopmental phenotype characterized by subtle problems with executive functioning, or very early, preclinical FXTAS (Hunter et al., 2011).

As we learn more about neurodegenerative diseases, it becomes increasingly clear that neuropsychologists must think more broadly about these conditions. That certainly is the case for FX-related disorders, for which knowledge of prevalence and pedigrees, among other things, facilitates diagnosis, assessment, prognosis, and management. Moreover, given that among women the fragile X premutation may be associated with inflammatory and immune disorders such as fibromyalgia and autoimmune hypothyroidism (Coffey et al., 2007), and with primary ovarian insufficiency (Allingham-Hawkins et al., 1999), immunologic and neuroendocrine contributions to cognitive impairment make the issues of assessment even more interesting, challenging, and important for neuropsychologists. One objective of this special issue is to demonstrate for practitioners the complexity of FXTAS and its related phenotypes, while providing a context in which to understand this important area.

This Special Issue on FXTAS begins with Grigsby's overview of the *FMR1* gene. For the reader who is unfamiliar with fragile X-associated disorders, he provides a broad-sweeping view of the research and clinical landscape of the *FMR1* mutations, their genetic basis and differential expression, the neurologic and neuropsychological manifestations of FXTAS, and insights into the history of discovery in the field.

Both clinicians and affected individuals report memory problems associated with FXTAS. This has led many in the field to suspect that memory impairment may precede the onset of neurological symptoms. However, as Birch and colleagues demonstrate, men with the premutation may not have more subjective memory complaints than matched controls. Interestingly, in their samples, subjective memory complaints were related to psychiatric symptoms, not objectively measured memory, raising important questions about how patients' memory concerns are interpreted and addressed in follow-up by the clinician.

Armed with recent brain MRI findings, detailed neurological profiles, and dementia perspectives, the papers by O'Keefe and Filley provide a "compare and contrast" view of FXTAS – where it sits in the spectrum of various motor and cognitive disorders. Given that a high percentage of patients with FXTAS are misdiagnosed (Hall et al., 2005), and many presumably are never tested for *FMR1* mutations, the comparison by O'Keefe and her colleagues of FXTAS to other movement disorders such as Parkinson's disease, spinocerebellar ataxias, and multiple system atrophy should aid the clinician in effectively detecting—or at least suspecting—the neuropsychological and motor profiles of FXTAS. This is important for improved medical management as targeted treatments become available, and for identification of extended family members with, or at risk for, other fragile X-associated disorders such as FXS, autoimmune thyroid disease, or fragile X primary ovarian insufficiency.

Filley's paper is an intensive focus on the prominent white matter disease observed in FXTAS, and he makes a strong case for its role in dementia and other forms of cognitive decline seen in people with this disorder. This provides a perspective on how FXTAS fits into the landscape of radiological and neuropathological signs of neurodegenerative disease, many of which are movement disorders. As with research on FXS, where intensive study of cognition and brain imaging data have shed light on the intellectual disability and autistic

features that accompany this disorder, Filley's paper highlights the importance of FXTAS by providing insights into other more common diseases of aging. Here again, however, we see how FXTAS as a progressive cognitive disorder is unique in many of the ways in which it typically presents to the clinical neuropsychologist.

In the papers by Bourgeois, Schneider et al., and Grigsby et al., neuropsychiatry takes center stage. Although the motor symptoms of action tremor and gait ataxia are the cardinal features of FXTAS, the Bourgeois review underscores the higher risk of mood and anxiety disorders in carriers well before any neurological problems develop, and addresses an important question: *Are psychiatric disorders a prodrome of FXTAS?* Schneider's demonstration of elevated broad autism phenotype (BAP) and obsessive-compulsive symptoms in premutation carriers raises questions about whether these behaviors are part of a broad spectrum involvement of patients who will eventually go on to develop FXTAS, or whether they are independent of FXTAS pathogenesis, and have a closer kinship with FXS. Indeed, FXS is caused by the reduction of absence of *FMR1* protein (FMRP) expression, contributing to prominent autistic-like behaviors and obsessive-compulsive features, and we know that some premutation carriers have subtle but significant deficits in FMRP expression that are correlated with atypical activation of brain regions mediating social-emotional processing (Hessl et al., 2011). Also, the similarities in BAP characteristics among premutation carriers and some parents of children with autism are of special interest. The third manuscript, by Grigsby et al., digs deeper into earlier work on FXTAS, exploring the anxiety and mood disorders that may affect both people with FXTAS and otherwise unaffected carriers. At the junction of neuropsychology and neuropsychiatry, it goes on to investigate the influential role of impaired executive functioning on the disinhibited and apathetic aspects of the psychiatric phenotype. Because psychiatric symptoms are so common in the general population, carefully designed studies, especially research utilizing population-based ascertainment of participants, will be important to clarify the true extent of the phenotype, and these papers may push the field in that direction.

The issue concludes with a paper focused on mouse models of the fragile X premutation by Foote and colleagues. As with FXS, animal models of the premutation can provide a great opportunity for understanding the genetic, neurobiological, behavioral, and cognitive aspects of the human disorder. The findings of researchers who study animal cognition and behavior help both to shape, and to test, human neuropsychological studies. Moreover, because they permit experimental research, animal models provide important clues into molecular therapies and a platform for evaluating compounds in preclinical models.

As research in the field progresses, pharmacological, behavioral, or cognitive interventions will be developed to minimize the risk to premutation carriers of developing FXTAS, and to slow its progression. Thus, clinical neuropsychologists are likely to be in a position to evaluate the efficacy of these treatments in both clinical and research settings. At present, however, there is no clear consensus on which measures and assessment methods will be used to track patient progress or response to intervention (e.g., Yang et al., 2016). Collaborative research is needed to identify and/or develop such measures that are sensitive to FXTAS progression and alleviation, and that can be used in future multi-site trials. In the field of FXS, multiple clinical trials were conducted without the needed outcome measure

development; the lack of this foundational work may have contributed, at least in part, to the limited success of this translational effort (e.g., Jacquemont et al., 2011; Berry-Kravis et al., 2012). This “cart before the horse” problem should not be repeated in FXTAS translational efforts. Clinical neuropsychology, with its historic strong ties to clinical neurology and movement disorders, will play an important role in ensuring the success of this future work.

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