

Preface

Fragile X-associated tremor/ataxia syndrome, or FXTAS, is one of the few examples of a disorder discovered entirely because of its familial relationship with another disorder, fragile X syndrome. The rather unique and interesting history of FXTAS is a story of families. The discovery of FXTAS illustrates pointedly to the physician, the importance of careful clinical histories and of listening to the patient (and the patient's parents) when they describe things that are concerning to the family but seem unrelated to the primary clinical problem. It stands as an example of what can be learned when the physician becomes so close to the families he or she follows that these families begin to share all of their problems.

FXTAS came into my life at a meeting in Steamboat Springs in early 2001, where Dr. Randi Hagerman and I (Dr. E. Berry-Kravis) were attending a symposium together. She said to me that she thought that premutation carrier grandfathers of her fragile X patients were developing tremor and gait problems. My first reaction was to play the devil's advocate. I said things like "tremor and parkinsonism are fairly common in the elderly" and "how do you know you are not just finding the grandfathers with problems because those are the ones the moms talk to you about" and "you'd have to do some kind of a more comprehensive screening to prove this is not just background neurological problems in the elderly." We agreed I would ask about neurological problems in the grandparents of my patients when I went back to Chicago. As I thought about it I realized that at least five families had asked me if Parkinson's disease is related to fragile X syndrome, and of course I had said "no" but I already knew I had been asked that question a few too many times. By the time I had talked to about 10 families in clinic, I knew that Randi was right, and there was a neurological disease in carrier grandfathers of children with fragile X syndrome. I have collaborated in studies of FXTAS since that time.

FXTAS is a condition that would never have been discovered if it was not genetically linked to fragile X. The condition itself is highly variable. Although tremor and ataxia are the hallmarks, it presents in a variety of disparate ways which are hard to place in a single category of disease, and hence, individuals with FXTAS are seen by a broad range of physicians and in all different neurological subspecialty clinics, including Parkinson's, ataxia, tremor, general movement disorders, dementia, multiple sclerosis, stroke, and neuropathy clinics. Because of the variable presentation in clinics focused on different problems and the varied phenotypes even

between brothers, it would have been extremely hard to ever identify FXTAS as a single genetic diagnosable condition without something to allow the patients with FXTAS to be grouped as a single entity. That something was the mothers of fragile X children, who talked about their children and behavior, the schools, family life and problems, and their fathers who had shaking, fell too much, were moody and socially reclusive, and in some cases were becoming demented. I will never forget my first visit with a little girl with mild developmental problems and ADHD symptoms who came to my clinic about 6 months after I talked to Randi in Steamboat Springs. I was taking the family history and the mother tearfully told me her father had died this year, but was diagnosed with Parkinson's disease and Alzheimer's disease and he had shaking and he had seen neurologists at Northwestern and the University of Chicago, and they were all baffled and thought he had a degenerative disease but was not typical of anything. For the first time I knew this little girl's DNA test would show fragile X just based on the description of her grandfather's disease and had the painful realization that I was about to shatter this mother's world for the second time in a year.

The dual presentation of disease in different generations of families reflects the fact that FXTAS and fragile X syndrome represent a rather unique situation of two entirely different diseases with completely distinct mechanisms resulting from exactly the same mutation, the CGG trinucleotide repeat expansion in *FMR1*. FXTAS results from premutation CGG repeat expansions containing roughly 55–200 repeats, while fragile X syndrome results from expansions of more than 200 repeats. Just a year before my conversation with Dr. Hagerman in Steamboat Springs, in 2000, Dr. Flora Tassone reported the discovery of elevated *FMR1* mRNA levels in premutation carriers, providing the molecular basis to explain the existence of FXTAS. In premutation carriers the mutation is transcribed into the *FMR1* mRNA, and it is this expanded CGG-containing RNA that is incorporated into nuclear inclusions observed in FXTAS and causes cellular toxicity through a gain-of-function mechanism. In fragile X syndrome, the long CGG repeat results in silencing of the gene, so neither the *FMR1* mRNA nor the protein product, FMRP, is made at levels near normal, and the condition thus results from a loss-of-function mechanism. Because the mutation tends to expand further as it is inherited through generations in families, the individuals with FXTAS are in older generations and those with fragile X syndrome in younger generations. Since FXTAS does not present until older age, it does not frequently provide clues about risk of fragile X syndrome in the family before children and grandchildren are born. Rather the mothers of affected children provide the “link” through which the grandparent with FXTAS has typically been ascertained and diagnosed.

Although the mechanisms for fragile X syndrome and FXTAS are distinct, individuals with a large premutation or small full mutation and partial mosaicism may show features of both conditions. Especially in the domain of executive function deficits, it appears that there is clinical overlap between the two conditions, and it is difficult to know whether these deficits represent very early FXTAS, developmental/congenitally determined effects of the premutation, or effects of minimal

reductions in FMRP that relate to diminished translation of large premutation-containing alleles and represent minimal forms of the fragile X phenotype. This of course contributes to the broad range of phenotypes seen in fragile X families.

With the discovery of FXTAS and fragile X-associated primary ovarian insufficiency (FXPOI), which like FXTAS appears to be caused by a mechanism of RNA toxicity and results in infertility problems and premature menopause in female premutation carriers, the concept of fragile X syndrome as a single condition related to a specific *FMR1* mutation has been revised. The three disorders, FXTAS, FXPOI, and fragile X syndrome, are now grouped as fragile X-associated disorders and produce a spectrum of diseases sprinkled throughout fragile X families, resulting in complex disease interactions within families not observed in other genetic conditions. Examples of these kinds of interactions would include the woman with infertility (early FXPOI) who is treated with fertility drugs and has twins or triplets with fragile X syndrome, and the mother who is struggling with her fragile X child's behavior, schooling, and medical issues and at the same time dealing with hot flashes and emotional lability from FXPOI while handling increasing care demands required by her father due to disability from FXTAS. These families need help and support. Increased awareness is needed for physicians to understand the fragile X-associated disorders and their relationships in families, so as to accurately diagnose symptomatic individuals, and avoid management errors due to lack of diagnosis. New treatments based on the underlying mechanisms are needed for all fragile X-associated disorders to provide hope and relief to affected individuals and the families that care for them.

In this book, we strive to present information on all aspects of FXTAS, including clinical features and current supportive management; radiological, psychological, and pathological findings; genotype–phenotype relationships; animal models; and basic molecular mechanisms. The book should serve as a resource for professionals in all fields regarding diagnosis, management, and counseling of patients with FXTAS and their families, while also presenting the molecular basis for the disease, that may lead to new markers to predict disease risk and eventually lead to mechanism-based treatments.

Resources:

<http://www.fragilex.org>

<http://www.FXTAS.ORG>

www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=300623

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