Fragile X-associated disorders: Don't miss them

Rachael C Birch, Jonathan Cohen, Julian N Trollor

Background

Fragile X-associated disorders are a family of inherited disorders caused by expansions in the Fragile X Mental Retardation 1 (*FMR1*) gene. Premutation expansions of the *FMR1* gene confer risk for fragile X-associated primary ovarian insufficiency and fragile X-associated tremor ataxia syndrome, as well as other medical and psychiatric comorbidities. Premutation expansions of the *FMR1* gene are common in the general population. However, fragile X-associated disorders are frequently under-recognised and often misdiagnosed.

Objectives

The aim of this article is to describe fragile X-associated disorders and identify specific considerations for general practitioners (GPs) during identification and management of these disorders.

Discussion

GPs have a critical role in the identification of fragile X-associated disorders, as well as coordination of complex care needs. Prompt recognition and appropriate management of these disorders and potential medical and psychiatric comorbidities will have important implications not only for the affected patient, but also other family members who may be at risk.

Fragile X-associated disorders are a family of X-linked genetic conditions caused by expansions of a cytosine–guanine–guanine (CGG) repetitive sequence in the Fragile X Mental Retardation 1 (*FMR1*) gene. Full mutation (>200 CGG repeats) of the *FMR1* gene results in fragile X syndrome (FXS),[1] the most common known inherited cause of intellectual disability. Smaller expansions, termed 'premutation' expansions (55–200 CGG repeats), are associated with increased risk for specific endocrine and neurological disorders distinct from FXS. These include fragile X-associated primary ovarian insufficiency (FXPOI)[2] and fragile X-associated tremor ataxia syndrome (FXTAS).[3] Individuals with the premutation may also experience increased rates of more general physical and mental health problems, including immune-mediated disorders,[4] thyroid problems,[4,5] migraine,[6] executive dysfunction,[7] and mood and anxiety disorders.[8]

Premutation expansions of the *FMR1* gene are common in the general population, being found in approximately one in 209 women and one in 430 men.[9] As such, it is likely that general practitioners (GPs) will have patients in their care currently experiencing, or at risk of developing, fragile X-associated disorders. As the first point of contact in the health system, GPs have a key role in the detection of physical and mental health problems, and the coordination of complex care needs for people with this broader group of fragile X-associated disorders (Box 1). This article describes key features of fragile X-associated disorders and outlines specific considerations for their identification and management in the general practice setting.

Fragile X syndrome

FXS is the most common form of inherited intellectual disability, affecting approximately one in 3600 males and one in 6000 females.[10] Clinical features include behavioural and emotional characteristics (anxiety, autistic behaviours, attention deficit hyperactivity disorder) and signs of developmental delay (intellectual disability, speech and communication difficulties, problems with fine and gross motor coordination). Physical characteristics are variably present but may include a long and narrow face with prominent ears, hypotonia and hypermobility.[11] Symptoms in females may seem less severe than in males because of a normal *FMR1* gene on the second X chromosome. The phenotype of FXS is caused by reduced production

Box 1. Fragile X-associated disorders

Full mutation (>200 CGG repeats)

- Fragile X syndrome

Premutation (55–200 CGG repeats)

- Fragile X-associated primary ovarian insufficiency
- Fragile X-associated tremor ataxia syndrome

CGG, cytosine–guanine–guanine

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of the Fragile X Mental Retardation Protein due to abnormal methylation and transcriptional silencing of the *FMR1* gene.[1] This protein has an important role in the regulation of several neuronal processes associated with healthy brain development, including synaptic development and neuroplasticity.[12,13] As clinical symptoms are not specific for FXS, diagnosis is confirmed by DNA testing. The Human Genetics Society of Australasia[14] recommends DNA testing for FXS be included as part of a basic genetic assessment of intellectual disability or developmental delay.

Fragile X-associated primary ovarian insufficiency

Approximately 10–30% of women who carry the *FMR1* premutation develop FXPOI.[2,4,15] This term encompasses a range of clinical signs of ovarian dysfunction, including irregular menses, increased follicle stimulating hormone, fertility problems and cessation of menstruation prior to 40 years of age.[15,16] For some patients, onset of menopause may occur in their early 20s. Although the mechanisms underlying the development of FXPOI are largely unknown, there is a non-linear relationship between severity of FXPOI and CGG repeats, with greatest risk and earlier onset observed among those with CGG repeat length in the mid-size range (80–100).[17] Approximately 5% of primary ovarian insufficiency cases are associated with an *FMR1* expansion.[18]

Fragile X-associated tremor ataxia syndrome

FXTAS affects approximately 45% of men and 16% of women with the premutation aged over 40 years.[4] Both the penetrance (ie the proportion of people with the premutation who have FXTAS) and severity of symptoms increase with advancing age.[19] Diagnosis is based on specific clinical, radiological and/or neuropathological criteria, and is confirmed by DNA testing[20] (Table 1). Additional neuropsychiatric features may include depression, anxiety, apathy, disinhibition, agitation and irritability.[21]

The estimated prevalence of FXTAS (two to six persons per 100,000) is similar to that of Huntington's disease and amyotrophic lateral sclerosis.[22] Challenges associated with making a diagnosis of FXTAS include variability in clinical presentations, possible compounding effects of comorbid age-related pathology (eg stroke, Alzheimer's disease) and the potential to misattribute these features to other more well-known disorders. Other disorders to consider in the differential diagnosis of FXTAS include essential tremor, multiple system atrophy, spinocerebellar ataxia, idiopathic Parkinson's disease and other atypical parkinsonian disorders.[23]

Role of the GP in the identification and management of fragile X-associated disorders

Recognition of possible disorders associated with the *FMR1* premutation

The majority of referrals for *FMR1* genetic testing are made by paediatricians, followed by GPs.[24] GPs have a central role in the identification, treatment and coordination of complex care needs of patients with, or at risk of developing, fragile X-associated disorders and potential medical and psychiatric comorbidities.

Indications for DNA testing for the premutation are summarised in Table 2. As the range of presenting symptoms suggestive of FXPOI and FXTAS are often seen by GPs, fragile X-associated disorders should be considered as one of a number of potential problems. However, timely and accurate diagnosis of fragile X-associated disorders is critical to ensure that the appropriate support services are made available. Further, identification of a premutation or full mutation expansion within a family affords other relatives the opportunity to choose whether they would like to undergo testing themselves, and to make informed decisions regarding their own health and reproductive risks. Where a premutation-associated disorder is suspected, patients should first be referred to appropriate specialists (eg a fertility specialist or neurologist) for further assessment, and to a genetic counselling service to discuss the implications of undergoing genetic testing. A list of genetic services in Australia can be found through the Centre for Genetics Education. Where a premutation or full mutation expansion is identified, consider cascade testing all other family members at risk.

Determining family history and identifying risk

Determining whether a patient may be at risk of developing a fragile X-associated disorder requires an understanding of how *FMR1* expansions are inherited. As the *FMR1* gene is located on the X chromosome, a man with the premutation will pass this on to all of his daughters and none of his sons. A woman with the premutation has a 50% chance of passing on an *FMR1* expansion (either a premutation or full mutation) to her children.[25] Where an *FMR1* expansion is suspected, it is important to take a careful family history of any cases of developmental delay or learning difficulties affecting both male and female relatives, as a family history of FXS or intellectual disability has been shown to be associated with increased likelihood of test-positive results.[24] However, because of the incomplete penetrance of FXTAS and FXPOI, some families will have no obvious family history of fragile X-associated disorders at all. As such, a lack of family history should not preclude genetic testing.

Management of disorders associated with the *FMR1* premutation

FXPOI

While there is currently no specific treatment available to restore ovarian function in women with FXPOI,

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management strategies include:

- provision of appropriate support for the patient and their partner, if applicable
- coordination of referrals to relevant health services, such as a genetic counsellor, psychologist, endocrinologist and/or fertility specialist
- continued review and management of common co-occurring issues such as depression and anxiety.

Consider a chronic disease management plan and team care arrangements for patients requiring ongoing care from a multidisciplinary team.

It is also important that women with the premutation are made aware of the full range of reproductive options available. Some women may opt to not have children or may choose to adopt. Given the risk of premature menopause, women who become aware of their carrier status before the onset of FXPOI may consider having children earlier in life. Those who conceive naturally may choose to undergo prenatal testing via chorionic villus sampling or amniocentesis (available to all carriers of FXS) and, if positive for FXS, some women may continue with the pregnancy, while others may terminate. Some may consider in vitro fertilisation treatments, including pre-implantation genetic diagnosis (enabling genetic testing of embryos prior to implantation), while others may consider the use of donor eggs or embryos.

FXTAS

There are currently no disease-modifying treatments for FXTAS, and there have been few randomised controlled trials assessing the efficacy of treatments targeting specific motor, cognitive or psychiatric signs. A randomised controlled trial of memantine, a glutamate receptor antagonist approved for use in the management of Alzheimer's disease, suggested no significant improvement in intention tremor or executive function[26] and limited benefit for language and memory function.[19] Other therapeutic modalities may improve motor, cognitive or psychiatric symptoms;[27] however,

Table 1. Diagnostic criteria for FXTAS*,[20]

Examination	Degree	Observation
Radiological	Major	White matter lesions in middle cerebellar peduncles and/or brain stem
	Major	White matter lesions in the splenium of the corpus callosum
	Minor	White matter lesions in cerebral white matter
	Minor	Moderate-to-severe generalised atrophy
Clinical	Major	Intention tremor
	Major	Gait ataxia
	Minor	Parkinsonism
	Minor	Neuropathy
	Minor	Moderate-to-severe short-term memory deficiency
	Minor	Executive function deficit
Diagnostic categories		
Definite	a) One major clinical + one major radiological sign, or b) One major clinical sign + presence of intranuclear neuronal and astrocytic inclusions on post-mortem examination of brain tissue	
Probable	a) One major radiological sign + one minor clinical symptom, or b) Two major clinical symptoms	
Possible	a) One major clinical + one minor radiological sign	

**Must have FMR1 grey zone (45–54 CGG repeats), premutation or full mutation*
FXTAS, fragile X-associated tremor ataxia syndrome; CGG, cytosine–guanine–guanine

Table 2. Indications for testing for an *FMR1* premutation[14] and key aspects of assessments

Indication	Assessment
i) Family history of disorders with known association with FXS (including intellectual disability, developmental delay, FXTAS, FXPOI) with plausible inheritance	• Patient interview: determine family history of intellectual disability, autism spectrum disorder, fertility problems, movement disorder and/or dementia
ii) Signs of decreased ovarian function, including elevated follicle-stimulating hormone, unexplained irregular menses, or cessation of menses before the age of 40 years	• Medical exam: note menstrual history, exercise level, recent stressful events • Blood test: follicle-stimulating hormone, estradiol, and anti-mullerian hormone
iii) Clinical or radiological signs of FXTAS, including onset of tremor or ataxia of unknown cause with parkinsonism or cognitive decline from 50 years of age	• Medical exam: assess extrapyramidal and cerebellar signs • Brain MRI: T1-weighted and T2 FLAIR • Patient and/or informant interview: determine changes in cognitive and behavioural function

FMR1, Fragile X Mental Retardation 1; FXS, fragile X syndrome; FXTAS, fragile X-associated tremor ataxia syndrome; FXPOI, fragile X-associated primary ovarian insufficiency; FLAIR, fluid attenuated inversion recovery

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Table 3. Potentially beneficial therapies for FXTAS[27]

Signs/symptoms	Therapies
Tremor	• Beta blockers • Primidone • Antiepileptics (levetiracetam, clonazepam)
Gait ataxia and parkinsonism	• Carbidopa/levodopa • Dopamine agonists • Physical therapy
Cognitive deficits and psychiatric symptoms	• Cholinesterase inhibitors • Antidepressants • Cognitive and behavioural therapies • Antipsychotics • N-methyl-D-aspartate receptor antagonists • Dietary supplements (B12, folate, vitamins C and E) • Aerobic exercise

FXTAS, fragile X-associated tremor ataxia syndrome

these have not been the subject of clinical trials (Table 3). Current clinical best practice involves implementing individual treatment programs comprising a combination of these management strategies.[27]

For patients with FXTAS, GPs should consider eligibility for a chronic disease management plan, and develop multidisciplinary team care arrangements where appropriate. Depending on individual patient requirements and disease stage, this may involve physiotherapists, occupational therapists, rehabilitation medicine physicians, psychologists and psychiatrists. Additional advice for younger patients with FXTAS can be sought from younger onset dementia services, as well as specific neuropsychiatric and behavioural neurology clinics and specialists.

Patients with more advanced FXTAS may require an assessment by an aged care assessment team to determine suitability for aged care services, respite, and/or home care and support. Importantly, the health and support needs of family carers should also be routinely assessed and managed, as carers of patients with FXTAS may be at risk of negative health outcomes, including psychological distress.[21]

Other considerations

Carriers of the premutation may be vulnerable to a wide range of physical and mental health conditions extending beyond FXPOI and FXTAS (eg hypothyroidism, depression, anxiety).[4,5,7,8] Although the mechanisms underlying vulnerability to more general health concerns are unclear, screening and management of potential medical and psychiatric comorbidities are important to minimise impact on functional abilities and quality of life.

Resources and additional support

Further information about fragile X-associated disorders and additional support can be sought from the Fragile X Association of Australia (https://fragilex.org.au) and the Fragile X Alliance Clinic (http://fragilex.com.au). A list of genetic services in Australia can be found through the Centre for Genetics Education website (www.genetics.edu.au/genetic-services/general-genetics-clinics). Additional information and resources to support carers can be accessed through the Carer Gateway (www.carergateway.gov.au).

Authors

Rachael C Birch BPsych (Hons), MBMSci, PhD, Lecturer, Department of Developmental Disability Neuropsychiatry, School of Psychiatry, UNSW Sydney, Sydney, NSW

Jonathan Cohen MBBS, FRACGP, FACTM, MastFamMed, Senior Adjunct Research Fellow, Centre for Developmental Disability Health, Monash University, Melbourne, Vic; and Medical Director, Fragile X Alliance Clinic and Genetic Clinics Australia, Melbourne, Vic

Julian N Trollor MBBS, MD, FRANZCP, Chair of Intellectual Disability Mental Health and Head of Department, Department of Developmental Disability Neuropsychiatry, School of Psychiatry, UNSW Sydney, Sydney, NSW; Centre for Healthy Brain Ageing, School of Psychiatry, UNSW Sydney, Sydney, NSW. j.trollor@unsw.edu.au

Competing interests: None.

Provenance and peer review: Not commissioned, externally and internally peer reviewed.

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